Observational Study/Post Authorization Safety Study (PASS) Information

Acronym/Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Protocol version and date	V1.0, 30 JUN 2020
IMPACT study number	21456
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	01 JUL 2020
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	N/A
Procedure number	N/A
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	The primary objective of this study is: •To assess the risk of recurrent venous thromboembolic (VTE) events in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon The secondary objective of this study is: •To assess the risk of fatal bleeding in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon Other objectives of this study are: •To assess the risk of end stage renal disease (CKD stage 5 or dialysis) in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon •To assess the health care resource consumption in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon •To assesses the overall and sector specific costs in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
Country(-ies) of study	This study will be conducted using secondary data from German sick funds.
Author	[redacted]

	[redacted]

Marketing authorization holder

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

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

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

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2. List of abbreviations

ATC	Anatomical Therapeutic Chemical Classification
CKD	Chronic kidney disease
CPN	Central pharmaceutical number
DDD	Defined daily dose
DOAC	Direct-acting oral anticoagulant
DVT	Deep vein thrombosis
EBM	Einheitlichen Bewertungsmaßstab für Ärzte (German ambulatory claims system)
HR	Hazard ratio
ICD-10 GM	International Statistical Classification of Diseases Version 10, German Modification
InGef	Institute for Applied Healthcare Research Berlin
IPTW	Inverse probability of treatment weighting
LMWH	Low molecular weight heparin
OPS	Operationen- und Prozedurenschlüssel (German Procedure Coding System)
pDDD	Personalized defined daily dose
PE	Pulmonary embolism
SHI	Statutory health insurance
VKA	Vitamin-K-antagonist
VTE	Venous thromboembolism

3. Responsible parties

3.1 Study initiator and funder

[redacted]

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

Name	Function
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]

4. Abstract

Acronym/Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Protocol version and date	V1.0, 29.06.2020
IMPACT study number	21456
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
Author	[redacted]
Rationale and background	Venous thromboembolism (VTE) manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). It is the third most common cardiovascular disease worldwide. Rivaroxaban, a direct-acting oral anticoagulants (DOAC), is indicated for VTE treatment, being increasingly used in routine clinical practice because of the fixed dosing and favorable pharmacological profiles (i.e. no requirement of INR monitoring; reduced rate of major bleeding while being comparable in terms of rates of recurrent VTE). Evidence on risk reduction for recurrent venous thromboembolism and major bleeding events between rivaroxaban and heparin followed by a vitamin-K-antagonist (VKA) in the real-world setting is still scarce.
Research question and objectives	The primary objective of this study is: • To assess the risk of recurrent VTE in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon The secondary objective of this study is: • To assess the risk of fatal bleeding in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon Other objectives of this study are:

	• To assess the risk of end stage renal disease (chronic kidney disease CKD stage 5 or dialysis) in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon • To assess the health care resource consumption in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon • To assesses the overall and sector specific costs in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
Study design	This is a non-interventional retrospective cohort study based on German claims data from the InGef (Institute for Applied Healthcare Research Berlin) research database between January 2013 and December 2019. Patients treated for acute VTE (i.e. PE or DVT) with rivaroxaban, or phenprocoumon with or without preceding heparin will be identified and follow-up from the first ambulatory dispensing of the respective anticoagulation regimen (the index date). Follow-up will end at the end of the study period, death, de-registration at the respective health insurance, or the outcome of interest, which ever will occur first.
Population	Patients with a new diagnosis of VTE, followed by ambulatory anticoagulation with rivaroxaban or phenprocoumon+-heparin, will be identified. All subjects with a diagnosis of VTE during the baseline period (i.e. 12 months prior to their index date) or anticoagulation treatment during the baseline period will be excluded. Patients with other medical conditions representing a potential indication of oral anticoagulation (e.g. atrial fibrillation; cardiac valve surgery) will also be excluded.
Variables	As exposure, we will assess dispensations of heparin, phenprocoumon and rivaroxaban. All dispensations will be assessed based on the documented dispensation date. Each patient will be assigned to one of the two exposure groups based on the index drug: new users of heparin+phenprocoumon, or rivaroxaban. As the effectiveness outcome, recurrent VTE will be analyzed (primary objective), while safety outcomes include fatal bleeding (secondary objective), and end stage renal disease (other objectives). Further outcomes include measures of health care resource consumption, and overall and sector specific costs from health insurance perspective. To adjust for potential confounding factors, several comorbidities and measures of health care utilization will be retrieved from the data source.
Data sources	This study will be conducted based on the InGef (former HRI) database which is an anonymized healthcare claims database covering all geographic regions of Germany. It includes

	longitudinal data from approx. 6.7 million Germans insured in one of >60 German SHIs currently contributing data to the database (mainly company or guild health insurances).
Study size	Based on a feasibility analysis, we estimate a sample size of approximately 13,000 new users of rivaroxaban and 5,000 new users of heparin+phenprocoumon with VTE during the inclusion period. The precision of the expected incidence rates of recurrent VTE in both treatment groups (12.1% and 18,7%) are considered to be sufficient to allow making meaningful conclusions, and address the study objectives.
Data analysis	Descriptive statistics will be generated to summarize the baseline characteristics of the study population. Cox proportional hazards regression models will be applied in the rivaroxaban group compared to phenprocoumon (reference) to estimate crude and confounder adjusted hazard ratios (HRs) of the outcomes of interest with accompanying 95% confidence intervals. Kaplan-Meier cumulative incidence plots will be generated to characterize risk of outcome events of interest over time. Information on confounding factors will considered in a multivariate COX model after selecting the most relevant factors using forward selection (significance level of 0.1 to enter the model). In a second step, we will use the stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in the baseline characteristics of different treatment groups. In a third step, we will additionally conduct a propensity score matched analyses. A 1:1 matching will be performed using the nearest-neighbor approach with a caliper of 0.2 without replacement. Adjusted hazard ratios (HRs) will be estimated based on a weighted COX model (IPTW), or a simple COX model with treatment as the only variable included (1:1 matching). For the analyses of healthcare resource consumption, negative binomial regression models will be applied to estimate adjusted rate ratios of healthcare resource consumption per day with 95%-confidence intervals during the follow-up period between rivaroxaban and phenprocoumon as the reference category. For the costs analyses, multivariate gamma regression models will be applied to estimate adjusted ratios of total cost per day with 95%-confidence intervals during the follow-up period between rivaroxaban and phenprocoumon as the reference category. In case of zero costs, a two-part model composed of a logistic regression model in patients with an indicator of non-zero costs as a dependent variable, and a gamma regression model patients with costs greater than zero and the total cost per day as a dependent variable will be considered. In addition, the

	absolute difference in mean costs between rivaroxaban vs. phenprocoumon users per person year will calculated with 95% confidence intervals.
Milestones	Registration in the EU PAS register 01 July 2020 Start of data collection 15 July 2020 End of data collection 31 July 2020 Final report of study results 30 October 2020

5. Amendments

N/A

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release and analysis do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document that is available upon request.

Table 1: Milestones

Milestone	Planned date
Registration in the EU PAS register	01 July 2020
Start of data collection	15 July 2020
End of data collection	31 July 2020
Final report of study results	30 October 2020

7. Rationale and background

Venous thromboembolism (VTE) manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). It is the third most common cardiovascular disease worldwide. VTE is a common disease with an incidence around 1-2 cases per 1000 patients per year. It is the third most common acute cardiovascular disease. In 10-30% of all cases a DVT leads to a PE which is the major reason for death after hospitalizations. 30% of these individuals will develop a recurrent venous thromboembolism within 10 years of their initial event. Continuing anticoagulation treatment can reduce the risk of recurrent venous thromboembolism but is associated with increased bleeding risk.

Rivaroxaban, a direct-acting oral anticoagulants (DOAC), is indicated for VTE treatment, being increasingly used in routine clinical practice because of the fixed dosing and favorable pharmacological profiles (i.e. no requirement of INR monitoring; reduced rate of major bleeding while being comparable in terms of rates of recurrent VTE). Evidence on risk reduction for recurrent venous thromboembolism and major bleeding events between rivaroxaban and heparin followed by VKA in the real-world setting is still scarce. The American College of Chest Physicians (CHEST)

guidelines recommends the use of DOACs over VKAs in patients with venous thromboembolism without an associated cancer diagnosis. Because patients with unprovoked venous thromboembolism are at higher risk of developing recurrent venous thromboembolism than are those with provoked venous thromboembolism, we aim to classify patients as having provoked or unprovoked venous thromboembolism at baseline.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is:

- To assess the risk of recurrent venous thromboembolic (VTE) events in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

8.2 Secondary objectives

The secondary objective of this study is:

- To assess the risk of fatal bleeding in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

8.3 Other objectives

Other objectives of this study are:

- To assess the risk of end stage renal disease (CKD stage 5 or dialysis) in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
- To assess the health care resource consumption in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon
- To assesses the overall and sector specific costs in VTE patients treated with rivaroxaban compared to patients treated sequentially with heparin and phenprocoumon

9. Research methods

9.1 Study design

We will conduct a non-interventional retrospective cohort study based on German claims data from the InGef (Institute for Applied Healthcare Research Berlin) research database between January 2013 and December 2019.

9.2 Setting

9.2.1 Study population

The source population of this study will include all insured members of more than 60 German statutory health insurances (SHIs) contributing data to the InGef database.

Treatment of VTE traditionally consists of acute anticoagulation treatment with heparin (mainly low molecular weight heparin; LMWH), followed by maintenance oral anticoagulation with vitamin-K antagonists (in Germany almost exclusively phenprocoumon). Direct acting oral anticoagulants (DOACs) are an alternative to this treatment approach, with some of them, including rivaroxaban, approved for both the acute and maintenance phase of VTE treatment. Treatment of VTE can occur in an ambulatory or an in-hospital setting, depending on severity of the condition, comorbidities, local health system environment etc.

A feasibility analysis confirmed that based on the available data, the following patient groups can be identified:

> *Patient group 1*: Initial in-hospital treatment with primary hospital discharge diagnosis of VTE (=Initial in-hospital treatment of VTE without prior ambulatory anticoagulation). These patients developed VTE out of hospital and were hospitalized for VTE.
>
> *Patient group 2*: Initial in-hospital treatment with secondary hospital discharge diagnosis of VTE (=Initial in-hospital treatment without prior ambulatory anticoagulation). It is assumed that these patients were admitted to hospital for a different reason, and developed VTE during their hospital stay.
>
> *Patient group 3*: Ambulatory treatment of VTE (Initiation of anticoagulation in ambulatory setting, without hospitalization for VTE within 14 days after treatment initiation). In these patients, treatment for VTE was administered out of hospital.
>
> *Patient group 4*: Initial ambulatory treatment, followed by in-hospital treatment with primary or secondary hospital discharge diagnosis of VTE within 14 days after treatment initiation. In these patients, initial treatment of VTE occurred in the outpatient setting, but patients were then (e.g. due to worsening or any other reasons) admitted to hospital due to the initial VTE event.

In the main analysis, patients from all four patient groups will be analyzed together. Potential differences between these four groups will be evaluated in subgroup analyses.

It should be noted that only patients with at least one dispensing of VKA; rivaroxaban for VTE will be included in the study, i.e. patients treated with heparins only will not be included.

9.2.2 Study time frame

Data from 2013 will only be used for the assessment of demographic and clinical characteristics, and to identify prevalent users of rivaroxaban and phenprocoumon (**Fehler! Verweisquelle konnte nicht gefunden werden.**). The enrollment period will be from 01 January 2014 to 31 December 2018. Data from 1 January to 31 December 2019 will considered as follow-up only to allow a follow-up of at least 12 months.

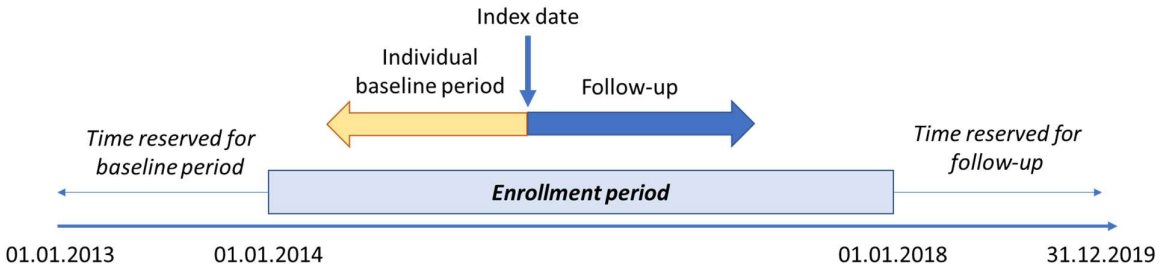

Figure 1. Study periods

9.2.3 Selection criteria

Inclusion criteria

All patients must meet all of the following inclusion criteria (see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information for detailed operationalization) to be eligible for the study:

- At least one new diagnosis of VTE during the inclusion period:
    - Ambulatory diagnosis, coded as verified
    - Primary hospital discharge diagnosis
    - Secondary hospital discharge diagnosis

  The quarter of the first VTE diagnosis in the inclusion period will be defined as the *index quarter*. For hospital diagnoses, the date of admission will be used to define the index quarter. The use of an index quarter is necessary as ambulatory diagnoses are recorded on quarterly basis only.

The assignment to patient groups one to four, and the definition of the *index date* will be done based on the following algorithm and additional inclusion criteria:

- Patients with only a hospital diagnosis of VTE in the index quarter (i.e. no ambulatory diagnosis): The hospitalization with the first diagnosis of VTE will be selected as the *index hospitalization*. Patients with a primary discharge diagnosis of VTE in index hospitalization will be assigned to **patient group 1.** Patients with only a secondary discharge diagnosis of VTE in index hospitalization will be assigned to **patient group 2**. Patients will be included if they had a first ambulatory dispensing of the following anticoagulation regimens within 14 days after hospital discharge:
    - Rivaroxaban
    - Phenprocoumon
    - heparin + phenprocoumon (dispensed on the same day)
    - heparin, followed by a first phenprocoumon dispensing within 14 days

  The date of the first anticoagulation dispensing after hospital discharge will be defined as the *index date* of the patient (Figure 2).

- Patients with only an ambulatory diagnosis of VTE in the index quarter (i.e. no in-hospital VTE diagnoses in the index quarter): Patients will be included if they had at least one pharmacy dispensing of a new anticoagulation treatment (heparin; phenprocoumon; rivaroxaban) in the index quarter and will be assigned to **patient group 3**. The day of the first anticoagulation dispensing will be defined as the *index date* (Figure 3). Patients will be included if they had a first ambulatory dispensing of the following anticoagulation regimens at the index date:
    - Rivaroxaban
    - Phenprocoumon
    - heparin + phenprocoumon (dispensed on the same day)
    - heparin, followed by a first phenprocoumon dispensing within 14 days
- Patients with both an ambulatory diagnosis of VTE and a hospital diagnosis of VTE in the index quarter:

- Patients *without* any anticoagulation treatment (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) before the hospitalization with the first diagnosis of VTE will be treated like *patients with only a hospital diagnosis of VTE in the index quarter* (see above).
- Patients who *had* a first anticoagulation treatment with heparin; heparin + phenprocoumon; or rivaroxaban within 14 days before the hospitalization with the first diagnosis of VTE will be assigned to **patient group 4**. These patients will only be included if they additionally had an ambulatory dispensing of the following anticoagulation regimens within 14 days after hospital discharge:
    - Rivaroxaban
    - Phenprocoumon
    - heparin + phenprocoumon (dispensed on the same day)
    - heparin, followed by a first phenprocoumon dispensing within 14 days

  The date of the first anticoagulation dispensing after hospital discharge will be defined as the *index date* of the patient (Figure 2). The rationale for defining group 4 is to ensure that the acute treatment phase of the patient (i.e. the time since initiation of the first anticoagulation prior to hospitalization until end of hospitalization) can be distinguished from the person-time at risk of developing the primary outcome of interest.
- Patients who *had* a first anticoagulation treatment dispensing (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) more than 14 days before the hospitalization with the first diagnosis of VTE will be treated like *patients with only an ambulatory diagnosis of VTE in the index quarter* (see above).

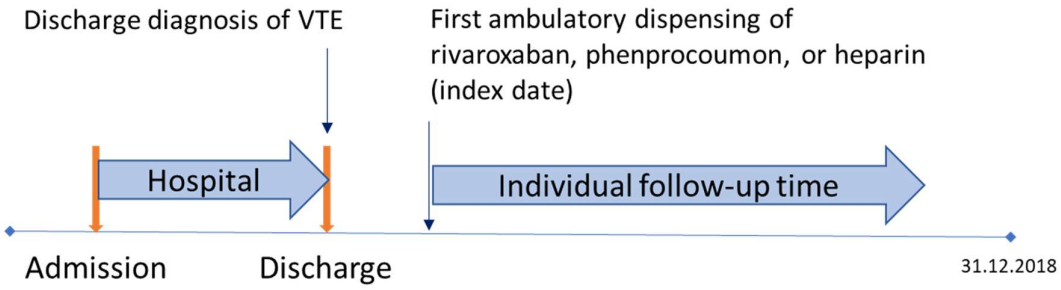

Figure 2. Definition of index date in patients who were hospitalized for VTE (patient groups 1,2, and 4)

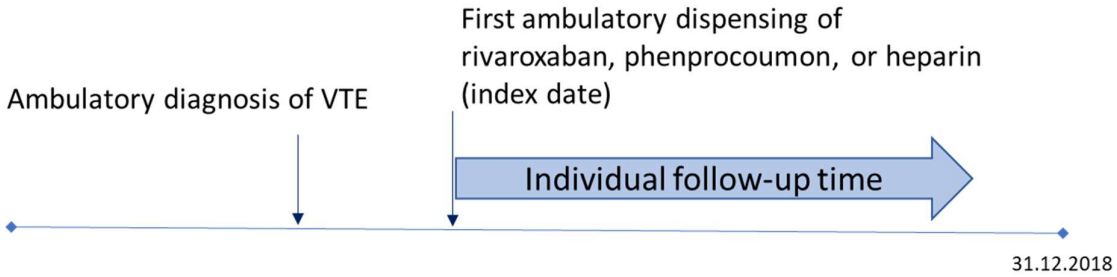

Figure 3. Definition of index date in patients who received ambulatory treatment for VTE (patient group 3)

The 12 months prior to the index date will define the *baseline period* for all included patients. Patients treated with anticoagulation regimens other than defined above (e.g. other DOACs) will not be included in the study.

All patients will have to fulfill the additional inclusion criteria:

- Continuous enrolment in the baseline period
- ≥ 18 years of age at index date

Exclusion criteria

Patients meeting any of the following exclusion criteria (see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. "tbd" indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information) will be excluded from the analysis:

- A verified ambulatory or primary/ secondary hospital discharge diagnosis of VTE in the baseline period
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of atrial fibrillation in the baseline period;
- A pharmacy dispensing of oral anticoagulation, heparin, or fondaparinux in the baseline period
- Individuals with documented cardiac valve surgery in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis indicating pregnancy in the baseline period;
- Any diagnosis indicating that the index VTE is pregnancy-related
- A dispensation of any anticoagulation treatment (heparins; vitamin-K antagonists; rivaroxaban; other DOACs) in the baseline period;
- A verified ambulatory or primary/ secondary hospital discharge diagnosis of end-stage kidney disease or a claim for dialysis in the baseline period;
- Patients assigned to rivaroxaban exposure groups who were initially treated with a dose strength other than 15 mg or 20 mg per tablet.

For the main analysis, patients will be followed from the index date until the first diagnosis of the respective outcome event, discontinuation of the index anticoagulation regimen, death, end of continuous insurance in the SHI or the end of the study period (31 December 2019), whichever comes first. A switch to a different anticoagulation regimen (i.e. from rivaroxaban to VKA or another DOAC; or from heparin/phenprocoumon to any DOAC) will also be considered as discontinuation of the index anticoagulation regimen.

For the analysis on healthcare resource consumption and costs, patients will be followed from the index date until discontinuation of the index drug, death, end of continuous insurance in the SHI, one year after the index date or the end of the study period (31 December 2019), whichever comes first. A switch to a different anticoagulation regimen (i.e. from rivaroxaban to VKA or another DOAC; or from heparin/phenprocoumon to any DOAC) will also be considered as discontinuation of the index anticoagulation regimen.

9.2.4 Representativeness

This study will be conducted based on the InGef (former HRI) database which is an anonymized healthcare claims database covering all geographic regions of Germany. It has been shown that this data source has a good representativeness for the German population (Andersohn F et al. 2016).

9.3 Variables

9.3.1 Exposure definition

As exposure, we will assess dispensations of heparin, phenprocoumon and rivaroxaban. All dispensations will be assessed based on the documented dispensation date. A detailed list of products with the corresponding central pharmaceutical number (CPN) of the study drugs is displayed in Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information.

Each patient will be assigned to one of the two exposure groups based on the index drug: new users of heparin+phenprocoumon, or rivaroxaban.

Exposure time for heparin+phenprocoumon and rivaroxaban starts on the index date for analyses of safety outcomes and the day after the index date for analyses of effectiveness outcomes and will be calculated as the sum of days of supply + a grace period of 14 days (in case of treatment discontinuation). A gap period of 30 days between the estimated end of supply and any following dispensation of the index drug is allowed. In-hospital stays during exposed person-time will be considered as exposed to the most recent anticoagulant used, as patients usually receive their drugs from the hospital (assuming treatment is continued).

For rivaroxaban, the days of supply corresponds to the number of tablets in a dispensed package (assuming daily use of one tablet). For heparin, the days of supply will be calculated based on the recommended application regimen for the respective product (e.g. based on the number of syringes to be administered daily). The exposure time calculation for phenprocoumon is, however, not straightforward due to interindividual variation in the number of tablets needed to reach a targeted INR range. To account for the intra- and interpersonal variability of phenprocoumon treatment, a personalized defined daily dose (pDDD) based on the observed phenprocoumon dispensations for each patient in the InGef database will be calculated. For this purpose, amount of active ingredient (AAI) dispensed to each patient of the phenprocoumon group will be obtained for each dispensation. A prescribed personalized daily dose (pPDD) representing the average daily dose taken during follow-up will be computed for each patient i such that:

$$pPDD_i = \frac{\sum_{k=1}^{K-1} AAI_{i,k}}{T_i}$$

- k= index of the dispensations received during follow-up ($k \in \{1, K\}$).
- T= number of days between the first and the last dispensation during follow-up

For the sake of simplicity, only dispensations of patients who were solely treated with phenprocoumon during follow-up will be included in the computation of the empirical DDD (eDDD). Patients with a pDDD below the 5th or above the 95th percentile and patients with only one dispensation for phenprocoumon will be assigned the median pDDD (=eDDD) over all patients.

The exposure time (ET) corrected from the intra- and interpersonal variability of phenprocoumon treatments can be computed for each patient i as:

$$ET_i = \frac{\sum_{k=1}^{K} AAI_{i,k}}{pDDD}$$

For rivaroxaban, heparin and phenprocoumon, stockpiling will be assumed, i.e. if a dispensation of the index drug is refilled before the estimated end of supply, the remaining supply of the dispensation will be added to following dispensation.

Patients will be considered as having discontinued treatment with the index drug, if they did not receive a subsequent dispensation of the respective drug between the last dispensation and a gap period of 30 days.

Patients will be considered as having switched from the index drug to a different anticoagulation regimen, if they received a dispensation of the respective drug during continuous exposure time to the index drug as described above. The date of the first dispensation of a different anticoagulation regimen will be defined as the date of treatment switch at which patients will be censored.

As a sensitivity to the primary approach of defining the person-time at risk, an intention-to-treat approach will be utilized. In this analysis, patients will be considered to be exposed to their initial anticoagulation regimen, independently from treatment discontinuation or switching. Person-time will censored at 6 months after the index date in this sensitivity analysis.

9.3.2 Outcomes definition

As the effectiveness outcome, recurrent VTE will be analyzed (primary objective), while safety outcomes include fatal bleeding (secondary objective), and end stage renal disease (other objectives).

A recurrent VTE event will be defined as a hospitalization with a primary hospital discharge diagnoses for VTE for which the admission date was >14 days after the index date. In a sensitivity analysis, only admissions later than 60 days after the index date will be considered to evaluate the impact of potentially including early hospital admissions that actually represent worsening of the index VTE. An additional sensitivity analysis will be conducted that combines the occurrence of a VTE hospitalization as defined above with treatment discontinuation. Recurrent VTE events will then only be counted as new events if there will be no ambulatory follow-up dispensation of the OAC where patients were exposed to at time point of event, after the calculated end of exposure time (+30 days gap period).

Cases of fatal bleeding will be defined as hospitalization with a primary hospital discharge diagnoses for bleeding with documented death as reason for hospital discharge or within 30 days after hospital discharge. The date of death will be set to the date of hospital discharge or date of disenrollment from the SHI, respectively.

The definition of end stage renal disease (CKD stage 5 or dialysis) will based on verified ambulatory or hospital discharge diagnoses, and on codes indicating dialysis (see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information). The date of the first code indicating end stage renal disease will be used to define the event date. For ambulatory diagnoses, the date of the first encounter with the diagnosing physician in the respective quarter will be used as the date of the ambulatory diagnosis.

Further outcomes include the number of hospitalizations (with at least one day between discharge from previous hospitalization), number of hospital days, number of emergency room visits defined as hospital admissions with "emergency" as reason for admission, number of distinct drugs used on the seven digit ATC-Code level as defined in Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. "tbd" indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

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Doc.Ref. EMA/540136/2009

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Adopted by the ENCePP Steering Group on 15/10/2018

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Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
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13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information. Overall costs (from SHI perspective) will be defined as sum of hospital costs, ambulatory care costs, drug dispensation costs, and remedies and aids costs. Costs for each of the mentioned healthcare sectors will also be analyzed as separate outcome. In addition, costs associated with renal impairment including hospital costs and ambulatory care costs for dialysis will be assessed as defined in Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. "tbd" indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

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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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information. To account for cost inflation over the study period, costs in each year will be standardized to the year 2018 for all analyses assuming the following inflation from 2013 onwards: 2012-2013: 1.5%, 2013-2014: 0.9%, 2014-2015: 0.5%, 2015-2016: 0.5%, 2016-2017: 1.5%; 2017-2018: 1.7%; 2018-2019: 1.7% (Source: https://data.oecd.org/price/inflation-cpi.htm; inflation for 2018-2019 assumed to be the same as 2017-2018.)

9.3.3 Covariate definition

All demographic and clinical characteristics will be assessed based on primary and secondary hospital diagnoses and verified ambulatory diagnoses (ICD-10 GM codes), OPS codes, EBM codes and ATC codes as defined in **Annex 1: List of stand-alone documents**

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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.

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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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information. In addition, healthcare resource consumption, i.e. number of hospitalizations, number of hospital days, number of emergency room visits, number of distinct drugs used on the seven digit ATC-Code level, as well as the overall costs and hospital costs, ambulatory care costs, drug prescription costs, remedies and aids costs and costs associated with renal impairment will be assessed. Unless otherwise mentioned, all information on covariates will be collected in the baseline period., i.e. in the 365 days prior to the index date. The assessment date for hospital diagnoses will be the admission date of the respective hospitalization and for ambulatory diagnoses the date of the first encounter with the diagnosing physician in the respective quarter (as ambulatory diagnoses are available on a quarterly basis only). Data derived from OPS codes and EBM codes will be assessed on the exact date.

Demographic characteristics

- Gender at index date
- Age at index date
- Age at index date categorized: 18–39, 40–44, 45–49, …, 85-89, 90+ years
- Federal State at the index date

Clinical characteristics

- Patient group (1,2,3, or 4) = treatment setting
- Type and localization of VTE index event:
    - PE (I26)
    - DVT lower extremity proximal (I80.1; I80.20)
    - DVT lower extremity localization not specified (I80.2 excluding I80.20; I80.3)
- $CHADS_2$ score
- CHA_2DS_2-VASc score
- modified HAS-BLED score (the INR will not be included in the calculation of the score because this information is not available in the InGef database, end-stage renal disease will not be considered as these patients will be excluded from the analysis)
- Comorbidities
    - Alcohol abuse
    - Anemia
    - Aortic plaque
    - Acute kidney injury
    - Coronary heart disease
        - Angina pectoris

- Myocardial infarction
- Acute ischemic heart diseases
- Chronic ischemic heart disease
- Coronary artery bypass graft(s)
- Percutaneous coronary intervention

- Dementia
- Depression
- Diabetes mellitus
- Drug abuse
- Gastric or peptic ulcer disease/diseases of gastrointestinal tract
- Heart failure
- History of major bleeding (hospitalization only)
- Hypertension
- Hypothyroidism
- Inflammatory bowel disease
- IS or transient ischemic attack
- Other cerebrovascular disease
- Liver disease
- Hyperlipidemia
- Volume depletion
- Other metabolic disorders
- Obesity
- Peripheral arterial disease
- Primary or secondary thrombophilia
- Psychosis
- Pulmonary disease
- Rheumatoid arthritis/collagen vascular disease
- Stroke or TIA
- Systemic embolism
- Tobacco abuse
- Other vascular disease
- Malignant cancer (except non-melanoma skin cancer)

- Last reported CKD stage
- Hospitalized CKD

- Comedications
  - Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
  - Antiarrhythmics
  - Antidepressants
  - Antiplatelets
  - Antiulcer drugs (except proton-pump inhibitors)
  - Beta Blockers
  - Calcium channel blockers
  - Diabetes drugs
  - Diuretics
  - Erythropoietin-simulating agents
  - Estrogens
  - Lipid modifying agents
  - Non-steroidal anti-inflammatory drugs
  - Proton-pump inhibitors

- Other indicators of overall health status
  - Number of hospitalizations
  - Number of different medications used (based on 7 digit ATC codes)
  - Number of ambulatory physician visits

Healthcare resource consumption and costs

- Overall costs
  - Hospital costs
  - Ambulatory care costs
  - Drug prescription costs
  - Remedies and aids costs
  - Costs associated with renal impairment
- Healthcare resource consumption
  - Number of hospitalizations

- Number of hospital days
- Number of emergency room visits
- Number of unique drugs used on a seven digit ATC code level

Others

- Year of cohort entry
- Initiator of treatment
- KV district of Initiator of treatment
- Duration of follow-up in days
- Type of cohort exit (end of study period, switch, discontinuation, death, etc.)

9.3.4 Subpopulations and Subgroups

Subgroups are only build on the basis of conditions already present at index date.

The following subgroups of special interest will be defined:

- Age group (<=60 vs. 60+ years)

Age will be assessed at the index date.

- Type of index event (DVT only; PE)

The categorization will be based on the diagnoses made during the index hospitalization (patient groups 1,2, and 4), or during the index quarter (patient group 3). For corresponding codes, see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				7+8
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)				7+8
2.1.4 Which hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?				9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period				9.2
4.2.2 Age and sex				9.2
4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information.

- Provoked and unprovoked VTE (Kearon et al. 2016; Journal of Thrombosis and Haemostasis,14: 1480–1483)

All patients will be classified based on identified transient and/or persistent risk factors of VTE into the following three categories:

  - VTE provoked by a transient risk factor: Patients who had at least one of the following medical events / conditions in the three months before their indext date:
    - Any surgery associated with hospitalization for at least 3 days
    - Emergency hospitalization for at least 3 days
    - Estrogen therapy
    - Leg injury
    - All patients in patient group 2 (developed VTE in hospital)
  - VTE provoked by a persistent risk factor: Patients who had at least one of the following chronic medical conditions in their baseline period:
    - Cancer (excl. non-melanoma skin cancer)
    - Inflammatory bowel disease
    - Primary or secondary Thrombophilia
  - VTE unprovoked: All patients not classified as having had a provoked VTE will be considered as having had unprovoked VTE.

- Treatment setting of index event (patient groups 1, 2, 3, 4)

The analysis will be performed within the four patient groups that define the study population, if feasible by sample size. Based on an initial feasibility analysis, it is unlikely that a subgroup analysis will be possible for patients in patient group 4 (initially treated ambulatory, then in hospital).

- Patients with lung, breast, or prostate cancer

Patients with lung, breast, or prostate cancer will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for these cancers as covariate (see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:				7+8
	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)				7+8
	2.1.4 Which hypothesis(-es) is (are) to be tested?				
	2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?				9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period				9.2
	4.2.2 Age and sex				9.2
	4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information).

- Chronic renal disease

Patients with chronic renal disease will be identified based on primary and secondary hospital diagnoses or verified ambulatory diagnoses in the baseline period according the definition for chronic renal disease as covariate (see Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	**Final version and date (if available)***
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection				6
1.1.2 End of data collection				6
1.1.3 Progress report(s)				
1.1.4 Interim report(s)				
1.1.5 Registration in the EU PAS Register®				6
1.1.6 Final report of study results.				6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				7+8
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)				7+8
2.1.4 Which hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?				9.7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)				9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?				9.2 + 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)				9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))				9.7
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:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?				9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period				9.2
4.2.2 Age and sex				9.2
4.2.3 Country of origin				9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication				9.2
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

Comments:

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)				9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)				9.3.1
5.3 Is exposure categorised according to time windows?				9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)				9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?				9.3.1

Comments:

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?				8
6.2 Does the protocol describe how the outcomes are defined and measured?				9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)				9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)				

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)				9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)				9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)				9.3.1, 9.9

Comments:

Section 8: Effect measure 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)				9.3.4, 9.7.2

Comments:

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)				9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)				9.3.2
9.1.3 Covariates and other characteristics?				9.3.3
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)				9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)				9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)				9.3.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)				9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))				9.3.2
9.3.3 Covariates and other characteristics?				9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)				

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?				9.7
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?				9.7.1
10.4 Are stratified analyses included?				9.3.4
10.5 Does the plan describe methods for analytic control of confounding?				9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?				9.7.3
10.7 Does the plan describe methods for handling missing data?				9.7.3
10.8 Are relevant sensitivity analyses described?				9.7.3

Comments:

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
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:

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).				9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)				9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?				10
13.2 Has any outcome of an ethical review procedure been addressed?				10
13.3 Have data protection requirements been described?				10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information).

For the healthcare resource consumption and costs analysis, the same subgroups as described above will be analyzed.

9.4 Data sources

This study will be conducted based on the InGef (former HRI) database which is an anonymized healthcare claims database covering all geographic regions of Germany. It includes longitudinal data from approx. 6.7 million Germans insured in one of >60 German SHIs currently contributing data to the database (mainly company or guild health insurances).

Claims data are transferred directly from health care providers to a specialized data center owned by SHIs, which provides data warehouse and IT services. In the data center (acting as a trust center), data is anonymized before entering the InGef database. Data are anonymized with respect to individual insured members, health care providers (e.g. physicians, practices, hospitals, pharmacies), and the respective SHI. The most important data elements included in the database are displayed in Table 2. The time period covered by the database is limited to a look-back period of 6 years starting with the most current complete year of data (Andersohn F et al. 2016).

Table 2 Information included in the InGef Database

Demographics	Age
	Gender
	Date of death
	Region for place of living
	Insurance status (e.g. retired, family insurance)
	Date of insurance start and end (observation period)
Outpatient Care	Diagnosis (ICD 10-GM Codes) and quarter in which the diagnosis was documented
	Procedures performed (e.g. laboratory, radiology, echocardiography) (EBM-Codes) and day of performance
	Type of specialist that documented the diagnosis and performed the procedure (e.g. cardiologist, general practitioner)
	Costs of outpatient care
Pharmacy	Drug dispensed by central pharmaceutical number (package level) – this is mapped to ATC codes and DDD's by InGef

	Quantity dispensed
	Day of prescription
	Day of dispensing
	Type of doctor prescribing (e.g. cardiologist, general practitioner)
	Costs of drugs dispensed from SHI perspective (without individual rebates between single sickness funds and pharmaceutical companies)
Hospital care	Main diagnosis (ICD 10-GM Codes) and additional diagnoses
	Performed procedures and surgeries (e.g. pacemaker implant, implantable cardioverter defibrillator
	Date of hospital admission
	Reason for admission (e.g. accident, emergency, normal)
	Date of end of hospital stay
	Reason of end of hospital stay (e.g. death in hospital, normal end)
	DRG-Code
	Type of hospital: psychiatric vs. somatic
Remedies and aids	Type of therapy (e.g. massage, occupational therapy, walker, wheel chair)
	Quantity prescribed
	Type of care provider
	Start date
	End date
	Costs of therapy/aids

9.5 Study size

Based on a feasibility analysis, we estimate a sample size of approximately 13,000 new users of rivaroxaban and 5,000 new users of heparin+phenprocoumon with VTE during the inclusion period. We used the cumulative incidence (incidence proportion) from a pooled analysis of the EINSTEIN-

DVT and EINSTEIN-PE studies (Prins MH et al. 2013) to estimate the expected number of recurrent VTE in users of anticoagulation regimens, assuming an average follow-up time of 200 days per person (as reported by Prins ME et al. 2013). The lower and upper 95% confidence intervals were calculated, assuming that the same incidence would be observed as in the pooled analysis of the RCTs. Precision was defined as the half width of the 95% confidence interval, related to the incidence estimate. Precision for the expected incidence estimates were 12.1% for rivaroxaban, and 18.7% for heparin+phenprocoumon, which was considered sufficient for the aims of this study.

Table 3 Expected precision of the cumulative incidence, assuming an average follow-up of 200 days per patient

Oral anticoagulant	Estimated number of drug users	Assumed cumulative incidence	Assumed number of events	Lower 95%-CI	Upper 95%-CI	Precision
Rivaroxaban	13,000	20.7 per 1,000	269	18.3 per 1,000	23.3 per 1,000	12.1%
heparin+phenprocoumon	5,000	23.0 per 1,000	115	19.0 per 1,000	27.6 per 1,000	18.7%

9.6 Data management

Completely anonymized analysis datasets comprising all observations and variables required for the planned analyses will be created from the information contained exclusively within the InGef database. The analytic datasets will be person-level, and will contain variables as specified in 9.3.

It is required that all analyses are conducted on the site of the data provider due to data protection requirements. The central statistical software programs used by InGef to evaluate data are R and SAS Enterprise Guide.

9.7 Data analysis

9.7.1 Descriptive analysis

Descriptive statistics will be generated to summarize the baseline characteristics of the study population. For continuous variables, the mean, median as well as the corresponding standard deviation, upper and lower quartiles and the minimum and maximum will be reported. For categorical variables, absolute counts and proportions of patients with given characteristics will be calculated relative to the total sample size of each treatment group.

The incidence rates of recurrent VTE, fatal bleeding, and end stage renal disease will be reported overall as well as in all subgroups as the number of events per 100 person-years. Corresponding 95%-confidence intervals will be calculated assuming a Poisson distribution. In addition, the mean number of hospitalizations and other healthcare consumption outcomes per patient per year as well as mean overall and sector specific costs per patient per year will be calculated with corresponding 95%-confidence intervals.

9.7.2 Main analysis

Analyses will be conducted in line with good statistical practices. There is no a priori hypothesis for this study. Models will use confounding factors to adjust for group differences. However, unmeasured confounding and resulting confounding bias affecting point estimates and confidence intervals in the treatment group comparisons may remain.

In a first step, Cox proportional hazards regression models will be applied in the rivaroxaban group compared to phenprocoumon (reference) to estimate crude and confounder adjusted hazard ratios (HRs) of the above mentioned outcomes with accompanying 95% confidence intervals. Kaplan-Meier cumulative incidence plots will be generated to characterize risk of outcome events of interest over time. Patients will be censored in case of discontinuation of the index anticoagulation regimen (including switch to a different anticoagulation regimen), death (except outcome fatal bleeding), end of continuous insurance in the SHI or the end of the study period (31 December 2019), whichever comes first.

For the analyses of healthcare resource consumption, negative binomial regression models will be applied to estimate adjusted rate ratios of healthcare resource consumption per day with 95%-confidence intervals during the follow-up period between rivaroxaban and phenprocoumon as the reference category. For the costs analyses, multivariate gamma regression models will be applied to estimate adjusted ratios of total cost per day with 95%-confidence intervals during the follow-up period between rivaroxaban and phenprocoumon as the reference category. In case of zero costs, a two-part model composed of a logistic regression model in patients with an indicator of non-zero costs as a dependent variable, and a gamma regression model patients with costs greater than zero and the total cost per day as a dependent variable will be considered. In addition, the absolute difference in mean costs between rivaroxaban vs. phenprocoumon users per person year will calculated with 95% confidence intervals.

Information on confounding factors which are included in the multivariable regression models can be found in section 9.3.3. We will use forward selection (significance level of 0.1 to enter the model) to select appropriate covariates. Federal State, initiator of treatment, KV district of Initiator of treatment, duration of follow-up in days and type of cohort exit, which are not independent risk factors of the outcome, will not be included in the respective models.

In a second step, we will use the stabilized inverse probability of treatment weighting (IPTW) approach based on the propensity score to adjust for potential confounding resulting from imbalances in the baseline characteristics of different treatment groups. The objective of IPTW based analysis is to create a weighted sample, for which the distribution of possible confounding variables is approximately the same between comparison groups (Xu et al. 2010; Austin 2011). The propensity score is defined as the patient's probability to receive a treatment under investigation (i.e. phenprocoumon) given a set of known patient's baseline characteristics. Propensity scores will be calculated using multiple logistic regression based on all patient characteristics listed in section 9.3.3 (except Federal State, initiator of treatment, KV district of Initiator of treatment, duration of follow-up in days and type of cohort exit)

Let Z be an indicator variable relating to the treatment received by a patient, $Z=1$ for an active treatment (e.g. rivaroxaban), $Z=0$ for a control treatment (warfarin), and let X denote a vector of observed patient baseline characteristics. Then the propensity score is $e=P(Z=1|X)$. The inverse probability of treatment weight is defined as $w=\frac{Z}{e}+\frac{1-Z}{1-e}$, i.e.

$w=\frac{1}{e}$ for patients receiving the active treatment, and

$w=\frac{1}{1-e}$ for patients receiving the control treatment.

Weighting by the inverse probability of treatment results in an artificial population or synthetic sample, in which treatment assignment is independent of measured baseline characteristics. Of note, a very low propensity score of subjects receiving an active treatment, or a propensity score close to 1 of subjects receiving a control treatment result in large weights. Such weights increase the variability of the estimated treatment effect (Xu et al. 2010). Moreover, it is known that the sample size of the synthetic sample is always greater that the sample size of the original data. Consequently, regression estimates with IPTW tend to have smaller confidence intervals because of the inflated sample sizes. In our analysis we will use IPTW with stabilized weights (12,13) which ensure more robust effect estimates. The stabilized weight is defined as $sw=\frac{P(Z=1)*Z}{e}+\frac{(1-P(Z=1))*(1-Z)}{1-e}$. The use of stabilized weights in the synthetic data preserves the sample size of the original data set (Xu et al. 2010). The application of propensity score methods via stabilized weights requires overlap of the propensity score distribution in the active and control treatment group. Therefore distributions of propensity scores will be inspected for original data and the synthetic sample. Furthermore, the distribution of stabilized weights in the original data will be examined to determine, if large weights remain after stabilization of weights. By applying IPTW method using the propensity score assessment needs to be done, whether weighting procedure succeeded to balance patient characteristics between treatment groups. The distributions of propensity scores and stabilized weights will be inspected for original data and the synthetic sample. The balance of patient characteristics between treatment groups will be checked by using standardized mean differences (SMD). An absolute SMD of 0.1 or less will be considered as a negligible difference between groups. For continuous variables, the SMD is calculated via

$$SMD_{cont}=\frac{\overline{X_T}-\overline{X_C}}{\sqrt{\frac{S_T^2+S_C^2}{2}}},$$

Where $\overline{X_T}, S_T^2$ and $\overline{X_C}, S_C^2$ denote the weighted sample mean and weighted sample variance of the variable in the treated and control patients, respectively. For binary variables, the SMD is calculated by

$$SMD_{cat}=\frac{(P_T-P_C)}{\sqrt{(P_T(1-P_T)+P_C(1-P_C))/2}},$$

Where P_T and P_C denote the weighted sample prevalence of the variable in the treated and control patients, respectively.

In a third step, we will additionally conduct a propensity score matched analyses. A 1:1 matching will be performed using the nearest-neighbor approach with a caliper of 0.2 without replacement. Again, the balance of patient characteristics between treatment groups will be checked in analogy to the description above.

Adjusted COX-regression models will be considered as the base case model, while IPTW and PS matching will be considered as sensitivity analyses to confirm robustness of results.

While the main time-to-event analysis will consider the total exposed person-time after index date (as defined above), risk estimates will additionally be provided for two time periods:

- For the treatment of VTE up to six months: In this analysis, follow-up times will be censored at 182 days after index date.
- For the extended treatment of VTE (after six months): In this analysis, only patients who were still at risk at day 183 after the index date will be included (Landmark analysis approach). In this analysis, the risk period will start at day 183.

To describe the risk of recurrent VTE events, the following analyses will be conducted. Analyses of recurrent events will be conducted for the unadjusted, matched as well as IPTW populations:

1) Mean cumulative function (MCF)

An important quantity is the mean number of recurrent events per subject by a certain time, i.e. the mean cumulative function (MCF) which is defined as

$$\mu(t) = E\big(N(t)\big).$$

The MCF is a marginal quantity, i.e. independent of the history of the event process. The common Nelson-Aalen estimator for survival analysis can be used as a non-parametric estimator for the MCF under the assumption of independent censoring, i.e. patients remaining are representative of the population.

Let $Y_i(t)$ indicate whether patient $i = 1, \dots, m$ is "at risk" for an event at time t and $Y_\Sigma(t) = \sum_{i=1}^{m} Y_i(t)$ the total number of patients at risk at time t. With $dN_\Sigma(t) = \sum_{i=1}^{m} Y_i(t) dN_i(t)$ being the total number of events at time t and H distinct event times across all m patients denoted as $t_1 \leq \cdots \leq t_H$ the Nelson-Aalen estimator is given as

$$\hat{\mu}(t) = \sum_{h:t_h \leq t} \frac{dN_\Sigma(t_h)}{Y_\Sigma(t_h)}.$$

In SAS the Nelson-Aalen estimator for the MCF can be calculated by means of the PHREG procedure. The following code plots the estimated MCFs of several treatment groups in one graph:

```
PROC PHREG DATA=dataset PLOTS(OVERLAY=ROW)=MCF;
     MODEL (TStart,TStop) * Status(0)= ;
     * start/stop time of inter-event times and censoring
       identifier;
     STRATA trt; * treatment group identifier;
RUN;
```

2) Andersen-Gill Model (AG) with robust standard errors (Wei Lin Weissfeld Model)

The Wei Lin Weissfeld (WLW) model models the total time from randomization to 1st, 2nd, 3rd, …, k-th event. Before applying the WLW model one has to pre-specify the maximum number of events k one wants to analyze. Therefore, one has to arrange the data in the right structure (a semi-restricted risk set) and also make sure to create 'dummy' events for patients with fewer than the maximal number of events k.

Semi-restricted risk sets

Semi-restricted risk sets have event-specific baseline hazards but allow subjects who have less than (k-1) events to be at risk for the k-th event through the creation of 'dummy' risk intervals. Thus a subject who has had none or one event can be considered at risk of a fourth event. However, a semi-restricted risk set does not allow information from the k-th event risk interval to contribute to the risk set for an earlier event. This risk set only applies to the total time and counting process formulation with event-specific baseline hazards.

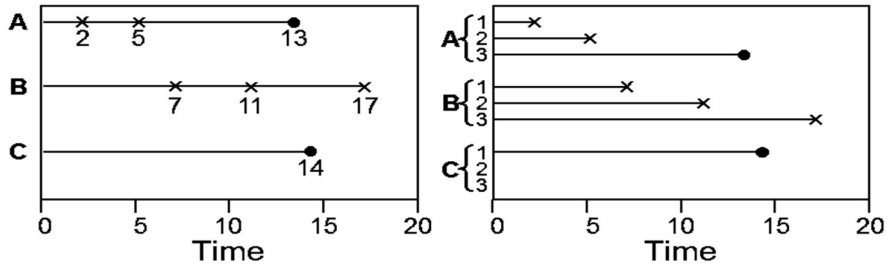

Figure 4 Hypothetical example with total time risk intervals

ID	time	num	event	total		cp	
				start	stop	start	stop
A	2	1	1	0	2	0	2
A	5	2	1	0	5	2	5
A	13	3	0	0	13	5	13
B	7	1	1	0	7	0	7
B	11	2	1	0	11	7	11
B	17	3	1	0	17	11	17
C	14	1	0	0	14	0	14
C	14	2	0	0	14	0	14
C	14	3	0	0	14	0	14

Figure 5 Semi-restricted risk sets in dataset representation

For example, in total time subject B is included with the second event time and subject C is included with a 'dummy' risk interval in the risk set for the second event of subject A (Figure 4). In the example above the maximum number of events per patient is three (for subject B). Accordingly, two dummy risk intervals need to be included for subject C for 'dummy' event number two and three. This results in a dataset as displayed in Figure 5.

One treatment effect estimate, which can be seen as an 'average effect' will be obtained. This average effect, however, is difficult to interpret, as for example the effect on the second event already includes the effect on the first event. Averaging the WLW treatment effects for first and second event would thus seem to double-count the effect on the first event.

Therefore, it is generally more advisable to obtain event-specific estimates by means of specifying interactions in the PROC PHREG call routine, i.e. treatment by event number. The following code gives an example of this for $k = 3$.

```
PROC PHREG DATA=<dataset> COVSANDWICH(AGGREGATE);
     MODEL totstop*event(0) = treat1 treat2 treat3;
     treat1 = treat*(num=1);
     treat2 = treat*(num=2);
     treat3 = treat*(num=3);
     STRATA num;
     ID pid;
RUN;
```

The event-specific estimate for the first event then coincides with the estimate of the Cox proportional hazards model for time-to-first event.

The distinctive feature of the WLW model is that each individual's time at risk for each event is considered to study entry, so that study entry is 'preserved' for all event-specific analyses.

9.7.3 Sensitivity analyses

The following sensitivity analyses will be performed for the main COX regression model and the outcomes of recurrent VTE; fatal bleeding; and end stage renal disease:

- In one sensitivity analysis, we will only consider recurrent VTE events that occurred more than 60 days after the index date. This analysis will allow to evaluate the impact of early (re-)hospitalizations and the fact that early hospitalizations may actually represent worsening of the index event, rather than a new VTE.
- As one would expect a change in the anticoagulation regimen after recurrent VTE, another sensitivity analysis will only consider recurrent VTE events if the respective oral anticoagulant is discontinued after the event (i.e. no follow-up dispensations within 3 months after hospital discharge).
- An additional sensitivity analysis will be conducted that combines the occurrence of a VTE hospitalization as defined above with treatment discontinuation. Recurrent VTE events will then only be counted as new events if there will be no ambulatory follow-up dispensation of the OAC where patients were exposed to at time point of event, after the calculated end of exposure time (+30 days gap period).
- In patients treated initially with heparin, followed by phenprocoumon or rivaroxaban within the next 14 days, the person-time between first heparin dispensing and subsequent OAC dispensing will be immortal by definition. The impact of this is expected to be low, but will be evaluated in another sensitivity analysis. In this analysis, the start of follow-up will be defined as the first OAC dispensing for all patients (i.e. also in those initially treated with heparin).

In addition, the following sensitivity analyses will be conducted for the healthcare resource consumption and cost analyses:

- First, we will use a modified intention-to-treat approach with a maximum follow-up of one year, i.e. patients will not be censored at treatment discontinuation or switch.
- Second, we will apply the modified intention-to-treat approach with a maximum follow-up of two years to account for possible differences in long-term costs including patients.
- Third, patients with extreme overall baseline costs defined as 75th percentile + 5*inter-quartile range of the overall costs of the underlying study population (for cost analysis only) will be excluded from the cost analysis.

No actions will be taken to deal with missing data, since data from all dimensions is assumed to be complete.

All analysis will be performed using SAS Enterprise guide version 7.1 or R.

The statistical concept of the study described above will be supplemented by the more detailed statistical analysis plan.

9.8 Quality control

Data quality management comprises data collection, management, and verification process, including quality control processes and documentation of the quality control steps.

Data quality management is built in to the core processing systems. In addition SAS/R is used to process data extracted from the production process to determine quality metrics.

- As part of the management strategy the InGef documents and implements:
- Quality control processes around reference data.
- Rules for raw data checks for completeness reasonability and volume
- Control processes for production files and outputs.
- Process flow and maintenance processes including standard operating procedures.
- Database metrics including quality and completeness
- Procedures for handling internal inquiries

The InGef routinely applies data quality assurance across data life-cycle stages. The following process is typical:

Data acquisition

The acquisition of the data follows a predefined statistical data-collection design/plan. The first control is the assurance that this plan is executed, i.e. all the required data items have been acquired and are in the collected-data-repository.

The data is then checked for compliance and completeness:

- File Completeness Check
- File format versus the predefined standard
- Data content – are all fields present with corresponding values?

Data-processing checks include:

- Control for correctness of the format and any input files format transformations
- Control of correctness of the bridged data

Processed-data checks include:

- Control of individual data-suppliers - total data volume versus expected and previous periods
- Checks for missing data estimations
- Check for aggregated data by analysis unit, e.g. values for surgeries, hospitals, regions

Data quality management is built in to the core processing systems, however, SAS/R is also used to process data extracted from the production process to determine quality metrics.

As part of the management strategy InGef documents and implements:

- Rules for raw data checks for completeness reasonability and volume
- Control processes for production files and outputs.
- Process flow and maintenance processes including standard operating procedures.
- Database metrics including quality and completeness
- Procedures for handling internal inquiries

Indicator Quality Assurance:

The InGef will output a series of descriptive statistics derived from the underlying data to validate the integrity of the field content. A sample of these statistics includes but is not limited to:

- Record counts with each data table
- Unique counts of patients
- Unique counts of patients continuously enrolled for specified one year increments
- Percentage of missing values in key data fields (e.g. date of birth, sex, billing and diagnosis codes, dates of service, etc.)
- Percentage of valid values in key data fields:
- Verify that a unique patient identifier is linked to only one individual

9.9 Limitations of the research methods

Although the analysis dataset obtained from the InGef database covers more than 6 million insured members of SHIs all over Germany, representativeness for all phenprocoumon and rivaroxaban users in Germany cannot be guaranteed if differences exist for instance by socioeconomic status or region. However, this will not affect the internal validity of the study results as the objectives of the study are related to relative risks rather than absolute risk estimates. Representativeness of the underlying data is therefore not a requirement.

As our study does not include a review of individual patient files to confirm the occurrence of individual outcomes, which for data protection reasons is generally not feasible, case validation is not possible and outcome misclassification cannot be ruled out.

The recurrent event analysis for VTE hospitalizations can only take into account those events which are recorded in the claims database. Therefore, patients could have deceased before any hospitalization.

For the patient group 2 (Initial in-hospital treatment with secondary hospital discharge diagnosis of VTE), it is assumed that these patients were admitted to hospital for a different reason, and developed VTE during their hospital stay. This may not be correct in all cases, e.g. if a historic diagnosis of VTE is recorded, and treatment with rivaroxaban or heparin/VKA is initiated for another indication. However, as patients with identified prior VTE are excluded from the cohort, the probability of such misclassification is considered rather low.

In the analysis of recurrent VTE events, only events treated in hospital will be included, as it is not possible to distinguish an ambulatory diagnosis of a recurrent VTE from a historical VTE diagnosis.

However, it can be expected that especially rather early events (occurring within the first year after the index date), will have a high probability of being treated in a hospital setting. In addition, it is expected that the number of missed events will be of a similar magnitude in both treatment groups.

With regard to drug usage, it has to be noted that the dispensation the respective drug does not necessarily imply that the patient actually took the medication. In addition, the estimation of duration of phenprocoumon treatment is limited by the fact that no information on the prescribed daily dose is available and thus have to be indirectly concluded from the treatment pattern (pDDD approach). Therefore, exposure misclassification is generally possible; however, in case of continuous drug dispensations to the same patient the amount of misclassification is expected to be low.

There is no cause-of-death information available for patients who died during their person-time at risk. Fatal bleeding events will thus have to be limited those events that led to hospitalization, and in which the patient died within the hospital. This may lead to a number of missed events (i.e. patients who die from bleeding before reaching the hospital), but it is considered that this proportion is probably low. In addition, it is expected that the number of missed events will be of a similar magnitude in both treatment groups.

In addition, unmeasured or residual confounding may affect the study results because several factors associated with the study outcomes cannot be measured adequately in claims data, e.g. laboratory values, physical activity, smoking. laboratory values and over the counter medications such as aspirin.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

All patient-level data in the InGef research database are de-identified to comply with German data protection regulations. Use of the study database for health services research is therefore fully compliant with German federal law and, accordingly, IRB/ethical approval is not needed. Since this study is based on anonymized claims data, informed consent of the patient is not required.

11. Management and reporting of adverse events/adverse reactions

For non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report, where applicable.

12. Plans for disseminating and communicating study results

The results of this study will be summarized in a study report. It further planned to submit at least one publication based on the results of this study to an international peer-reviewed journal.

13. References

Andersohn F, Walker J. Characteristics and external validity of the German Health Risk Institute (HRI) Database. Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):106–9.

Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivar Behav Res. 2011 May;46(3):399–424.

Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013 Sep 20;11(1):21. doi: 10.1186/1477-9560-11-21. PMID: 24053656; PMCID: PMC3850944.

Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2010 Apr;13(2):273–7.

Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
None	None

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)

EU PAS Register® number:
Study reference number (if applicable):

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 Progress report(s)	☐	☐	☐	
1.1.4 Interim report(s)	☐	☐	☐	

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7+8
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)	☒	☐	☐	7+8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2 + 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
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:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
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

Comments:

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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

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?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.3, 9.7.2, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.1, 9.9

Comments:

Section 8: Effect measure 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)	☒	☐	☐	9.3.4, 9.7.2

Comments:

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)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.3.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.3
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3

Comments:

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

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
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:

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).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

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: Frank Andersohn

Date: dd/Month/year 29/06/2020

Signature: _____

Annex 3: Additional information

Variable definition – Inclusion criteria

Variable/covariate	Definition / codes
VTE	ICD-10 GM: I80.1, I80.2, I80.3, O87.1, I26

Variable definition – exclusion criteria

Variable/covariate	Definition / codes
VTE	ICD-10 GM: I26, I80, I81, I82.2, I82.9, O22.3
Atrial fibrillation	ICD-10 GM: I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Cardiac valve surgery	OPS: 5351, 5352, 5353, 5358, 535a
Pregnancy	ICD-10 GM: O00 – O99, Z34 – Z39, O22.3
Hip or knee replacement	OPS: 5820, 5821, 5822, 5823
Oral anticoagulation	B01AA, B01AE, B01AF
Heparin **or fondaparinux**	ATC: B01AB, B01AX05
Azole antifungals	ATC: J02AB, J02AC
HIV protease inhibitors	ATC: J05AE
End-stage kidney disease or dialysis	ICD-10 GM: N18.5, Z49, Z94.0 OR OPS: 8853, 8854, 8855, 8857 OR EBM: (**valid from until Q4 2012**) 40800, 40801, 40802, 40803, 40805,40806, 40807, 40808, 40810, 40811, 40812, 40813; 40820, 40821, 40822, (**valid from Q1 2013 onwards**) 13602, 13610, 13611, 40815, 40816, 40817, 40818, 40819,40823, 40824, 40825, 40826, 40827, 40828, 40829, 40830, 40831, 40832, 40833, 40834, 40835, 40836, 40837, 40838

Rivaroxaban dosages not approved for use in VTE:

CPN	Name
05995074	Xarelto 10 mg
05995080	Xarelto 10 mg
07536850	Xarelto 10 mg
07536927	Xarelto 10 mg
09154791	Xarelto 10 mg
09941276	Xarelto 10 mg
09721534	Xarelto 10 mg CC Ph.
07799012	Xarelto 10 mg Emra
07799029	Xarelto 10 mg Emra
05459513	Xarelto 10 mg Eurim
07572633	Xarelto 10 mg Gerke Ph.
07572662	Xarelto 10 mg Gerke Ph.
09777888	Xarelto 10 mg Haemato-Ph.
05748766	Xarelto 10 mg Kohl Ph.
07610606	Xarelto 10 mg Kohl Ph.
11617270	Xarelto 10 mg Abacus
10402662	Xarelto 10 mg Axicorp Pharma
10852626	Xarelto 10 mg Beragena
10852632	Xarelto 10 mg Beragena
02088536	Xarelto 10 mg CC Ph.

CPN	Name
06410420	Xarelto 10 mg CC Ph.
14447816	Xarelto 10 mg CC Ph.
10339455	Xarelto 10 mg Docpharm
10743771	Xarelto 10 mg Docpharm
15204369	Xarelto 10 mg Emra
11898174	Xarelto 10 mg Filmtabletten
12636016	Xarelto 10 mg Filmtabletten
14166218	Xarelto 10 mg Filmtabletten
14417206	Xarelto 10 mg Filmtabletten Abacus
15861340	Xarelto 10 mg Filmtabletten Axicorp
14227440	Xarelto 10 mg Filmtabletten Originalis
14254247	Xarelto 10 mg Kohl Ph.
11565001	Xarelto 10 mg Mevita
10381894	Xarelto 10 mg Milinda
10381902	Xarelto 10 mg Milinda
10764520	Xarelto 10 mg Orifarm
14440814	Xarelto 10 mg Orifarm
06454481	Xarelto 10 mg Westen Ph.
05995097	Xarelto 10mg
13902388	XARELTO 10MG
14445591	Xarelto 2,5 mg CC Ph.
15569591	Xarelto 2,5 mg Emra
15569616	Xarelto 2,5 mg Emra

CPN	Name
14328678	Xarelto 2,5 mg Eurim
14328684	Xarelto 2,5 mg Eurim
08461261	Xarelto 2,5 mg Filmtabletten
08717186	Xarelto 2,5 mg Filmtabletten
09647915	Xarelto 2,5 mg Filmtabletten
09676408	Xarelto 2,5 mg Filmtabletten
12590136	Xarelto 2,5 mg Filmtabletten
14166247	Xarelto 2,5 mg Filmtabletten
08461290	Xarelto 2,5 mg Filmtabletten 1x10x10
14406467	Xarelto 2,5 mg Kohl Ph.
14406473	Xarelto 2,5 mg Kohl Ph.
14852468	Xarelto 2,5 mg Orifarm
14852474	Xarelto 2,5 mg Orifarm
13902371	XARELTO 2.5MG

Variable definition – exposure

ATC Code	Drug[1]
B01AA04	Phenprocoumon
B01AF01	Rivaroxaban
B01AB	Heparin

Variable definition – outcomes

Variable/covariate	Definition / codes
Recurrent VTE	ICD-GM: I80.1, I80.2, I80.3, O22.3, O87.1, I26

Variable/covariate	Definition / codes
Fatal bleeding	ICD-GM: D62, H11.3, H21.0, H31.3, H35.6, H43.1, H45.0, H92.2, I32.1, I60, I61, I62, I85.0, J94.2, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1 K92.0, K92.1. K92.2, M25.0, N02, N42.1, N83.6, N85.7, N89.7, N93.0, N93.8, N93.9, N95.0, R04.0, R04.1, R04.2, R04.8, R04.9, R23.3, R31, R58, S06.4, S06.5, S06.6, S06.8
End-stage kidney disease or dialysis	ICD-10 GM: N18.5, Z49, Z94.0 OR OPS: 8853, 8854, 8855, 8857 OR EBM: (**valid from until Q4 2012**) 40800, 40801, 40802, 40803, 40805,40806, 40807, 40808, 40810, 40811, 40812, 40813; 40820, 40821, 40822, (**valid from Q1 2013 onwards**) 13602, 13610, 13611, 40815, 40816, 40817, 40818, 40819,40823, 40824, 40825, 40826, 40827, 40828, 40829, 40830, 40831, 40832, 40833, 40834, 40835, 40836, 40837, 40838
Number of hospitalizations	Number of hospitalizations with at least one day between discharge from previous hospitalization
Number of hospital days	Number of hospital days calculated as date of (date of discharge - date of admission)+1 per hospitalization
Number of emergency room visits	Number of hospital admissions with "emergency" as reason for admission
Number of distinct drugs used	Number of distinct drugs used based on the seven digit ATC-Code level
Overall costs	Sum of hospital costs, ambulatory care costs incl. material costs for dialysis, drug prescription costs, and remedies and aids costs from the perspective of the German SHI
Hospital costs	Hospital costs from the perspective of the German SHI

Variable/covariate	Definition / codes
Ambulatory care costs	Ambulatory care costs incl. material costs for dialysis from the perspective of the German SHI
Drug prescription costs	Drug prescription costs from the perspective of the German SHI
Remedies and aids costs	Remedies and aids costs from the perspective of the German SHI
Costs associated with renal impairment	Sum of costs for hospitalizations with main discharge diagnosis of renal impairment or acute kidney injury or a coded OPS code for dialysis as, material costs for dialysis in ambulatory care, and other ambulatory care costs associated with EBM codes

Variable definition – covariates

Operational definition of CHA_2DS_2-VASc Score:

Conditions	ICD-10 GM code	Assigned weights
Hypertension	I10 – I15, I67.4	1
Diabetes mellitus	E10 – E14	1
Heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50, I09.9	1
Age between 65 and 74 years		1
Vascular disease (previous MI, peripheral arterial disease or aortic plaque)	I21 – I23, I25.2, I70.0, I70.2 – I70.9, I71, I73.9	1
Stroke or TIA	G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4, I64	2
Age ≥ 75 years		2
Female sex		1

Operational definition of $CHADS_2$ Score:

Conditions	ICD-10 GM code	Assigned weights
Hypertension	I10 – I15, I67.4	1
Diabetes mellitus	E10 – E14	1
Heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50, I09.9	1
Stroke or TIA	G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4, I64	2
Age ≥ 75 years		1

Operational definition of modified HAS-BLED Score:

Criteria	ICD-10 GM / ATC /OPS code	Assigned weights
Hypertension	I10 – I15, I67.4	1
Liver or renal disease	B18.0, B18.1, B18.2, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.1, K73, K74, K75.4, K75.8, K76.0, K76.6, K76.9, Z94.4, D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61	1
Stroke history	I63, I69.3, I69.4, I64	1
Major bleeding event	ICD-GM: D62, H21.0, H31.3, H35.6, H43.1, H45.0, I32.1, I60 - I62, J94.2, M25.0, S06.4, S06.5, S06.6, S06.8	1
Alcohol abuse	F10	1
Non-steroidal anti-inflammatory drugs or antiplatelet	B01AC, M01A	1
Age >65		1

Operational definition of claims based frailty indicator (10):

Criteria	ICD-10 GM / ATC /OPS code	Assigned weights
Impaired mobility	U50, Z99.3	1.24
Depression	F31, F32 – F34, F39, F43.1, F43.2,	0.54
Congestive heart failure	I11.0, I13.0, I13.2, I25.5, I42, I43, I50	0.50
Parkinson's disease	G20-G22	0.50
White race (yes vs. no)	1	-0.49

Arthritis (any type)	M05, M06, M08, L90.0, L94.0, L94.1, L94.3, M32 – M35, M45, M46, M48, M49	0.43
Cognitive impairment	F01 – F05, F06.0, F06.7, F06.8, F07.0, F07.8, F09, G30, G31.0, G31.1, G31.8, R41	0.33
Charlson comorbidity index (>0, 0)	As defined above	0.31
Stroke	I60-I64, I69.0-4	0.28
Paranoia	F06.0, F06.2, F20, F22-F29, F32.3, F33.3, F44.8	0.24
Chronic skin ulcer	I70.24, I70.25, I83.0, I83.2, I87.21, L89, L97	0.23
Male (yes vs. no)		-0.19
Skin and soft tissue infection	L00-L06	0.18
Mycoses	B35-B45	0.14
Pneumonia	J10.0, J11.0, J12-J18	0.21
Age (in 1 year categories)		0.09
Hospital admission in past 6 months		0.09
Gout or other crystal-induced arthropathy	M10, M11	0.08
Falls	N/A	0.08
Muscoskeletal problems	G45, M12-M14, M24, M25, M36, M43, M46, M47.1, M47.8, M50-M54, M67.8, M80, M81. M84.3, M84.4, M96.1, R26.2, R29.8, Z87.3	0.05
Urinary tract infection	N10, N30, N34, N39.0	0.05

Other covariates

Variable/covariate	Definition / codes
Alcohol abuse	ICD-GM: F10
Anemia	ICD-GM: D50 – D53, D63, D64.9
Aortic plaque	ICD-GM: I70.0
Chronic renal disease	ICD-GM: N18.3, N18.4

Variable/covariate	Definition / codes
Latest reported CKD stage	Latest ICD-GM of the following codes: N18.1 (stage 1), N18.2 (stage 2), N18.3 (stage 3), N18.4 (stage 4); N18.8/N18.9 (unknown) will only be considered, if no stage was coded previously
Acute kidney injury	ICD-GM: N17
Angina pectoris	ICD-GM: I20
Myocardial infarction	ICD-GM: I21 – I23, I25.2
Acute ischemic heart diseases	ICD-GM: I24
Chronic ischemic heart disease	ICD-GM: I25 (excl. I25.2)
Coronary artery bypass graft(s)	ICD-GM: Z95.1 OPS: 5361, 5362
Percutaneous coronary intervention	OPS: 8837
Dementia	ICD-GM: F01 – F03, G30, G31.0
Depression	ICD-GM: F31, F32 – F34, F39, F43,1, F43.2
Diabetes mellitus	ICD-GM: E10 - E14
Drug abuse	ICD-GM: F11 – F19 (excl. F17.2)
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	ICD-GM: K21, K25.4 – K25.9, K26.4 – K26.9, K27.4 – K27.9, K28.4 – K28.9, K29, K30, K64
Heart failure	ICD-GM: I11.0, I13.0, I13.2, I25.5, I42, I43, I50
History of major bleeding (hospitalization only)	ICD-GM: D62, H21.0, H31.3, H35.6, H43.1, H45.0, I32.1, I60 - I62, J94.2, M25.0, S06.4, S06.5, S06.6, S06.8
Hypertension	ICD-GM: I10 - I15, I67.4
Hypothyroidism	ICD-GM: E00, E01.8, E02, E03, E89.0
Inflammatory bowel disease	ICD-GM: K51, K52

Variable/covariate	Definition / codes
Ischemic stroke or transient ischemic attack	ICD-GM: G45.0 – G45.2, G45.4 – G45.9, I63, I69.3, I69.4
Systemic embolism	ICD-GM: I74
Other cerebrovascular disease	ICD-GM: I64 - I69 (excl. I69.3, I69.4)
Leg injury	ICD-GM; S70-S79; S80-S89; S90-S99
Liver disease	ICD-GM: B18.0, B18.1, B18.2, I85, K70.0, K70.2, K70.3, K70.4, K70.9, K72.1, K73, K74, K75.4, K75.8, K76.0, K76.6, K76.9, Z94.4
Hyperlipidemia	ICD-GM: E78.0 – E78.5
Volume depletion	ICD-GM: E86
Other metabolic disorders	ICD-GM: E87
Obesity	ICD-GM: E66
Peripheral artery disease	ICD-GM: I70.2 – I70.9, I71, I73.9
Pregnancy	ICD-10 GM: O00 – O99, Z34 – Z39
Primary or secondary Thrombophilia	ICD-GM: D68.5, D68.6
Psychosis	ICD-GM: F20, F22 – F25, F28, F29 – F31, F32.3 – F32.5, F33.3, F33.4, F34.8, F34.9, F39, F44.8
Pulmonary disease	ICD-GM: I27, I28.9, J44
Rheumatoid arthritis/collagen vascular disease	ICD-GM: M05, M06, M08, L90.0, L94.0, L94.1, L94.3, M32 – M35, M45, M46, M48, M49
Renal impairment	ICD-GM: D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61
Surgery (any)	OPS: 501 - 599

Variable/covariate	Definition / codes
Overall costs	Sum of hospital costs, ambulatory care costs incl. material costs for dialysis, drug prescription costs, and remedies and aids costs from the perspective of the German SHI
Hospital costs	Hospital costs from the perspective of the German SHI
Ambulatory care costs	Ambulatory care costs incl. material costs for dialysis from the perspective of the German SHI
Drug prescription costs	Drug prescription costs from the perspective of the German SHI
Remedies and aids costs	Remedies and aids costs from the perspective of the German SHI
Costs associated with renal impairment	Sum of costs for hospitalizations with main discharge diagnosis of renal impairment or acute kidney injury or a coded OPS code for dialysis, material costs for dialysis in ambulatory care, and other ambulatory care costs associated with EBM codes
Number of hospitalizations	Number of hospitalizations with at least one day between discharge from previous hospitalization
Number of hospital days	Number of hospital days calculated as date of (date of discharge - date of admission)+1 per hospitalization
Number of emergency room visits	Number of hospital admissions with “emergency” as reason for admission
Number of distinct drugs used	Number of distinct drugs used based on the seven digit ATC-Code level
Acute kidney injury	ICD-GM: N17
Tobacco abuse:	ICD-GM: F17.2
Other vascular disease	ICD-GM: I70.1, I72, I73.1, I73.8, I74, I79, K55.1, K55.8, K55.9, Z95
Malignant cancer (excl. non-melanoma skin cancer)	ICD-GM: C00-C97 (excl. C44)
Angiotensin-converting enzyme inhibitors or	ATC: C09

Variable/covariate	Definition / codes
angiotensin-receptor blockers	
Antiarrhythmics	ATC: C01B
Antidepressants	ATC: N06A
Antiplatelets	ATC: B01AC
Antiulcer drugs (except proton-pump inhibitors)	ATC: A02BA, A02BB, A02BX
Beta blockers	ATC: C07
Calcium channel blockers	ATC: C08
Diabetes drugs (incl. insulin)	ATC: A10A, A10B
Diuretics	ATC: C03
Erythropoietin-simulating agents	ATC: B03XA
Estrogens	ATC: G03C, L02AA
Lipid modifying agents	ATC: C10
Non-steroidal anti-inflammatory drugs:	ATC: M01A
Proton-pump inhibitors	ATC: A02BC

Annex 4: Signature pages

Signature Page – OS Conduct Responsible

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Protocol version and date	V1.0, 30.06.2020
IMPACT study number	21456
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Will be added once registered (after approval)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

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Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – OS Safety Lead

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Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – OS Medical Expert

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Signature Page – OS Medical Expert

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Signature Page – OS Medical Expert

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Study Initiator and Funder	Bayer AG 13353 Berlin, Germany

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Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – OS Statistician

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IMPACT study number	21456
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Will be added once registered (after approval)
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Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – OS Epidemiologist

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
Protocol version and date	V1.0, 30.06.2020
IMPACT study number	21456
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Will be added once registered (after approval)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Comparator / Reference therapy	Heparins (B01AB) Vitamin-K antagonist, Phenprocoumon (B01AA04)
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany

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Print Name: [redacted]

Date, Signature:_____, _____

Signature Page – OS Outcomes Data Generation

Title	Real-world comparative effectiveness of rivaroxaban versus heparin and phenprocoumon for the treatment and secondary prevention of venous thromboembolism (RECENT)
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Date, Signature:_____, _____