Observational Study/Post Authorization Safety Study (PASS) Information

Acronym/Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	21616
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Direct factor Xa inhibitors B01AF01 rivaroxaban, B01AF02 apixaban, B01AF03 edoxaban Direct thrombin inhibitors B01AE07 dabigatran etexilate Vitamin K antagonist B01AA03 warfarin Heparins (B01AB)
Medicinal product	Rivaroxaban
Product reference	N/A
Procedure number	N/A
Comparator	Apixaban, dabigatran, edoxaban, warfarin, heparins
Study Initiator and Funder	Bayer AG, Müllerstrasse 173, 13353 Berlin
Research question and objectives	Research questions related to occurrence of VTE and treatments for VTE in cancer patients in Sweden The objectives are: 1. To estimate the risk of recurrent VTE, major bleeding and all-cause death in individuals with cancer not associated with a high risk of bleeding in Sweden (Annex 1, Table 3)

	2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment 3. To estimate the risk of a recurrent VTE, major bleeding and all-cause death by type of anticoagulation treatment (LMWH, VKA or NOAC) as independent outcomes 4. To compare incidence rates of recurrent VTE, major bleeding and death in subjects treated with rivaroxaban versus LMWH; and NOACs versus LMWH
Country of study	Sweden
Authors	PPD Sweden PPD for Bayer AG PPD Bayer AG PPD Bayer AG PPD Bayer AG

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, Müllerstrasse 173, 13353 Berlin
MAH contact person	PPD

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

CI	Confidence interval
DVT	Deep Venous Thrombosis
EU	European Union
GPP	Good Publication Practice
LMWH	Low molecular weight heparin
MAH	Marketing Authorization Holder
NA	Not Applicable
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulant
OS	Observational Study
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
PS	Propensity Score
VKA	vitamin K antagonist
VTE	Venous ThromboEmbolism

3. Responsible parties

3.1 Study initiator and funder

Role:	OS Conduct Responsible and Epidemiologist
Name:	PPD
E-mail:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Statistician- External, KI
Name:	PPD
Role:	OS Epidemiologist
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Contact details of the responsible parties at Bayer AG are available upon request.

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

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4. Abstract

Acronym/Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	21616
Study type / Study phase	Observational
Authors	PPD PPD for Bayer AG PPD Bayer AG PPD Bayer AG PPD Bayer AG
Rationale and background	Cancer is one of the leading causes of death globally and is known to increase the risk of Venous ThromboEmbolism (VTE) including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Cancer Associated Thrombosis (CAT) is a major cause of morbidity and mortality in cancer patients. During recent years treatment options for VTE have expanded to include non-vitamin K antagonist oral anticoagulants (NOACs) have increased and is recommended in non-cancer patients. Most recently, NOACs are also recommended as an alternative treatment to Low Weight Molecular Heparins (LWMH) in cancer patients after careful consideration of the risk of bleeding and possible interaction with cancer therapy. While their cancer is active, patients remain at increased risk of VTE. For reasons of convenience and route of administration, NOACs provide a less burdensome alternative to LMWH and are likely to improve adherence. However, there is a need to better understand how NOACs are used to treat VTE in cancer patients, in particular in relation to cancer therapies, duration of use and risks of recurrent VTE events, major bleeding and death.
Research question and objectives	The research questions are to examine the occurrence of recurrent VTE, major bleeding and death; and associated treatments for VTE among subjects with cancer in Sweden. The objectives are: 1. To estimate the risk of recurrent VTE, major bleeding and all-cause death in individuals with cancer not

	associated with a high risk of bleeding in Sweden (Annex 1, Table 3) 2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment 3. To estimate the risk of a recurrent VTE, major bleeding and all-cause death by type of anticoagulation treatment (LMWH, VKA or NOAC) as independent outcomes 4. To compare incidence rates of recurrent VTE, major bleeding and death in subjects treated with rivaroxaban versus LMWH; and NOACs versus LMWH
Study design	Retrospective cohort study
Population	All patients diagnosed with cancer in Sweden from year 2013 to 2019.
Variables	Type of cancer identified through ICD10 codes C00-C97 (malignant neoplasms) including data on cancer stage and type at diagnosis. Baseline characteristics including demographic information as well as data on comorbidities through ICD10 codes from hospitalizations and open care visits at hospitals (Annex 1, Table 2). Prescribed drugs through ATC codes to capture dispensed prescriptions of NOACs, VKA and LMWH as well as other relevant medicines including cancer treatments, whenever available (Annex 1, Table 1). ICD10 codes for DVT, PE, VTE, major bleeding or death (Annex 1, Table 2).
Data sources	Swedish registries including the Cancer Registry, National Patient Registry, Prescribed Drug Registry, and Cause of Death Registry
Study size	We expect to observe about 450,000 cases of cancer and an estimated number of 15,000 of a first VTE.
Data analysis	Baseline characteristics will be analyzed using descriptive statistics The anticoagulation treatment initiated after index VTE will be summarized. This covers anticoagulation prescribed for the treatment of the in index VTE as well as those prescribed for the prophylaxis of recurrent VTE.

	The cumulative incidence and incidence rate incl. corresponding 95% confidence intervals will be computed for each of the outcomes recurrent VTE, major bleeding, and all-cause death. They will be summarized for 3, 6, 12, and 24 months after end of treatment of index VTE. The comparisons of the outcomes recurrent VTE, major bleeding, and all-cause death between treatment groups (rivaroxaban vs. LMWH, and NOAC vs. LMWH) will apply Cox proportional hazards regression with the aid of propensity score overlap weights. An intention-to-treat as well as a censored follow-up approach will be applied As a sensitivity analysis, death will be considered as a competing risk for the outcomes recurrent VTE and major bleeding. Appropriate statistical methods will be applied.
Milestones	Study start: September 2021 Completion of analysis: February 2022 Final report of study results: August 2022

5. Amendments.

None

6. Milestones

This study will be conducted between September 2021 and July 2022

Table 1: Milestones

Milestone	Planned date
Study start	September 2021
Completion of the analysis	February 2022
Final report of study results	August 2022

7. Rationale and background

Cancer is the second leading cause of death globally, accounting for about 9.6 million deaths in 2018 according to WHO (1). Lung, prostate and colorectal are among the most common types of cancer in men; and breast, colorectal and lung are among the most common cancers is women. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a serious complication and a leading cause of death in patients with cancer (29). Whether or not the long-term mortality is increased in case of survival the initial VTE is less clear (4). Risk of VTE is 4- to7-fold higher in cancer patients compared to the general population (28). For example, even though breast cancer is associated with a relatively low incidence of VTE compared to other cancer types (27), these women have 3 to 4 times increased risk of VTE (5,6) with an incidence rate being estimated to be 8.9 cases per 1000 person-years at risk. VTE is the second cause of death in women with breast cancer (2,3). A similar pattern is observed in prostate cancer in men with two- to three-fold increased risk of VTE as compared to the general population with an incidence of 4.9 to 12.2 cases per 1000 person-years 0-5 years after cancer diagnosis and depending on if the cancer was local or distant (32). Corresponding estimate for all cancer sites ranges between 2 to 12 cases per 100 person-years (7). The risk of recurrent events is also increased in cancer patients as well as the risk of major bleeding when treated with antithrombotic and cancer specific treatments.

The pathogenesis of VTE in cancer include a process induced by malignant cells, patient factors, and cancer- as well as therapy-related factors, the exact mechanisms for why the risk of VTE is increased in cancer patients is however not completely understood (3).

Cancer is a complex group of several diseases and treatment choices are many depending on the mix of cells stage of each individual cancer and patient preference in therapeutic choices. The occurrence of VTE in cancer complicates several anti-cancer treatments, for example chemotherapy because of increased risk of bleeding via a potential drug-drug interaction effect (9). For thromboprophylaxis, an individual assessment to identify cancer patients at high risk of VTE who may benefit the most is

recommended (10). Individual considerations depending on the type of tumor and individual patient risk profile must be considered when treating individuals with cancer.

The recommended treatments of VTE in cancer patients have changed recently. Low molecular weight heparin (LMWH) use to be the standard of care for VTE for short-term treatment and Vitamin K Antagonists (VKA) for long-term treatment. However, VKA introduces serious potential problems for cancer patients including risks of drug interactions, malnutrition, vomiting, kidney and liver dysfunction and chemotherapy-induced thrombocytopenia, consequently potentially resulting in suboptimal anticoagulation treatment and may even be harmful for the patient (11). In addition, RCTs found that warfarin was associated with an increase in the composite of major bleeding or recurrent VTE, as well as an increase in mortality as compared to LMWH in a 3-months treatment trial; and an increase in recurrent VTE and no statistically significant difference in major bleeding in a trial with 6-months treatment period. Although meta-analyses confirmed the role of LMWH in both the initial anticoagulation period and in the long-term, in reality the patient adherence was low in long-term treatment studies (11).

In more recent studies, rivaroxaban, edoxaban and apixaban have been associated with decreased recurrence of VTE, but with increased occurrence of major bleeding as compared to LMWH in randomized trials for 6-month and up to 12-month treatment periods in cancer patients (12-14, 30, 31). Patients with gastrointestinal cancers have been reported to be at increased risk of major bleeding (13,14). The results of these trials were pivotal for the amendment of international guidelines for treatment of cancer associated thrombosis. Rivaroxaban and edoxaban are currently the only two DOACs recommended as an alternative to LMWH in cancer patients with an acute diagnosis of VTE and a low risk of gastrointestinal or urogenital bleeding considering also possible interactions with current cancer therapy. A shared decision-making with patients is recommended, considering the potential lower risk of recurrences associated with NOACs but higher bleeding risk as compared to LMWH, according to the guideline (15). Additionally, patient convenience and preference attributes are likely to play important roles in patient treatment adherence and therapeutic effectiveness.

The duration of anticoagulation treatment in cancer patients remain an open question. Most RCTs have evaluated a maximum duration of 6 months after an acute thrombotic event. A minimum of 6 months treatment period is recommended and even longer treatment duration when risk factors of VTE recurrence are present (16). Preventing VTE recurrence must be balanced versus increased risk of major bleeding during anticoagulation therapy. A recent meta-analysis of all observational studies found that treatment duration was longer for NOACs than for LMWH which may support the idea that administration of NOACs may result in better patient adherence in particular for extended treatment duration (17).

Previous studies on all cancer have observed estimates of recurrent VTE ranging from 1% to 8.9% for studies with 3 months follow-up time and 4.0% to 13.2% for studies with 6-month follow-up time, according to the authors (18). A recent meta-analysis of six observational studies recurrent VTE in cancer patients (all sites) treated with rivaroxaban found an average cumulative incidence for 6 months (most studies) to be 4.2% (95% confidence interval 4.1%-26.2%) (19).

One strength with the currently planned study is the population-based design covering almost all cases of cancer in Sweden during a specified time period, allowing estimation of an overall risk of recurrent VTE in patients with cancer suffering from VTE, as well as allowing restricted analysis to certain common cancer sites, such as breast cancer in women and prostate cancer in men. This study

also constitutes the basis for examinations of the risk of recurrent VTE in other common cancer sites if sufficient sample size.

The present study will examine the incidence of VTE recurrence and treatment practices in patients diagnosed with cancer and VTE based on data from available registries in Sweden through record-linkage by the unique person identification number.

8. Research questions and objectives

8.1 Primary objective

The main objectives are:

1. To estimate the risk of the independent outcomes recurrent VTE, major bleeding and all-cause death in individuals with cancer not associated with a high risk of bleeding in Sweden (Annex 1, Table 3)
2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment
3. To estimate the risk of a recurrent VTE, major bleeding and all-cause death by type of anticoagulation treatment (LMWH, VKA or NOAC) as three independent outcomes
4. To compare incidence rates of the independent outcomes recurrent VTE, major bleeding and all-cause death in patients treated with rivaroxaban versus LMWH; and NOACs versus LMWH

9. Research methods

9.1 Study design

This study will be designed as a retrospective cohort study based on available data sources in Sweden. All individuals with a diagnosis of cancer and a diagnosis of a subsequent VTE will be identified and followed until date of recurrent VTE event, bleeding or death, or end of follow-up.

The first VTE will be the index event. The date of index VTE will determine the index date. It is the start of the follow-up time. The 15-year lookback prior to the index date will be referred to as the baseline period.

9.2 Setting

All residents in Sweden diagnosed with cancer at any time during the time period from 2013 through 2019 will be identified through the national Cancer Register and linked to other national health registers (National Patient Register, Prescribed Drug Register, Population Register, and Death Register).

9.2.1 Study population

Inclusion criteria

- a resident in Sweden of 18+ years of age

- a Swedish Person Identification Number
- a diagnosis of cancer ((ICD10 = C00-C97) in the Swedish Cancer registry during 2013-2019 and a diagnosis of VTE subsequent to the cancer diagnosis.

Exclusion criteria

- a diagnosis of atrial fibrillation, total hip or knee replacement or acute coronary syndrome (for evaluation of treatment patterns) before the date of VTE diagnosis
- a dispensed prescription for any OAC before the date of VTE diagnosis
- a cancer diagnosis associated with high bleeding risk (see listed diagnoses to be included)

9.2.2 Study time frame

The study observation period will be from January 1, 2013 to December 31, 2020, the time period when NOACs were introduced to treat or relapse prevention of VTE in cancer patients.

9.2.3 Follow-up and ascertainment case

All individuals with a diagnosis of cancer and VTE subsequent to cancer diagnosis will be studied from the date of VTE diagnosis until the date of recurrent VTE (DVT or PE), bleeding, death, emigration or end of follow-up on December 31, 2020, whichever comes first. Individuals with VTE anytime prior to cancer in the entire baseline period will be excluded from the cohort.

9.2.4 Representativeness

The study population included in this study is nationally representative for all residents in Sweden.

9.3 Variables

9.3.1 Exposure definition

A filled prescription of any anticoagulant (low molecular weight heparin, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, or vitamin K antagonist) from a Swedish pharmacy will be the way to define exposure. We will classify the type of anticoagulant(s) dispensed during the four weeks after the index VTE date. Duration of an individual prescription will be based on all dispensed prescriptions any time after index VTE using information on pack size and the numbers of packs dispensed. An episode of use will be defined by summing the lengths of individual consecutive prescriptions including a defined grace period. We will focus on the first continuous episode of anticoagulant use in this study. Exposure duration will be classified into ≤3 months, >3 to 6 months, >6 to 9 months and >9 months irrespective of anticoagulant type.

9.3.2 Outcomes definition

VTE is defined as a diagnosis of DVT (ICD10= I80.1-80.3, I80.8, I80.9) or PE (ICD10= I26, O88.2) recorded as main diagnosis as reason for hospitalization or an open care visit to hospital, based on the Patient register.

Major bleeding is defined as a diagnosis of intracranial, gastrointestinal, urogenital or other bleeding (See Annex 1, Table 2) recorded as a main diagnosis as reason for hospitalization based on the Patient register.

Death will also be recorded from the Death register.

9.3.3 Case validation

Cases of VTE and major bleedings defined from the Patient registry and deaths from the Cause of Death registry will not be individually validated in this study. Several validation studies of the Swedish registries have been performed previously (20-23). Death is a hard outcome with good accuracy, several systems are interlinked to ascertain accuracy. Major bleeding defined as being hospitalized with main diagnosis has been evaluated in a validation study with convincing accuracy (23). The accuracy in VTE diagnosis is likely to vary depending on if the diagnosis is DVT or PE, the latter is more accurate (22). It is also likely to vary by geographical area in Sweden driven by the presence by interested physicians. The results from a small study in northern Sweden indicated that the predicted value was relatively low, especially for DVT (22).

9.3.4 Covariate definition

The study cohort of patients with cancer and who experienced an index VTE will be described at baseline. The variables displayed will be age (at index VTE), baseline comorbidities defined as a diagnosis from Patient register (look-back of 15 years up until date of cancer diagnosis) as well as concomitant medications defined by filled prescriptions from the Drug register (look-back to 2007). Comorbidities of interest are cancer, cardiovascular disease (myocardial infarction, coronary artery disease, peripheral artery disease, diabetes mellitus, hyperlipidaemia, and major bleeding). The medications of interest are antiplatelet drugs, anticoagulants, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, and antipsychotic drugs.

9.4 Data sources

This is a record-linkage study containing information from national Swedish registries covering 10 million inhabitants, the entire population in Sweden. These registries are owned and governed by the National Board of Health and Welfare. For all individuals with cancer information will be linked from the sources described below.

Reporting to the Cancer registry is mandatory in Sweden and captures all incidence primary tumors diagnosed in Sweden since 1958. The Patient registry contains data on all hospitalizations as well as open care visits at hospitals and this register has a national coverage since 1987. The Dispensed Drug register includes information on all prescribed drugs dispensed from pharmacies. The start of this register was July 1, 2005. The Cause-of-death registry holds information of causes of death including underlying as well as contributory causes of death.

An ethical application must be submitted to the national ethical committee. Similarly, a scientific application must be submitted to the national board of health and welfare asking for permission to obtain the necessary record linkages and release of data from named sources. All analyses will be conducted on pseudo-anonymized individual data.

9.5 Study size

All persons with cancer not associated with a high risk of bleeding (per section 6.1 of the Xarelto® SmPC and international treatment guidelines) in Sweden (Annex 1, Table 3) and a diagnosis of VTE subsequent of the cancer during 2013-2019 will constitute the study cohort.

A feasibility assessment showed that approximately 450,000 patients with cancer not associated with a high risk of bleeding will be in the database. A recent evaluation of Danish medical registries showed that in the period 2011 to 2017 3% of the cancer patients developed a VTE within the first 12 months after the cancer diagnosis (33). Under this assumption, about 13,000 to 15,000 cancer patients with first VTE may be found in the study population.

The cumulative incidence (incidence proportion) of cancer patients treated with rivaroxaban which experienced recurrent VTE varies depending on type of cancer and time point of assessment after cancer diagnosis. Average cumulative incidence of 6.1% and 4.2% were seen (18, 19). Major bleedings were observed in about 2% of the patients. The average cumulative incidences of all-cause death were 17.1% and 16.1%. Table 2 shows scenarios of 95% exact confidence intervals and the resulting width for various incidences, assuming a sample of 15,000 patients. (Objective #1)

Table 2: Cumulative incidence (%) and two-sided 95% Clopper-Pearson confidence intervals for 15,000 patients

Cumulative incidence (%)	95% CI Lower Limit (%)	95% CI Upper Limit (%)	Actual width (%)
2	1.78	2.24	0.46
4	3.69	4.33	0.63
6	5.64	6.39	0.77
8	7.57	8.45	0.88
10	9.52	10.49	0.97
12	11.48	12.53	1.05
14	13.45	14.57	1.12
16	15.42	16.60	1.18
18	17.39	18.62	1.23
20	19.36	20.65	1.29

In SELECT-D trial (14), rivaroxaban reduced the risk (hazard ratio) of recurrent VTE by 57% (HR=0.43, 95% CI = 0.19-0.99) compared to dalteparin. The cumulative incidence at 6 months after cancer diagnosis was 4%.in the rivaroxaban arm. Based on this, and assuming a type-1-error of 5% and a power of 80%, a hazard ratio ≤ 0.86 can be detected given the expected sample size of 15,000 patients. The computed scenarios took balanced and imbalanced distribution of rivaroxaban and LMHW, and various cumulative incidences in the LMWH group into account. (Objective #4)

9.6 Data management

The data files released from the national board of health and welfare and all documentation including study protocol, ethics committee approval, national board of health and welfare approval, computer programs and all related other documentation will be kept at the Center for Pharmacoepidemiology accessed by staff involved in the study. All material will be archived for at least 10 years.

9.7 Data analysis

9.7.1 Missing data

It is assumed that general demographic information like sex and age is complete for all patients. If information on a particular confounding variable is provided, patients will be coded as not having the factor if there is no evidence for its presence (i.e., values for confounder variables will be coded as '0' rather than 'missing' if data on that confounder is not observed). Missing data will not be imputed but might be allocated to a missing category. Specifically, no imputation will be performed for potentially missing outcomes/endpoint data.

9.7.2 Descriptive analyses

Baseline characteristics will be reported using descriptive statistics. This covers demographics, comorbidities, concomitant medications as well as details of the primary cancer including time between cancer diagnosis and index event.

9.7.3 Analysis of exposure

The anticoagulation treatment (section 9.3.1) initiated after index VTE will be summarized. The number and proportion of patients will be presented as well as the duration of initial therapy. Subsequent changes of the anticoagulation treatment will be presented similarly (i.e. 2nd treatment, 3rd treatment, etc.). Sankey plots will visualize the paths of treatment. The analysis will end at the date of recurrent VTE, death, emigration, or end of follow-up, whichever comes first.

9.7.4 Analysis of outcomes

The cumulative incidence function will be computed and plotted for each of the outcomes

- recurrent VTE
- major bleeding
- all-cause death.

It will be summarized for 3, 6, 12, and 24 months after index VTE together with corresponding 95% confidence intervals.

The incidence rate and 95% Poisson confidence intervals will be calculated for the same time points. It is the number of cases of a specific outcome divided by the person-years of observation.

In general, the follow-up time will end at the date of a certain outcome of interest, death, emigration, or end of follow-up, whichever comes first.

The cumulative incidences as well as the incidence rates will be presented overall and by subgroups (age, gender and certain comorbidities know to be risk factors of VTE) and types of initial anticoagulation treatment.

For latter, two types of analyses will be applied: Similar to an intention-to-treat analysis, patients will be followed regardless of whether they are still treated with the anticoagulation they start on. Secondly, an analysis censoring follow-up time at the end-of-prescription or switch to another anticoagulation therapy.

9.7.5 Time to event analysis

The comparisons of the independent outcomes recurrent VTE, major bleeding, and all-cause death between treatment groups will apply propensity score (PS) overlap weights (35). Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group. Specifically, treated patients are weighted by the probability of not receiving treatment (1 - PS) and untreated patients are weighted by the probability of receiving the treatment (PS). The propensity score model will include all variables presented in section 9.7.1. Propensity score models will be set up independently of each other for both planned comparisons, rivaroxaban vs. LMWH, and NOAC bs LMWH.

Subsequently, Cox proportional hazards regression models will be applied to compare time to event for the outcomes of interest between treatment groups. Overlap weight will be incorporated in the regression models, robust variance estimate will be applied. As propensity score-based methods are assumed to balance key characteristics of the treatment cohorts. Thus, the only independent variable that will be included into Cox regression models will be anticoagulant received. As before, an intention-to-treat as well as a censored follow-up approach will be applied.

A patient is considered as censored if the outcome of interest has not been observed by time of death, emigration, or end of follow-up, whichever comes first. To note, a patient will not be censored at time of death when outcome “all-cause mortality” is evaluated.

As a further sensitivity analysis, death will be considered as a competing risk for the outcomes recurrent VTE and major bleeding. Cumulative incidences and Fine-Gray regressions (34) will be computed with the help of the overlap weights.

9.8 Quality control

All study relevant information, such as documents, data sets, computer scripts, will be archived at the Center for PharmacoEpidemiology, Karolinska Institutet according to local requirements, considering possible audits and inspections from the sponsor or local authorities. Study relevant information will also be archived at Bayer (see Data Management section).

9.9 Limitations of the research methods

All persons diagnosed with incident cancer in the entire Sweden during the study period will be included in the study, thus there is no selection of patients.

Through the person identification number, almost no patients will be lost during the follow-up period. All prescribed drugs in out-patient settings are dispensed through pharmacies in Sweden with mandatory reporting to the Drug registry. Drugs provided during hospitalizations will not be captured in this study. There will be some misclassification on information on the duration of use of a specific drug since duration of use is based on an estimation from available information on the prescription. Therefore, some sensitivity analysis will be done applying various assumptions (see analysis section).

The Patient register records diagnoses at hospitals (in-patients and open care visits). Sudden or acute diseases with a high probability of a health care contact (MI, stroke, major bleedings) are generally well recorded. Diseases will less clear onset and not in acute state (hypertension, diabetes mellitus) are sometimes not recorded. Such conditions are most likely under recorded and is probably correct

if they are recorded. Also, no visits to primary care units will be captured. We anticipate some misclassification of VTE, most likely an under reporting of VTE events.

For the comparative element of the study, we are aware that all potential confounders such as systemic treatment for cancer, severity of cancer, lifestyle factors, family history of VTE, and reasons for prescriptions are not captured. Thus, one should bear in mind that residual confounding somewhat limits interpretability of the results. For a confounder to distort the results two associations must exist, the variable must be a risk factor of VTE, bleeding or death, and be unequally present among users of NOACs and LMWH patients. Although general principles are known for how unadjusted confounders will impact results given the two associations are known, most real-life situations these associations remain unknown a priori. Therefore, the magnitude and direction of unadjusted confounders may differ on a case by case basis and is difficult to predict. Another bias more likely to influence results in a systematic way are channeling. As an example, if hypothetically physicians preferentially prescribe LMWH rather than NOACs to patients with a high bleeding risk, the resulting relative risk estimate comparing NOACs vs LMWH could potentially be markedly underestimated, i.e. biased in direction toward zero.

9.10 Other aspects

NA

10. Protection of human subjects

The national registries in Sweden are owned by the National Board of Health and Welfare can be used for research purposes without informed consent from individual patients. The procedure is to apply to the Ethics Committee and another application to the National Board of Health and Welfare at study start. The data files released are pseudo anonymized, meaning that the person identification number, names and residential addresses have been removed. Gender, year of birth and county of residence including all their morbidities and medications are the identification variables left to be released. No other data will be collected than what is already recorded in the existing registries. No individual data will be displayed, results will be presented in an aggregated form in tables or graphs.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (24).

12. Plans for disseminating and communicating study results

This study will be registered at www.clinicaltrials.cov as well as in the EU PAS registry at the European Medicines Agency. Achieved results from this study will be disclosed in a publicly available database and are intended to be submitted for publication in a peer-reviewed scientific journal. We will follow guidelines and recommendations for reporting of observational studies and good publication practice (25,26). Publishing results from this study is not allowed without prior review by the MAH.

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Annex 1: List of stand-alone documents

Include a table of ATC codes for the drugs of interest
Include a table of ICD10 codes for outcomes of interest and comorbidities
Include a table of cancer sites to be included and excluded, respectively from the analysis

Table 1. ATC codes for anticoagulant drugs

Class	Drug name	ATC code
1. Parenteral anticoagulants	Heparin	B01AB01
	Enoxaparin	B01AB05
	Dalteparin	B01AB04
	Nadroparin	B01AB06
	Tinzaparin	B01AB10
	Reviparin	B01AB08
	Parnaparin	B01AB07
	Bemiparin	B01AB12
	Fondaparinux	B01AX05
	Danaparoid	B01AB09
	Bivalirudin	B01AE06
	Argatroban	B01AE03
2. Vitamin K antagonists	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
	Dicoumarol	B01AA01
	Tioclomarol	B01AA11
	Ethyl biscoumacetate	B01AA08
	Fluindione	B01AA12
	Phenindione	B01AA02
	Chlorindione	B01AA09
	Diphenadione	B01AA10
3. Non-vitamin K oral anticoagulants (NOACs)	Rivaroxaban (Xarelto)	B01AF01
	Dabigatran (Pradaxa)	B01AE07
	Apixaban (Eliquis)	B01AF02
	Edoxaban (Savaysa/Lixiana)	B01AF03

Tabel 2. ICD-10 codes used to define disease conditions

Condition	**ICD-10 or Swedish procedure code beginning with**
Intracranial bleeding	I60-62, S064, S065, S066
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, procedure code DR029
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Ischaemic stroke	I63
Heart failure	I50,I110,I130,I132,I255,K761,I42-43
Unspecified stroke	I64
TIA	G45
Peripheral systemic emboli	I74
Thromboembolism (composite)	I63-64, G45, I74
Pulmonary embolism	I26
Deep venous thrombosis	I801-802
Venous thromboembolism (composite)	I26, I801-802
Myocardial infarction	I21,I252
Ischaemic heart disease	I20-25

Table 3: Cancer sites to be included and excluded, respectively from the analysis

Cancer Types	Include	Exclude
Ear	Y	
Nose	Y	
Oral	Y	
Throat	Y	
Oesophagus		Y
Gastric		Y
Small bowel	Y	
Kidney	Y	
Liver	Y	
Other Hepatobiliary	Y	
Pancreatic	Y	
Colorectal (irrespective of resection)		
Colorectal RESECTED	Y	
Colorectal UNRESECTED		Y (if it can be identified, otherwise, it's ok to keep it)
Prostate	Y	
Bladder		Y
CNS		Y
Haematological malignancies (myeloma, lymphoma and MPNs)		Y (except for myeloma)
Breast	Y	
Lung	Y	
Ovarian	Y	

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

Study title: Observational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)

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]	☒	☐	☐	9
1.1.2 End of data collection[2]	☒	☐	☐	9
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Title page
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:	☒	☐	☐	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)	☒	☐	☐	9.2.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

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

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

Section 3: Study design		**Yes**	**No**	**N/A**	**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
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2
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))	☒	☐	☐	9.7.2
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)	☒	☐	☐	9.3.2

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.2 and 9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.2.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
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?	☒	☐	☐	9.3.2
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)	☐	☐	☒	
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)	☒	☐	☐	9.7
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.1
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	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)	☐	☒	☐	

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)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☐	☒	☐	
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?	☐	☒	☐	9.9
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	9.9
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

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?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

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: PPD

Date: 30/Aug/2021 PPD

Signature: _____ PPD

Annex 3: Signature pages

Signature Page – Study Conduct Responsible

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/23/2021, PPD

Signature Page – Study Statistician

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/23/2021, PPD

Signature Page – Study Epidemiologist

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/28/2021, PPD

Signature Page – Study Safety Lead

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/27/2021 PPD

Signature Page – Study Medical Expert

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/23/2021, PPD

Signature Page – Study Statistician – Karolinska Institutet

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

Date, Signature: 9/23/2021, PPD _____

Signature Page – Principal Investigator

Title	**O**bservational **S**tudies in **C**ancer **A**ssociated Thrombosis for **R**ivaroxaban in **S**w**E**den (**OSCAR-SE**)
Protocol version and date	v 1.0, 30 August 2021
IMPACT study number	
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Registration number in the EU PAS register>, *or* <Study not yet registered>
Medicinal product	Xarelto (rivaroxaban)
Comparator / Reference therapy	VKAs
Study Initiator and Funder	Bayer AG, 51368 Leverkusen

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

Print Name: PPD

PPD

Sweden

Date, Signature: 9/27/2021 , PPD

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

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: PPD

Date: 30/Aug/2021

Signature: _____