Observational Study/Post Authorization Safety Study (PASS) Information

Acronym/Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	v 1.0, 02 FEB2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	Rivaroxaban Warfarin
Medicinal product	Xarelto (rivaroxaban) Warfarin
Product reference	<<EU registration number to go here when registered>>
Procedure number	<<EMA number to go here>>
Comparator	Vitamin K antagonists
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	The primary objective of this study is to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care. The secondary objective in this study is to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression such as patients

	with/without diabetes and patients with/without heart failure.
Country of study	United Kingdom
Authors	[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

AE	Adverse event
AF	Atrial fibrillation
AKI	Acute kidney injury
ARN	Anticoagulant-related nephropathy
CI	Confidence interval
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
ESRD	End-stage renal disease
EU	European Union
GPP	Good Publication Practice
MAH	Marketing Authorization Holder
NA	Not Applicable
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
OS	Observational Study
PASS	Post-Authorization Safety Study
QPPV	Qualified Person Responsible For Pharmacovigilance
SCr	Serum creatinine
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VKA	vitamin K antagonist
UK	United Kingdom
US	United States

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible
[redacted]

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
[redacted]

Role: MAH contact person (Regulatory Affairs)
[redacted]

Role: OS Safety Lead
[redacted]

Role: OS Medical Expert
[redacted]

Role: OS Statistician- External, CEIFE
[redacted]

Role: OS RWE Outcomes Data Generation
[redacted]

Role: OS Epidemiologist
[redacted]

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

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

4. Abstract

Acronym/Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	v 1.0, 02 FEB 2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV
Authors	[redacted]
Rationale and background	Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common conditions that become more prevalent with advancing age, and they frequently co-exist. Patients with AF are at increased risk of thromboembolism and require long-term anticoagulation. For those with concomitant CKD, the risk of thromboembolism is particularly higher, and patients with advanced stage CKD present a clinical dilemma as they are also at high risk of bleeding. For patients with non-valvular AF (NVAF), guidelines recommend non-vitamin K antagonist oral anticoagulants (NOACs) as the preferred oral anticoagulant (OAC), yet vitamin-K antagonists (VKAs) are still extensively used in clinical practice, including among patients with co-morbid CKD. Anticoagulant-related nephropathy is a complication associated with the use of anticoagulants that has been reported in recent years, especially in patients on warfarin. Four large population-based observational cohort studies (three Bayer-funded, and one conducted externally) have been consistent in showing that among patients with NVAF, rivaroxaban is associated with lower risks of adverse renal outcomes when compared with VKAs. Further evidence demonstrating a benefit of rivaroxaban over VKAs on adverse renal outcomes in patients with NVAF in other settings would help prescribers make more informed benefit–risk decisions regarding choice of anticoagulant therapy for their patients.
Research question and objectives	The primary objective of this study is to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the

	presence of CKD and its severity at the start of OAC therapy in UK primary care. The secondary objective in this study is to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression such as patients with/without diabetes and patients with/without heart failure.
Study design	Retrospective cohort study with nested case–control analysis
Population	Patients aged ≥18 years with NVAF and no record of ESRD, with a first prescription for rivaroxaban or a VKA and no previous OAC use between 01 January 2014 and 30 September 2019
Variables	**Outcomes**: %change in serum creatinine, doubling of serum creatinine, rate of eGFR change, %eGFR change, incidence of ESRD and AKI. **Exposure of interest**: exposure to rivaroxaban or a VKA (at start of follow-up in the cohort analysis, and in relation to time before the index date (the date of an adverse renal outcome among cases) in the case–control analysis). **Co-variates:** demographics, comorbidities (including renal function at baseline), CHA_2DS_2-VASc score for stroke risk, HAS-BLED score for major bleeding risk, frailty, lifestyle factors, co-medications, healthcare use
Data sources	The IQVIA Medical Research Data-UK (IMRD-UK) database of primary care electronic health records (EHRs) in the UK
Study size	We expect to identify approximately 25,000 new users of either rivaroxaban or a VKA who were OAC naïve and anticipate that approximately a quarter of these patients will experience at least one adverse renal outcome during follow-up.
Data analysis	**Cohort analyses:** The median number of serum creatinine measurements among patients starting on rivaroxaban and those starting on a VKA will be compared. The difference in the eGFR slopes after initiation between patients starting on rivaroxaban and those starting on a VKA will be assessed using a linear mixed regression model. Only individuals with at least two recorded eGFR measurements after treatment initiation will be included in this analysis. Incidence rates of each adverse renal outcome will be calculated with 95% confidence intervals (CIs) assuming a Poisson distribution. Incidence rates will also be stratified by age-group, sex, CKD stage based on calculated eGFR (if any) at baseline, the starting OAC, and for rivaroxaban, the dose of the starting prescription (20 mg/day or 15 mg/day). A survival analysis will be

	performed to compare the time to the occurrence of the study outcomes according to the starting OAC. This will be undertaken using Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% CIs with adjustment for potential confounders. **Case–control analyses:** Unconditional logistic regression will be used to calculate odds ratios (ORs) with 95% CIs to estimate the associations between current exposure to rivaroxaban/VKA and the study outcomes adjusted for confounders
Milestones	Study start: March 2020 Completion of analysis: November 2020 Final report of study results: March 2021

5. Amendments.

None

6. Milestones

This study will be conducted between February 2020 and December 2020

Table 1: Milestones

Milestone	Planned date
Study start	March 2020
Completion of the analysis	November 2020
Final report of study results	March 2021

7. Rationale and background

Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common conditions that become more prevalent with advancing age,(1, 2) and they frequently co-exist.(3) Among 33,024 patients in the GARFIELD AF registry, 27.9% had at least some degree of CKD,(4) while among 9019 patients in the ORBIT AF registry, 38.7% had at least stage 3 CKD.(5) The majority of patients with AF are at high risk of stroke and systemic embolism and therefore require preventative therapy with long-term anticoagulation. Patients with both AF and CKD have a further increased risk of thromboembolic events, and they are also at higher risk of bleeding.(6-8) The risk of both thromboembolism and bleeding increases with progressively declining renal function(9) – a factor also highly correlated with age – thus bleeding risk is particularly high among patients with end-stage renal disease (ESRD; stage 5 CKD) on dialysis.(10-12)

For patients with non-valvular AF (NVAF), international guidelines recommend non-vitamin K antagonist oral anticoagulants (NOACs) as the preferred OAC,(1, 13, 14) yet vitamin-K antagonists (VKAs) are still extensively used in clinical practice, including among patients with concomitant CKD. Data from the ORBIT AF registry show that nearly three-quarters (73.9%) of patients with stage III CKD were treated with warfarin (the most commonly used VKA).(5)

Anticoagulant-related nephropathy (ARN) is a complication associated with the use of anticoagulants that has been reported in recent years, especially in patients on warfarin. It is believed that the pathophysiological mechanisms associated with ARN are multifactorial (15). Anticoagulant-related nephropathy accelerates the progression of CKD and is a significant risk factor for mortality within the first 2 months of diagnosis.(16) In addition, a recently published and robustly-designed large-scale observational study(17) demonstrated that among patients with NVAF, warfarin use is associated with higher risks of adverse renal outcomes – both long-term (declining renal function) and acute (acute kidney injury) – than rivaroxaban. A potential pathophysiological explanation to support an observed difference in risks of adverse renal outcomes between these two OACs relates

to their differential effect on vitamin K inhibition. Warfarin has been shown to decrease carboxylation of the matrix G1a protein, which is an important vitamin-K-dependent inhibitor of medial and intimal vascular calcification.(18, 19) As vitamin K deficiency is common in patients with CKD, these patients are particular susceptible to vascular calcification.(20)

Since publication of the study by Yao *et al*, three large population-based observational cohort studies (two in the United States, and one in Germany) funded by Bayer have been consistent in showing that among patients with NVAF, rivaroxaban is associated with lower risks of adverse renal outcomes when compared with VKAs.(21-23). Further observational evidence demonstrating a differential effect between rivaroxaban and VKAs on adverse renal outcomes in patients with NVAF in other settings would help prescribers make more informed benefit–risk decisions regarding choice of anticoagulant therapy for their patients. This is an increasingly important issue because the ageing population means that increasing numbers of people will be living with both AF and CKD in need of anticoagulation. Renal function is expected to be monitored regularly in patients taking anticoagulant therapy and managing these patients in a way that helps to preserve their renal function is essential for the effective prevention of stroke and bleeding.

This study aimed to evaluate the incidence of acute and chronic adverse renal outcomes among patients with NVAF in UK primary care.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care.

8.2 Secondary objective

The secondary objective in this study is to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression:

- patients with/without diabetes
- patients with/without heart failure

9. Research methods

9.1 Study design

This study will have retrospective cohort study design with nested case–control analysis using secondary data collection. A new user design will be applied(24) – patients with NVAF newly initiated on OAC therapy with either rivaroxaban or a VKA will be identified and followed up to identify adverse renal outcomes.

9.2 Setting

This study will be set in UK primary care. In the UK, nearly all residents are registered in a primary care practice that uses a system of electronic health records (EHRs). This study will use the IQVIA Medical Research Data-UK (IMRD-UK; formerly known as The Health Improvement Network [THIN]), which is a database of primary care EHRs that is used for research purposes (see **Section 9.4**).

9.2.1 Study population

Inclusion criteria

- aged ≥18 years in the IMRD-UK database
- a first prescription for either rivaroxaban or a VKA (see **Table S1** and **Table S2** for codes) between 01 January 2014 and 31 March 2019. The date of the first rivaroxaban/VKA prescription will be set as the start date (start of follow-up for that patient). The follow-up will be extended until 30 September 2019 to ensure that each patient has at least 6 months of potential follow-up.
- A diagnosis of AF (see **Table S3** for codes) recorded any time before start date or within 2 weeks after start date.
- registered with their general practice at least 1 year before the start date and have a recorded prescription of any drug at least 1 year before the start date.
- registered with a general practice with data considered to be up-to-standard quality.

Exclusion criteria

- a prescription for any OAC (see **Table S4** for codes) before the start date – all first-time rivaroxaban/VKA users will therefore be OAC naïve
- a record of heart valve replacement or mitral stenosis (see **Table S5** for codes) any time before the start date or in the 2 weeks after the start date.
- a record of deep vein thrombosis, pulmonary embolism, or hip/knee surgery in the 3 months before the start date (because these are all alternative reasons for NOAC initiation; see **Table S6** for codes).
- a record of ESRD (including renal transplant patients) on/before the start date

9.2.2 Study time frame

The study period will be from 01 January 2014 to 30 September 2019.

9.2.3 Follow-up and case ascertainment

Patients will be followed up from their start date until the occurrence of an adverse renal outcome. Independent follow-ups will be undertaken for each renal decline outcome, and for the outcome of AKI (see **Section 9.3.2**) starting from the start date. Patients will be censored at:

- recorded diagnosis of the adverse renal outcome: (Read codes; see **Table S7** and **Table S8**)
- death
- last date of data collection from the general practice
- end of the study period (30 September 2019).

Section 9.7.1 describes how patients who switch OAC during follow-up will be handled.

Index date: The date of the adverse renal outcome will be set as the index date (see **Section 9.3.2** for details on outcome ascertainment).

9.2.4 Representativeness

Individuals in the IMRD-UK database are representative of the UK as a whole in terms of age, sex and geographic distribution (25, 26), and the database is validated for pharmacoepidemiology research.(27)

9.3 Variables

9.3.1 Exposure definition

Cohort analysis: the exposure of interest will be the first OAC prescribed to the patient – either rivaroxaban or a VKA (the starting OAC).

Nested case–control analysis, exposure to 15 or 20 mg rivaroxaban or a VKA will be categorised according to recency of use as follows:

Current use: when the end of a prescription lasted to 0–30 days before index date (the date of an adverse renal outcome among cases) or over the index date

Recent use: when the end of a prescription lasted to 31–90 days before index date

Past use: when the end of a prescription lasted to 91–365 days before index date

Distant past use (i.e. "no-use"): when the end of a prescription occurred more than 366 days before the index date

9.3.2 Outcomes definition

Two adverse renal outcomes will be evaluated using recorded laboratory test values, Read codes (see **Table S7**) and through manual review of coded entries in the patient records:

1. **<u>Renal decline</u>: several operational definitions will be applied**:
    - a 20%, 30%, 40%, or 50% increase in SCr at any point of time during follow-up (confirmed by a subsequent measurement)
    - doubling of serum creatinine (SCr) from initiation (start date) at any point of time during follow-up
    - rate of change in eGFR from initiation (start date). To be included in the eGFR slope analyses at least two post-baseline assessments were required, where the first measurement was less than 120 days after index and the last was more than 180 days after the first post-baseline (reflecting sufficient time for a potential change to occur)
    - a 20%, 30%, 40%, or 50% decline of eGFR at any point of time during follow-up (confirmed by a subsequent measurement). These eGFR-based endpoints were assessed because they have been recommended as alternative endpoints in trials of chronic kidney disease progression.
- incidence of end-stage renal disease: identified by the presence of a Read code in the patient's EHR indicating ESRD, stage 5 CKD, chronic dialysis (defined as dialysis for 30 days or more), or an eGFR value <15ml/min/1.73m2 during follow-up (confirmed at a subsequent measurement).

2. **<u>Incidence of acute kidney injury</u>:**

    We will use 2 approaches:

- based on a Read code in the patient's EHR indicating AKI (see **Table S8** for the codes) or a code indicating acute dialysis (defined as a presence of a code for dialysis and non-continuation of dialysis after 30 days after the initial dialysis code) along with a record of an outpatient visit to secondary care/ hospitalization.
- using recorded (SCr) values: based on the algorithm used by Sawhney *et al*(28) a change in SCr levels greater than 1.5 times the median of all creatinine values recorded during the previous 8–90 days (reference period), or the previous 91–365 days if no tests were conducted in the previous 8–90 days. Only patients without AKI (according to our operational definition) at baseline will be included in this outcome follow-up.

9.3.3 Case validation

To validate cases, patients experiencing a study outcome will have the coded entries in their anonymised EHRs manually reviewed.

9.3.4 Covariate definition

To establish patient characteristics at baseline (date of the inclusion into the study), the following variables will be extracted/determined from the database on/ever before the start date (for the cohort analysis)

- Demographics (at the start date): age, sex, and Townsend index score of deprivation(25)

- Lifestyle factors (using the most recently status/values recorded before the start date): smoking status, alcohol intake, body mass index (BMI, calculated using recorded height and weight measurements)
- Renal function will be ascertained by using estimated glomerular filtration rates (eGFR) expressed mL/min/1.73m^2 as using the closest valid serum creatinine value recorded in the year before the start date and applying the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation,(29) but omitting ethnicity because this is not routinely recorded in UK primary care: **eGFR = 141 × min (serum creatinine [SCr] /κ, 1)α × max(SCr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]**, where: SCr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males; α is –0.329 for females and –0.411 for males; min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr/κ or 1. Coded clinical entries indicating CKD stage, acute or chronic dialysis will also be used to determine renal function. Patients will be categorised as having no renal impairment or as having renal impairment of a certain stage (i.e. CKD stages 1–5) according to the National Kidney Foundation guidelines: normal renal function (eGFR >50 ml/min/1.73 m^2), mild-to-moderate impairment (eGFR 30–50 ml/min/1.73m^2) and severe impairment (eGFR<30 ml/min/1.73m^2). In situations where the CKD stage based on the calculated eGFR differed from the CKD stage based on Read codes, we will use the eGFR value (this is due to the fact that CKD stage coding can be used in an imprecise manner). In few cases when eGFR is directly recorded in the database, we will not use these values
- Comorbidities and prior clinical events of interest (at the start date or any time before the start date): cardiovascular disease (including myocardial infarction, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, angina, coronary artery disease, peripheral arterial disease, hypertension), diabetes mellitus, hyperlipidaemia, obesity, major bleeding events, AKI, cancer.
- CHA_2DS_2-VASc score for stroke risk: using patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/ transient ischaemic attack [TIA] ($CHADS_2$ score will also be calculated because this was assessed in the pivotal studies for the NOACs investigated in this study).
- HAS-BLED score for major bleeding risk: using the recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication use predisposing to bleeding, history of alcohol use).
- Frailty using a frailty index developed for research using primary care databases,(30) based on a wide range of symptoms, signs, diseases, disabilities, abnormal laboratory values and social circumstances, and categorising patients as fit, mildly frail, moderately frail or severely frail.
- Comedications (prescription in the year before the start date or on the start date) including SGLT2 inhibitors, ACE inhibitors, ARBs and diuretics. Polypharmacy will also be evaluated by determining the number of different medications prescribed in the month before (but not including) the start date.
- Healthcare use in the year before the index date and in the year after the index date (number of primary care practitioner [PCP] visits, outpatient visits and hospital admissions).

For the case–control analysis, these variables will be evaluated in the same time frames above but in relation to the index date rather the start date. In addition, we will extract information from the database on common reasons for AKI around the time of the index date, including infection, pneumonia, sepsis, contrast overdosing (see **Table S9** for codes).

9.4 Data sources

IMRD-UK is a structured de-identified UK database of anonymized primary care EHRs. It holds clinical and prescribing information entered by PCP as part of routine patient care, and covers approximately 6% of the UK population (including practices across England, Wales, Scotland, and Northern Ireland).(31) Medical events (e.g. symptoms, diagnosis, hospital referrals) are entered using Read codes,(32) although there is a free text field for manual data entry. Demographics, lifestyle factors and results of laboratory tests, including those for renal function (e.g. SCr values) are also recorded. Data received from secondary care via email or postal letter are entered into the patient's EHR retrospectively. Prescriptions are entered using multilex codes,(33) and are automatically recorded upon issue. Prescriptions include details on the drug quantity, dose, dosing instructions and the number of days of supply.

Broad ethical approval for the collection of data in IMRD-UK was approved by the NHS South-East multicenter research committee in 2003. Ethical approval is not required for individual studies using IMRD-UK but individual study protocols required approval by the Independent Scientific Research Committee for IMRD-UK.

9.5 Study size

All patients enrolled in IMRD-UK and meeting the inclusion criteria will be included. Based on a recent study on NVAF and OACs using the IMRD-UK database over a similar study period, we expect to identify approximately 25,000 new users of either rivaroxaban or a VKA who were OAC naive. Based on the study by Yao *et al*(17) we anticipate that approximately a quarter of these patients will experience at least one adverse renal outcome during follow-up.

9.6 Data management

Data from the THIN database will be extracted using CEIFE proprietary tools (Powerfilter, Datacreator, etc.). We will import these datasets into STATA software to prepare the final study datasets (both cohort and case-control datasets) and run all the analyses.

All research project materials: the study protocol, a copy of Scientific Review Committee approval, computer algorithms, data collections, datasets, STATA programs and the final report and publications will be kept in one folder cross-shared by the CEIFE team. Monthly back-ups will be performed and kept in a secure location. All material will be kept for a minimum of 10 years.

9.7 Data analysis

9.7.1 Descriptive analyses

The characteristics of patients in the study cohort will be described according to the starting OAC. Characteristics of cases and controls in the nested case–control analyses will be described.

9.7.2 Cohort analyses

The median number of SCr measurements among patients starting on rivaroxaban and those starting on a VKA will be defined.

The eGFR slopes after initiation between patients starting on rivaroxaban (as an average for the total sub-cohort) and those starting on a VKA (as an average for the total sub-cohort) will be assessed using a linear mixed regression model, where the treatment group (rivaroxaban or VKAs), time (linear), and the interaction between treatment group and time, will be included as fixed variables and each initiation will be included as a random factor. Covariates at baseline (including comorbidities and comedications as well as frequency of SCr testing) will be introduced in the model to obtain estimates adjusted for confounders. Only individuals with at least two SCr measurements (and hence, calculated eGFR values) after treatment initiation will be included in this analysis. Furthermore, the first eGFR measurement will be required to be recorded less than 120 days after treatment initiation, and the last eGFR measurement will be required to be recorded more than 180 days after the first post-initiation measurement (to reflect the time sufficient for a change to occur).

Incidence rates of each adverse renal outcome will be calculated using the number of incident cases during follow-up as the numerator and total person-years as the denominator, with 95% confidence intervals (CIs) assuming a Poisson distribution. Incidence rates will also be stratified by age-group, sex, CKD stage (if any) at baseline, the starting OAC, and for rivaroxaban, the dose of the starting prescription (20 mg/day or 15 mg/day).

A survival analysis will be performed to estimate the time to the occurrence of the study outcomes according to the starting OAC. This will be undertaken using Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% CIs with adjustment for potential confounders such as patient characteristics, comorbidities and CKD stage at the start date.

These analyses will be undertaken using two approaches:

- An intention-to-treat-approach where patients will be followed for their whole available follow-up irrespective of changes in the starting OAC
- A current treatment approach where follow-up will be censored at the time a patient discontinues treatment with their starting OAC or switches to a different OAC. Data from a recent study of NVAF patients in the IMRD-UK database showed that permanent discontinuing of OAC treatment is rare, yet short gaps in treatment (i.e. stopping and re-starting treatment) is common.(34)

<u>Sensitivity analyses</u>

- in the cohort analysis, patients will also be censored at the date of OAC therapy discontinuation/switch.
- excluding people from the cohort analysis with missing data on lifestyle variables
- analyses for eGFR slope will be repeated across multiple patient subgroups to examine the consistency of the findings. Prespecified subgroups will include those by baseline eGFR, estimated Frailty index, CHA2DS2-VASc score, established atherosclerotic cardiovascular disease, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and use of diuretics.

Variables to be used in these analyses are detailed in Table 1 below.

Table 1. Variables for cohort analysis

Variable name	Categories	Definition & lookback period	Comments
Identification variables			
Patient ID	N/A		
Start date	N/A	Date of first rivaroxaban/VKA prescription	
Stop date	N/A	Treatment switching/discontinuation (current treatment analysis only), first occurrence of the outcomes of interest, date of last available information, end of study period or death	Each outcome will be analyzed separately, thus different stop dates are expected for different outcomes. To this end, a separate dataset will be created for each outcome.
Cohort status	1. New user of rivaroxaban 2. New user of VKA		
Case status	1. Non-case 2. Case	Whether the patient experienced the outcome of interest during follow-up.	One variable per outcome as described in 9.3.2
Date of event	N/A	Date of the outcome of interest during follow-up	One variable per outcome as described in 9.3.2
Covariates			

Variable name	Categories	Definition & lookback period	Comments
Sex	1. Male 2. Female		
Age at start date	1. ≤ 49 2. ≥ 50–≤ 59 3. ≥ 60–≤ 69 4. ≥ 70–≤ 79 5. ≥ 80–≤ 89 6. ≥ 90		
Exposure to rivaroxaban	Current use	**End of supply method** 1. Within prescription supply or up to 30 days after end of supply	
Exposure to VKA	Current use	**End of supply method** 1. Within prescription supply or up to 30 days after end of supply	
Hospitalization	1. None 2. 1 3. ≥ 2	Number of hospitalizations in the one year prior to start date	
Visits to the GP	1. 0–4 2. 5–9 3. 10–19 4. ≥ 20	Number of visits to the GP in the one year prior to start date	
BMI	1. < 20 2. 20.0–24.9 3. 25.0–29.9 4. ≥ 30 5. Unknown	Calculated using most recent recorded height and weight measurements any time prior to start date	
Smoking	1. Non-smoker 2. Smoker 3. Ex-smoker 4. Unknown	Most recent measure any time prior to start date	
Alcohol use	1. 0–1 units/week 2. 2–9 units/week 3. 10–20 units/week 4. 21–41 units/week 5. ≥ 42 units/week	Most recent measure any time prior to start date	

Variable name	Categories	Definition & lookback period	Comments
	6. Unknown		
Polypharmacy	1. < 5 2. 5–9 3. ≥ 10	Number of individual drugs at the level of ATC code in the month prior to start date	
Socioeconomic index	Quintiles of Townsend deprivation index.		
Frailty	1. Fit 2. mildly frail 3. moderately frail 4. severely frail.	Based on data recorded before start date, estimated using a frailty index developed for research using primary care databases	
Medical history	1. Yes 2. No	Cardiovascular disease (including myocardial infarction, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, angina, coronary artery disease, peripheral arterial disease, hypertension), diabetes mellitus, hyperlipidaemia, obesity, major bleeding events, past AKI, cancer any time prior to or on the start date	
Comedication use	1. Yes 2. No	End of supply up to 30 days before or on start date of antiplatelets, parenteral anticoagulants, SGLT2 inhibitors, ACE inhibitors, ARBs and diuretics.	
CHA_2DS_2VASc	1. 0–1 2. 2 3. 3 4. 4 5. 5 6. ≥ 6	Calculated from sex, age and comorbidities recorded any time prior to start date	

Variable name	Categories	Definition & lookback period	Comments
Modified HAS-BLED	1. 0–1 2. 2 3. 3 4. ≥ 4	Calculated from sex, age and comorbidities recorded any time prior to start date.	
Glomerular filtration rate (eGFR) before start date	1. eGFR >50 ml/min/1.73 m^2 2. eGFR 30–50 ml/min/1.73m^2 3. eGFR<30 ml/min/1.73m^2 4. Unknown	Based on the closest eGFR available in the year before start date. eGFR will be estimated from SCr recordings using CKD-EPI equation or from diagnostic Read codes.	
Glomerular filtration rate (eGFR) during follow-up	N/A	eGFR during follow-up will be estimated from SCr recordings using CKD-EPI equation. Dates of these estimations will be ascertained.	This variable will be used for estimating the slope using the mixed model.

9.7.3 Case–control analyses

These will be carried out for each study outcome in order to analyse the effect of OAC exposure relative to the date of the adverse renal outcomes (index date) as well as the impact of treatment discontinuation, short-term gaps in treatment, and switching of OACs. These analyses will also enable the evaluation of associations between other patient variables (e.g. comorbidities including major bleeding, infections, and sepsis, and hospitalisations) and study outcomes to be investigated. For the case–control analyses, controls will be sampled using incidence density sampling and frequency matching to cases by year of birth, sex and date of case occurrence. Incidence-density sampling is an approach intended to produce a set of controls for epidemiological case-control studies that mimic the underlying risk-pool of person-time of the population from which the sample was drawn. Under these circumstances, odds ratios are unbiased estimators of the incidence rate ratios.

Unconditional logistic regression will be performed to calculate odds ratios (ORs) with 95% CIs adjusted for confounders. Statistical significance will be established based on confidence intervals around estimates as well as on two-sided p-values from Wald tests. All variables to be used in these analyses are detailed in Table 2 below.

Table 2. Variables for nested case control analyses

Variable name	Categories	Definition & lookback period	Comments
Identification variables			
Patient ID	N/A		
Start date	N/A	Date of first prescription for rivaroxaban/VKA	
Index date	N/A	Date of outcome occurrence in cases	Date will differ for each outcome of interest (one dataset per outcome)
Study drug at start date	1. New user of rivaroxaban 2. New user of VKA		
Case status	0. Control 1. Case	Whether the patient is a case or a matched control.	One dataset per outcome
Covariates			
Sex	1. Male 2. Female		
Age at index date	1. ≤ 49 2. ≥ 50–≤ 59 3. ≥ 60–≤ 69 4. ≥ 70–≤ 79 5. ≥ 80–≤ 89 6. ≥ 90		
Calendar Year	1. 2014–2015 2. 2016–2017 3. 2018–2019	Year of index date	
Rivaroxaban recency	1. Current use 2. Recent use 3. Past use 4. Non-use in the prior year	End of supply method 1. End of supply up to 30 days before or on the index date 2. End of supply from 31 and 90 days before the index date 3. End of supply from 91 and 365 days before the index date	

Variable name	Categories	Definition & lookback period	Comments
		4. End of supply > 365 days before the index date or no supply before the index date	
VKA recency	1. Current use 2. Recent use 3. Past use 4. Non-use in the prior year	**End of supply method** 1. End of supply up to 30 days before or on the index date 2. End of supply from 31 and 90 days before the index date 3. End of supply from 91 and 365 days before the index date 4. End of supply > 365 days before the index date or no supply before the index date	
Hospitalization	1. None 2. 1 3. ≥ 2	Number of hospitalizations in the one year prior to index date	
Visits to the GP or open care	1. 0–4 2. 5–9 3. 10–19 4. ≥ 20	Number of visits to the GP or to open care in the one year prior to index date	
BMI	1. < 20 2. 20.0–24.9 3. 25.0–29.9 4. ≥ 30 5. Unknown	Calculated using most recent recorded height and weight measurements any time prior to index date	
Smoking	1. Non-smoker 2. Smoker 3. Ex-smoker 4. Unknown	Most recent measure any time prior to index date	
Alcohol use	1. 0–1 units/week 2. 2–9 units/week 3. 10–20 units/week 4. 21–41 units/week 5. ≥ 42 units/week 6. Unknown	Most recent measure any time prior to index date	

Variable name	Categories	Definition & lookback period	Comments
Polypharmacy	1. < 5 2. 5–9 3. ≥ 10	Number of individual drugs at the level of ATC code in the month prior to index date	
Socioeconomic index	Quintiles of Townsend deprivation index.		
Frailty	1. Fit 2. mildly frail 3. moderately frail 4. severely frail.	Estimated using a frailty index developed for research using primary care databases	
Medical history	1. Yes 2. No	Cardiovascular disease (including myocardial infarction, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, angina, coronary artery disease, peripheral arterial disease, hypertension), diabetes mellitus, hyperlipidaemia, obesity, major bleeding events, AKI, cancer any time prior to or on the index date	
Comedication use	1. Yes 2. No	End of supply up to 30 days before or on index date of antiplatelets, parenteral anticoagulants, SGLT2 inhibitors, ACE inhibitors, ARBs and diuretics.	
CHA_2DS_2VASc	1. 0–1 2. 2 3. 3 4. 4 5. 5 6. ≥ 6	Calculated from sex, age and comorbidities recorded any time prior to index date	
Modified HAS-BLED	1. 0–1 2. 2 3. 3	Calculated from sex, age and comorbidities recorded any time prior to index date.	

Variable name	Categories	Definition & lookback period	Comments
	4. ≥ 4		
Glomerular filtration rate (eGFR) before index date	1. eGFR >50 ml/min/1.73 m^2 2. eGFR 30–50 ml/min/1.73m^2 3. eGFR<30 ml/min/1.73m^2 4. Unknown	Based on the closest eGFR available in the year before index date. eGFR will be estimated from SCr recordings using CKD-EPI equation or from diagnostic Read codes.	

9.8 Quality control

The Heath Improvement Network (THIN) contains electronic health records for 3.1 million patients were registered with a general practice contributing patient data to THIN, corresponding to approximately 5% of the UK general population. The data held are those entered by the primary care practitioner (PCP) as part of routine patient care, and include clinical, demographic and lifestyle information, and all prescriptions issued. The database has been validated for pharmacoepidemiology research and is representative of the UK demographic in terms of age, sex and geographical distribution.

As a standard process, one researcher will prepare the list of codes, test the computer algorithms to be used and run statistical analyses after agreement on all phases of analyses with the rest of the team. As one measure of quality control and to minimise data errors, another researcher will independently perform several methodological checks including the review of STATA programming and analyses.

9.9 Limitations of the research methods

All patients meeting the study inclusion and exclusion will be included in the study, thereby selection bias is not expected.

Given the nature of real-world data, missing data are likely to be present in a minority of instances. No data imputation strategies will be applied to supplement missing data. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable.

Medications prescribed at hospital will not be captured nor will over-the-counter medications (OTC). This might induce some exposure misclassification that we expect to be non-differential between patients prescribed rivaroxaban and those prescribed a VKA. This might introduce some bias towards the null in study estimates. While bias towards the null is generally considered as conservative in effectiveness analyses, it is considered as anticonservative in safety analyses (tends to conclude treatment strategies are similar even if they are not). This will be taken into account when interpreting study results.

Potential for misclassification of exposure (in particular, estimation of the end of supply) to a VKA due to complex dosing with multiple strengths of tablets prescribed concomitantly. There is an

additional risk for misclassification of exposure affecting all types of treatment, because a patient might have stopped treatment already sometime before the end of supply. Also, OAC prescriptions started in-hospital or events in the immediate post-discharge period may be missed in the IMRD-UK database.

Potential for misclassification of renal outcomes due to coding/recording errors or errors in laboratory test results.

Potential detection bias due to patients in one of the two OAC exposure groups (rivaroxaban or a VKA) being more likely to have laboratory tests performed and therefore being more likely to have an adverse renal outcome detected. To explore any differences in the frequency of laboratory tests, the number of SCr tested conducted in rivaroxaban and VKA cohorts will be compared.

Residual confounding from unknown or unmeasurable confounders.

9.10 Other aspects

NA

10. Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practices.(35) In this investigation we will use a medical record linkage database where the information of patients is anonymized and there is no need to obtain informed consent from patients. The study protocol is dependent on approval by a Scientific Research Committee for studies performed in IMRD-UK.

Centro Español de Investigación Farmacoepidemiológica (CEIFE) will comply with all applicable data protection, security and privacy laws, rules and regulations with respect to the collection, production, use, processing, storage, transfer, modification, deletion, and/or disclosure of any information related to this study under this Agreement. CEIFE will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. CEIFE will ensure that appropriate technical and organizational measures are taken to protect information against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access and against all other unlawful forms of processing. CEIFE will store the Database used to perform this study at the premises of CEIFE. Privacy issues will be addressed and respected at each stage of the study. All analyses and reporting will be done on appropriately de-identified data and only in aggregate form.

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 (37).

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov" and in in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”. Results will be disclosed in a publicly available database within the standard timelines.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. .

Study results will be published following guidelines of the International Committee of Medical Journal Editors (38) and communication in appropriate scientific venues will be considered.

When reporting results of this study, the appropriate STROBE checklist (39) will be followed.

No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

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Annex 1: List of stand-alone documents

Table S1. Multilex codes for rivaroxaban.

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
59454978	02.08.02.00	Rivaroxaban 2.5mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60767979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60768979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60769979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60770979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80953998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80954998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80955998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80956998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83418998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83425998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN

Table S2. Multilex codes for Vitamin K antagonist oral anticoagulants (VKAs).

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
96749997	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
96749998	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
99138997	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
99138998	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
92313998	02.08.02.00	Coumarin 100mg			1939	COUMARIN
95556996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556997	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556998	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
96447990	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293997	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293998	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
52818979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
58667979	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
61036979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
62209979	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN
79051979	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN
81727998	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
82804978	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
83005998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
83976998	02.08.02.00	Warfarin sodium 5mg/ml oral suspension			1904	WARFARIN
83977998	02.08.02.00	Warfarin 5mg/5ml oral solution			1904	WARFARIN
84565998	02.08.02.00	Warfarin 1mg/5ml oral suspension			1904	WARFARIN
85529998	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free			1904	WARFARIN
86425998	02.08.02.00	Warfarin 3mg/5ml oral solution			1904	WARFARIN
88944998	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
92245998	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
93227990	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
93532990	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
94878990	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
94879990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95232990	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95514990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95617996	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95617997	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95617998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
95630990	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
95741992	02.08.02.00	Warfarin 10 mg tab			1904	WARFARIN
96161990	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96162990	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96163990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96308988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96308990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97688979	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
97690979	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
97694979	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97696979	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97700979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97701979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97702979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97711988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97711989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
97711990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289996	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289997	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906996	02.08.02.00	Warfarin sodium 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906997	02.08.02.00	Warfarin sodium 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906998	02.08.02.00	Warfarin sodium 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99035989	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99035990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99331988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
99331989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99331990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Table S3. READ codes for atrial fibrillation

READ	Description
3272.00	ECG: ATRIAL FIBRILLATION
3273.00	ECG: ATRIAL FLUTTER
3274.00	ECG: PAROXYSMAL ATRIAL TACHY.
7936A00	IMPLANT INTRAVENOUS PACEMAKER FOR ATRIAL FIBRILLATION
G570.00	PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA
G570000	PAROXYSMAL ATRIAL TACHYCARDIA
G573.00	ATRIAL FIBRILLATION AND FLUTTER
G573000	ATRIAL FIBRILLATION
G573100	ATRIAL FLUTTER
G573200	PAROXYSMAL ATRIAL FIBRILLATION
G573z00	ATRIAL FIBRILLATION AND FLUTTER NOS
14AN.00	H/O: ATRIAL FIBRILLATION
212R.00	Atrial fibrillation resolved
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G573300	Non-rheumatic atrial fibrillation

Table S4. Multilex codes for OACs.

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
53246979	02.08.02.00	Apixaban 5mg tablets	B01A	ANTITHROMBOTIC AGENTS	60396	APIXABAN
53247979	02.08.02.00	Apixaban 5mg tablets	B01A	ANTITHROMBOTIC AGENTS	60396	APIXABAN
81167998	02.08.02.00	Apixaban 2.5mg tablets	B01A F02	APIXABAN	60396	APIXABAN
81168998	02.08.02.00	Apixaban 2.5mg tablets	B01A F02	APIXABAN	60396	APIXABAN
81214998	02.08.02.00	Dabigatran etex150mg cap	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
81215998	02.08.02.00	Dabigatran etexilate 150mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83971998	02.08.02.00	Dabigatran etexilate 110mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83972998	02.08.02.00	Dabigatran etexilate 75mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83973998	02.08.02.00	Dabigatran etexilate 75mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
83974998	02.08.02.00	Dabigatran etexilate 110mg caps	B01A E07	DABIGATRAN ETEXILATE	60278	DABIGATRAN
59454978	02.08.02.00	Rivaroxaban 2.5mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60767979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60768979	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60769979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
60770979	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80953998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80954998	02.08.02.00	Rivaroxaban 20mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80955998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
80956998	02.08.02.00	Rivaroxaban 15mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83418998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN
83425998	02.08.02.00	Rivaroxaban 10mg tablets	B01A F01	RIVAROXABAN	60320	RIVAROXABAN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
46894978	02.08.02.00	Edoxaban 60mg tablets	B01AF03	EDOXABAN	60488	EDOXABAN
46895978	02.08.02.00	Edoxaban 60mg tablets	B01AF03	EDOXABAN	60488	EDOXABAN
46896978	02.08.02.00	Edoxaban 30mg tablets	B01AF03	EDOXABAN	60488	EDOXABAN
46897978	02.08.02.00	Edoxaban 30mg tablets	B01AF03	EDOXABAN	60488	EDOXABAN
46899978	02.08.02.00	Edoxaban 15mg tablets	B01AF03	EDOXABAN	60488	EDOXABAN
96749997	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
96749998	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
99138997	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
99138998	02.08.02.00	Acenocoumarol	B01AA07	ACENOCOUMAROL	1906	ACENOCOUMAROL
92313998	02.08.02.00	Coumarin 100mg			1939	COUMARIN
95556996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556997	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556998	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
96447990	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293997	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
98293998	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
95556996	02.08.02.00	Phenindione	B01AA02	PHENINDIONE	1905	PHENINDIONE
52818979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
58667979	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
61036979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
62209979	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
79051979	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN
81727998	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free	B01AA03	WARFARIN	1904	WARFARIN
82804978	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
83005998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
83976998	02.08.02.00	Warfarin sodium 5mg/ml oral suspension			1904	WARFARIN
83977998	02.08.02.00	Warfarin 5mg/5ml oral solution			1904	WARFARIN
84565998	02.08.02.00	Warfarin 1mg/5ml oral suspension			1904	WARFARIN
85529998	02.08.02.00	Warfarin 1mg/ml oral suspension sugar free			1904	WARFARIN
86425998	02.08.02.00	Warfarin 3mg/5ml oral solution			1904	WARFARIN
88944998	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
92245998	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
93227990	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
93532990	02.08.02.00	Warfarin 500microgram tablets	B01AA03	WARFARIN	1904	WARFARIN
94878990	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
94879990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95232990	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95514990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
95617996	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95617997	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95617998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
95630990	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
95741992	02.08.02.00	Warfarin 10 mg tab			1904	WARFARIN
96161990	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96162990	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96163990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96308988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96308990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
96318990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97089990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97688979	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
97690979	02.08.02.00	Warfarin 500microgram tab1	B01AA03	WARFARIN	1904	WARFARIN
97694979	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97696979	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97700979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97701979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
97702979	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97711988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97711989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97711990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
97941990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98014990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98031990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289996	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289997	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98289998	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906996	02.08.02.00	Warfarin sodium 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906997	02.08.02.00	Warfarin sodium 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
98906998	02.08.02.00	Warfarin sodium 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99034990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Multilex code	BNF-code	Generic Name	ATC	ATC name	BCD	BCD name
99035989	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99035990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99331988	02.08.02.00	Warfarin 5mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99331989	02.08.02.00	Warfarin 3mg tablets	B01AA03	WARFARIN	1904	WARFARIN
99331990	02.08.02.00	Warfarin 1mg tablets	B01AA03	WARFARIN	1904	WARFARIN

Table S5. READ codes for mitral stenosis/valvular replacement.

Read code	Description
G11..11	Rheumatic mitral valve disease
G110.00	Mitral stenosis
G110.11	Rheumatic mitral stenosis
G112.00	Mitral stenosis with insufficiency
G112.12	Mitral stenosis with incompetence
G112.13	Mitral stenosis with regurgitation
G113.00	Nonrheumatic mitral valve stenosis
G130.00	Mitral and aortic stenosis
G131.00	Mitral stenosis and aortic insufficiency
G131.13	Mitral stenosis and aortic incompetence
G131.14	Mitral stenosis and aortic regurgitation
P65..00	Congenital mitral stenosis
P650.00	Congenital mitral stenosis, unspecified
P651.00	Fused commissure of the mitral valve
P65z.00	Congenital mitral stenosis NOS
P6yyC00	Fusion of mitral valve cusps
7910.12	Replacement of mitral valve
7910000	Allograft replacement of mitral valve
7910100	Xenograft replacement of mitral valve
7910200	Prosthetic replacement of mitral valve
7910211	Bjork-Shiley prosthetic replacement of mitral valve
7910212	Bjork-Shiley prosthetic replacement of mitral valve
7910213	Carpentier prosthetic replacement of mitral valve
7910214	Edwards prosthetic replacement of mitral valve
7910300	Replacement of mitral valve NEC
7911.12	Replacement of aortic valve
7911000	Allograft replacement of aortic valve
7911100	Xenograft replacement of aortic valve
7911200	Prosthetic replacement of aortic valve
7911300	Replacement of aortic valve NEC
7911500	Transapical aortic valve implantation
7911600	Transluminal aortic valve implantation
7912.11	Replacement of tricuspid valve
7912000	Allograft replacement of tricuspid valve
7912100	Xenograft replacement of tricuspid valve
7912200	Prosthetic replacement of tricuspid valve

7912300	Replacement of tricuspid valve NEC
7913.12	Replacement of pulmonary valve
7913000	Allograft replacement of pulmonary valve
7913100	Xenograft replacement of pulmonary valve
7913200	Prosthetic replacement of pulmonary valve
7913300	Replacement of pulmonary valve NEC
7914.11	Replacement of unspecified valve of heart
7914000	Allograft replacement of valve of heart NEC
7914100	Xenograft replacement of valve of heart NEC
7914200	Prosthetic replacement of valve of heart NEC
7914211	Edwards prosthetic replacement of valve of heart
7914212	Starr prosthetic replacement of valve of heart
7914300	Replacement of valve of heart NEC
7914600	Replacement of truncal valve
7919600	Percutaneous transluminal pulmonary valve replacement
791C000	Aortic root replac us pul val auto ri vent pulm art val cond
791C100	Ao ro repl us pulm val auto ri vent pul art val cond aortov
791C200	Aortic root replacement using homograft
791C300	Aortic root replacement using mechanical prosthesis
791C400	Aortic root replacement
14S4.00	H/O: heart valve recipient
14T3.00	H/O: artificial heart valve
SP00200	Mechanical complication of heart valve prosthesis
SP00400	Infect and inflammatory reaction due to cardiac valve pros
SyuK611	[X] Embolism from prosthetic heart valve
TB01200	Implant of heart valve prosthesis + complication, no blame
ZV42200	[V]Heart valve transplanted
ZV43300	[V]Has artificial heart valve
ZV45H00	[V]Presence of prosthetic heart valve
ZVu6e00	[X]Presence of other heart valve replacement

Table S6. Read codes for DVT, PE or hip/knee surgery.

Read	Description
G801.00:G80zz00	Code range
G80..00	Phlebitis and thrombophlebitis
G800.11	Saphenous vein phlebitis
G800.12	Saphenous vein thrombophlebitis
G800000	Phlebitis of the long saphenous vein
G800100	Phlebitis of the short saphenous vein
G800300	Thrombophlebitis of the long saphenous vein
G800400	Thrombophlebitis of the short saphenous vein
G401.00	Pulmonary embolism
G401.12	Pulmonary embolus
14A8.12	H/o: thrombosis
2I17.00	O/e - phlebitis
G402.00	Pulmonary infarct
G82..00	Other venous embolism and thrombosis
L096400	Pulmonary embolism following abortive pregnancy
L414.12	Phlegmasia alba dolens - obstetric
L43..00	Obstetric pulmonary embolism
L432.00	Obstetric blood-clot pulmonary embolism
L432000	Obstetric blood-clot pulmonary embolism unspecified
L432100	Obstetric blood-clot pulmonary embolism - delivered
L432300	Obstetric blood-clot pulmonary embolism + a/n complication
L432400	Obstetric blood-clot pulmonary embolism + p/n complication
L432z00	Obstetric blood-clot pulmonary embolism nos
L43y.00	Other obstetric pulmonary embolism
L43y000	Other obstetric pulmonary embolism unspecified
L43y100	Other obstetric pulmonary embolism - delivered
L43y200	Other obstetric pulmonary embolism - delivered + p/n comp
L43y300	Other obstetric pulmonary embolism with antenatal comp
L43y400	Other obstetric pulmonary embolism with postnatal comp
L43yz00	Other obstetric pulmonary embolism nos
L43z.00	Obstetric pulmonary embolism nos
L43z000	Obstetric pulmonary embolism nos
L43z100	Obstetric pulmonary embolism nos - delivered
L43z200	Obstetric pulmonary embolism nos - delivered with p/n comp
L43z300	Obstetric pulmonary embolism nos with antenatal complication
L43z400	Obstetric pulmonary embolism nos with postnatal complication
L43zz00	Obstetric pulmonary embolism nos

ZV12900	[V] personal history of pulmonary embolism
7K2..00	Hip joint operations
7K20.00	Total prosthetic replacement of hip joint using cement
7K20.12	Aufranc total replacement of hip joint using cement
7K20.13	Charnley total replacement of hip joint using cement
7K20.14	Exeter total replacement of hip joint using cement
7K20.15	Farrer total replacement of hip joint using cement
7K20.16	Freeman total replacement of hip joint using cement
7K20.17	Furlong total replacement of hip joint using cement
7K20.18	Howse total replacement of hip joint using cement
7K20.19	Ilch total replacement of hip joint using cement
7K20.1A	Mckee total replacement of hip joint using cement
7K20.1B	Monk total replacement of hip joint using cement
7K20.1C	Muller total replacement of hip joint using cement
7K20.1D	Pretoria total replacement of hip joint using cement
7K20.1E	Stanmore total replacement of hip joint using cement
7K20.1F	Turner total replacement of hip joint using cement
7K20.1G	Thr - total prosthetic replacement of hip joint using cement
7K20000	Primary cemented total hip replacement
7K20011	Charnley cemented total hip replacement
7K20100	Conversion to cemented total hip replacement
7K20200	Revision cemented total hip replacement
7K20300	Primary hybrid total replacement of hip joint nec
7K20400	Conversion to hybrid total hip replacement nec
7K20500	Revision of hybrid total hip replacement nec
7K20x00	Conversion from cemented total hip replacement
7K20x11	Removal prev cemented total prosthetic replacement hip joint
7K20y00	Total prosthetic replacement of hip joint using cement os
7K20z00	Total prosthetic replacement of hip joint using cement nos
7K21.00	Total prosthetic replacement of hip joint not using cement
7K21.11	Freeman total replacement of hip joint not using cement
7K21.12	Furlong total replacement of hip joint not using cement
7K21.13	Lord total replacement of hip joint not using cement
7K21.14	Madreporique total replacement of hip joint not using cement
7K21.15	Monk total replacement of hip joint not using cement
7K21.16	Ring total replacement of hip joint not using cement
7K21.17	Thr - total prosthetic replacement hip joint without cement
7K21000	Primary uncemented total hip replacement
7K21100	Conversion to uncemented total hip replacement
7K21200	Revision uncemented total hip replacement
7K21x00	Conversion from uncemented total hip replacement

7K21x11	Removal previous uncement total prosthet replacem hip joint
7K21y00	Total prosthetic replacement hip joint not using cement os
7K21z00	Total prosthetic replacement hip joint not using cement nos
7K22.00	Other total prosthetic replacement of hip joint
7K22.12	Thr - other total prosthetic replacement of hip joint
7K22000	Primary total prosthetic replacement of hip joint nec
7K22011	Primary hybrid total replacement of hip joint nec
7K22100	Conversion to total prosthetic replacement of hip joint nec
7K22112	Conversion to hybrid total hip replacement nec
7K22200	Revision of total prosthetic replacement of hip joint nec
7K22211	Revision of hybrid total hip replacement nec
7K22300	Attention to total hip replacement nec
7K22x00	Conversion from prev total pros replace hip joint nec
7K22x11	Removal previous total prosthetic replacement hip joint nec
7K22x12	Conver from hybrid total prosth hip joint replace nec
7K22y00	Other specified total prosthetic replacement of hip joint
7K22z00	Total prosthetic replacement of hip joint nos
7K23.00	Prosthetic cemented hemiarthroplasty of hip
7K23.12	Austin - moore hemiarthroplasty of hip joint using cement
7K23.13	Hastings hemiarthroplasty of hip joint using cement
7K23.14	Monk hemiarthroplasty of hip joint using cement
7K23.16	Thompson hemiarthroplasty of hip joint using cement
7K23000	Primary cemented hemiarthroplasty of hip
7K23100	Conversion to cemented hemiarthroplasty of hip
7K23200	Revision cemented hemiarthroplasty of hip
7K23x00	Conversion from cemented hemiarthroplasty of hip
7K23y00	Other specified prosthetic cemented hemiarthroplasty of hip
7K23z00	Prosthetic cemented hemiarthroplasty of hip nos
7K24.00	Prosthetic uncemented hemiarthroplasty of hip
7K24.12	Austin moore hemiarthroplasty of hip joint not using cement
7K24.13	Bateman hemiarthroplasty of hip joint not using cement
7K24.14	Brown hemiarthroplasty of hip joint not using cement
7K24.15	Judet hemiarthroplasty of hip joint not using cement
7K24.16	Matchett hemiarthroplasty of hip joint not using cement
7K24.17	Monk hemiarthroplasty of hip joint not using cement
7K24.18	Austin moore hemiarthroplasty of hip joint not using cement
7K24.19	Thompson hemiarthroplasty of hip joint not using cement
7K24000	Primary uncemented hemiarthroplasty of hip
7K24100	Conversion to uncemented hemiarthroplasty of hip
7K24200	Revision uncemented hemiarthroplasty of hip
7K24x00	Conversion from uncemented hemiarthroplasty of hip

7K24y00	Other specified prosthetic uncemented hemiarthroplasty hip
7K24z00	Prosthetic uncemented hemiarthroplasty of hip nos
7K25.00	Other prosthetic hemiarthroplasty of hip
7K25000	Primary prosthetic hemiarthroplasty of hip nec
7K25100	Conversion to prosthetic hemiarthroplasty of hip nec
7K25200	Revision of prosthetic hemiarthroplasty of hip nec
7K25300	Attention to prosthetic hemiarthroplasty of hip nec
7K25x00	Conversion from previous hemiarthroplasty of hip nec
7K25y00	Other specified other prosthetic hemiarthroplasty of hip
7K25z00	Other prosthetic hemiarthroplasty of hip nos
7K2y.00	Other specified operations on hip joint
7K2z.00	Hip joint operations nos
7K30.00	Total prosthetic replacement of knee joint using cement
7K30.11	Anametric total replacement of knee joint using cement
7K30.13	Attenborough total replacement of knee joint using cement
7K30.15	Cavendish total replacement of knee joint using cement
7K30.16	Charnley total replacement of knee joint using cement
7K30.17	Deane total replacement of knee joint using cement
7K30.18	Denham total replacement of knee joint using cement
7K30.19	Freeman total replacement of knee joint using cement
7K30.1A	Geomedic total replacement of knee joint using cement
7K30.1B	Geometric total replacement of knee joint using cement
7K30.1C	Guepar hinge replacement of knee joint using cement
7K30.1D	Gunston total replacement of knee joint using cement
7K30.1E	Herbert total replacement of knee joint using cement
7K30.1F	Ilch total replacement of knee joint using cement
7K30.1G	Irving total replacement of knee joint using cement
7K30.1H	Liverpool total replacement of knee joint using cement
7K30.1I	Manchester total replacement of knee joint using cement
7K30.1J	Marmor total replacement of knee joint using cement
7K30.1L	Melbourne total replacement of knee joint using cement
7K30.1N	Polycentric total replacement of knee joint using cement
7K30.1P	Sheehan total replacement of knee joint using cement
7K30.1Q	Shiers total replacement of knee joint using cement
7K30.1R	Stanmore total replacement of knee joint using cement
7K30.1S	Swanson total replacement of knee joint using cement
7K30.1T	Uci total replacement of knee joint using cement
7K30.1V	Tkr -total prosthetic replacement of knee joint using cement
7K30000	Primary cemented total knee replacement
7K30100	Conversion to cemented total knee replacement
7K30200	Revision cemented total knee replacement

7K30x00	Conversion from cemented total knee replacement
7K30x11	Removal previous cemented total prosthetic replacement knee
7K30y00	Total prosthetic replacement of knee joint using cement os
7K30z00	Total prosthetic replacement of knee joint using cement nos
7K31.00	Total prosthetic replacement of knee joint not using cement
7K31.12	Tkr - total prosthetic replacement knee joint without cement
7K31000	Primary uncemented total knee replacement
7K31100	Conversion to uncemented total knee replacement
7K31200	Revision uncemented total knee replacement
7K31x00	Conversion from uncemented total knee replacement
7K31x11	Removal previous uncemented total prosthet replacement knee
7K31y00	Total prosthetic replacement knee joint not using cement os
7K31z00	Total prosthetic replacement knee joint not using cement nos
7K32.00	Other total prosthetic replacement of knee joint
7K32.12	Tkr - other total prosthetic replacement of knee joint
7K32000	Primary total knee replacement nec
7K32011	Primary hybrid total knee replacement nec
7K32100	Conversion to total knee replacement nec
7K32111	Removal of prosthetic knee joint
7K32112	Conversion to hybrid total knee replacement nec
7K32200	Revision of total knee replacement nec
7K32211	Revision hybrid total knee replacement nec
7K32400	Attention to total knee replacement nec
7K32411	Attention to hybrid total knee replacement nec
7K32x00	Conversion from total knee replacement nec
7K32x11	Removal previous total prosthetic replacement knee joint nec
7K32x12	Conversion from hybrid total knee replacement nec
7K32y00	Other total prosthetic replacement of knee joint os
7K32z00	Other total prosthetic replacement of knee joint nos
7K37.00	Cemented unicompartmental knee replacement
7K37000	Primary cemented unicompartmental knee replacement
7K37100	Conversion to cemented unicompartmental knee replacement
7K37200	Revision cemented unicompartmental knee replacement
7K37x00	Conversion from cemented unicompartmental knee replacement
7K38.00	Uncemented unicompartmental knee replacement
7K38000	Primary uncemented unicompartmental knee replacement
7K38100	Conversion to uncemented unicompartmental knee replacement
7K38200	Revision uncemented unicompartmental knee replacement
7K38x00	Conversion from uncemented unicompartmental knee replacement

7K39.00	Hybrid unicompartmental knee replacement
7K39000	Primary hybrid unicompartmental knee replacement
7K39100	Conversion to hybrid unicompartmental knee replacement
7K39200	Revision hybrid unicompartmental knee replacement
7K39x00	Conversion from hybrid unicompartmental knee replacement
8L80.00	Hip replacement planned
7K20.11	Arthroplasty of hip joint using cement
7K20600	Conver from hybrid total prosth hip joint replace nec
7K22.11	Other arthroplasty of hip joint
7K30.12	Arthroplasty of knee joint using cement
7K30.14	Autophor arthroplasty of knee joint using cement
7K30.1K	Mckee arthroplasty of knee joint using cement
7K30.1M	Platt arthroplasty of knee joint using cement
7K30.1O	Pretoria arthroplasty of knee joint using cement
7K30.1U	Wallidus hinge arthroplasty of knee joint using cement
7K31.11	Arthroplasty of knee joint not using cement
7K32.11	Other arthroplasty of knee joint
7K68500	Excision arthroplasty of hip
7L0G200	Secndry arthroplasty hip for correctn congenital deformity
7L0G211	Colonna arthroplasty of hip

Table S7. Read codes for CKD.

Read	Description
1Z12.00	Chronic kidney disease stage 3
K05..00	Chronic renal failure
1Z13.00	Chronic kidney disease stage 4
1Z1..00	Chronic renal impairment
9hE0.00	Except chronic kidney disease qual indic: Patient unsuitable*
66i..00	Chronic kidney disease monitoring
K06..00	Renal failure unspecified
1Z14.00	Chronic kidney disease stage 5
9Ot0.00	Chronic kidney disease monitoring first letter
6AA..00	Chronic kidney disease annual review
1Z1C.00	Chronic kidney disease stage 3 without proteinuria
9Ot..00	Chronic kidney disease monitoring administration
9hE1.00	Exc chronic kidney disease quality indicators: Inform dissent*
K050.00	End stage renal failure
7L1A200	Haemodialysis NEC
7L1A.11	Dialysis for renal failure
9hE..00	Exception reporting: chronic kidney disease quality indicato*
7A60100	Creation of arteriovenous fistula NEC
7L1A100	Peritoneal dialysis
K08z.00	Impaired renal function disorder NOS
K06..11	Uraemia NOS
14V2.00	H/O: renal dialysis
4519.00	Deteriorating renal function
D215000	Anaemia secondary to chronic renal failure
D215.00	Anaemia secondary to renal failure
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
1Z1B.00	Chronic kidney disease stage 3 with proteinuria
1Z15.00	Chronic kidney disease stage 3A
8L50.00	Renal transplant planned
7L1A000	Renal dialysis
K05..11	Chronic uraemia
K0D..00	End-stage renal disease
G22..11	Nephrosclerosis
ZV45100	[V]Renal dialysis status
7L1B100	Removal of ambulatory peritoneal dialysis catheter
1Z16.00	Chronic kidney disease stage 3B
1Z1E.00	Chronic kidney disease stage 3A without proteinuria

Read	Description
1Z1J.00	Chronic kidney disease stage 4 without proteinuria
1Z1H.00	Chronic kidney disease stage 4 with proteinuria
SP08300	Kidney transplant failure and rejection
1Z1G.00	Chronic kidney disease stage 3B without proteinuria
SP05613	[X] Peritoneal dialysis associated peritonitis
K054.00	Chronic kidney disease stage 4
K055.00	Chronic kidney disease stage 5
1Z1a.00	CKD with GFR category G4 & albuminuria category A1
1Z1b.00	CKD with GFR category G4 & albuminuria category A2
1Z1c.00	CKD with GFR category G4 & albuminuria category A3
1Z1d.00	CKD with GFR category G5 & albuminuria category A1
1Z1e.00	CKD with GFR category G5 & albuminuria category A2
1Z1f.00	CKD with GFR category G5 & albuminuria category A3
1Z1H.11	CKD stage 4 with proteinuria
1Z1J.11	CKD stage 4 without proteinuria
1Z1K.00	Chronic kidney disease stage 5 with proteinuria
1Z1K.11	CKD stage 5 with proteinuria
1Z1L.00	Chronic kidney disease stage 5 without proteinuria
1Z1L.11	CKD stage 5 without proteinuria
7L1A300	Haemofiltration
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1A700	Haemoperfusion

Table S8. Read codes for AKI.

Read code	Description
K04..00	Acute renal failure
K040.00	Acute renal tubular necrosis
K041.00	Acute renal cortical necrosis
K042.00	Acute renal medullary necrosis
K043.00	Acute drug-induced renal failure
K044.00	Acute renal fail urin obstruct
K04y.00	Other acute renal failure
K04z.00	Acute renal failure NOS
Kyu2000	[X]Other acute renal failure
G500400	Acute pericarditis - uraemic
K101000	Acute pyelonephritis without medullary necrosis
K101100	Acute pyelonephritis with medullary necrosis
K04..11	ARF - Acute renal failure
K04..12	Acute kidney injury
K043000	Acute renal failure due to ACE inhibitor
K043100	Acute renal failure induced by aminoglycoside
K043300	Acute renal failure induced by cyclosporin A
K043400	Acute renal failure induced by non-steroid anti-inflamm drug
K045.00	Acute renal failure due to non-traumatic rhabdomyolysis
K046.00	Acute renal failure induced by toxin
K04B.00	Acute renal failure due to traumatic rhabdomyolysis
K04C.00	Acute kidney injury stage 1
K04D.00	Acute kidney injury stage 2
K04E.00	Acute kidney injury stage 3

Table S9. Causes of AKI: exposures and susceptibilities for non-specific AKI.

Exposure	**Susceptibility**
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female sex
Burns	Black ethnicity
Trauma	CKD
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic disease (e.g. heart. lung, liver)
Major non-cardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anaemia
Poisonous plants and animals	

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

Study title: Adverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Vitamin K Antagonists or Rivaroxaban (**ANTENNA**)

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 6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
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?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
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?	☒	☐	☐	9.1
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 and 9.7.3
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?	☒	☐	☐	9.4.2
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 and 9.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
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)?	☐	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year

Signature: _____

Annex 3: Signature pages

Signature Page – Study Conduct Responsible

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	V1.0, 02 FEB 2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	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: [redacted]

Date, Signature: _____,
_____

Signature Page – Study Epidemiologist

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	V1.0, 02 FEB 2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	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: [redacted]

Date, Signature: _____,
_____

Signature Page – Study Safety Lead

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	V1.0, 02 FEB 2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
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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: [redacted]

Date, Signature: _____,

_____

Signature Page – Study Medical Expert

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Protocol version and date	V1.0, 02 FEB 2020
IMPACT study number	21347
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	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: [redacted]

Date, Signature: _____,
_____

Signature Page – Qualitifed Person responsible for Pharmacovigilance (QPPV)

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
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Print Name: [redacted]

Date, Signature: _____,
_____

Signature Page – MAH Contact Person (Regulatory Affairs)

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
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Print Name: [redacted]

Date, Signature: _____,
_____

Signature Page – OS RWE Outcomes Data Generation Representative

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
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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: [redacted]

Date, Signature: _____,
_____

Signature Page – Study Statistician – External (CEIFE)

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
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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: [redacted]

Date, Signature: _____,
_____

Signature Page – Principal Investigator

Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
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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: [redacted]

[redacted]

Date, Signature: _____,

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