Observational Study Information

Acronym/Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	V2.0, 09 November 2020
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: Yes Joint PASS: ☐ YES ☒ NO
EU PASS register number	EUPAS36634
Active substance	Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Medicinal product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®
Product reference	Not applicable
Procedure number	Not applicable
Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	The objective of the study is to evaluate the effectiveness and safety of rivaroxaban as compared to warfarin in non-valvular atrial fibrillation patients with co-morbid diabetes mellitus in routine clinical practice
Country(-ies) of study	USA (US Optum® De-Identified EHR data)
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	PPD IEG Data Science, Research & Analytics, Bayer AG, Berlin, Germany

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.

1. Table of contents

2. List of abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ARB	Angiotensin-receptor blockers
DVT	Deep vein thrombosis
DM	Diabetes mellitus
CAD	Coronary artery disease
CKD	Chronic kidney disease
CI	Confidence interval
CPT	Current Procedural Terminology
CrCl	Creatinine clearance
GFR	Glomerular filtration rate
HCPCS	Healthcare Common Procedure Coding System
ICD-CM	International Classification of Diseases – Clinical Modification
ICD-PCS	International Classification of Diseases – Procedure Coding System
ICH	Intracranial hemorrhage
IPTW	Inverse probability of treatment weighting
IS	Ischemic stroke
GI	Gastrointestinal
HR	Hazard ratio
MALE	Major adverse limb events
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulation
OD	Once daily
OS	Observational study
PAD	Peripheral artery disease
PASS	Post-authorization safety study
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PY	Person-year
RI	Renal impairment
SSE	Stroke or systemic embolism
TIA	Transient ischemic attack
VKA	Vitamin K antagonist

VTE	Venous thromboembolism
CFR	Code of Federal Regulations
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
ICD	International Classification of Diseases
IRB	Institutional Review Board
N/A	Not Applicable
OS	Observational Study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

3. Responsible parties

3.1 Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
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Role:	OS Epidemiologist
Name:	PPD
Role:	OS Outcomes Data Generation
Name:	PPD

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

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

PPD

MetaEvidence, LLC, 559 North Stone Street, West Suffield, CT 06093

4. Abstract

Acronym/Title	**RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data**
Protocol version and date	V1.1, 20 October 2020
IMPACT study number	21449
Study type / Study phase	Observational / Phase 4
Author	PPD
Rationale and background	Patients with diabetes are at a greater risk of developing NVAF. Comorbid diabetes and NVAF increases the risk of stroke and systemic embolism, lower extremity arterial disease and progression to end-stage renal disease.
Research question and objectives	What is the comparative effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and comorbid type 2 diabetes managed in routine clinical practice. We will compare the effectiveness and safety of rivaroxaban versus warfarin by assessing the risk of major thrombotic adverse events and bleeding-related hospitalization in patients with NVAF and comorbid type 2 diabetes, as well as, secondary endpoints (e.g. development of new-onset neurologic impairment, adverse renal outcomes).
Study design	Retrospective cohort analysis.
Population	Patients with type 2 diabetes and NVAF, oral anticoagulant (OAC)-naïve, newly initiated on rivaroxaban or warfarin and with ≥12-months of EHR activity prior to the index date and documented care in the EHR by at least one provider in the 12-months prior.
Variables	Baseline demographics, comorbidities and concomitant (prescription and over-the-counter) medications.
Data sources	United States Optum® De-Identified Electronic Health Records data
Study size	We anticipate having ~75,000+ patients eligible for analysis
Data analysis	Patients receiving rivaroxaban will be *1:n* matched to warfarin patients based on propensity scores. We will also use stabilized-inverse probability of treatment weighting (IPTW), overlap weighting and multivariable regression, competing risk regression approaches to adjust for potential confounding. Analysis of the primary effectiveness and safety endpoints by key subgroups will be performed as well.
Milestones	This study will be conducted between August 2020 and August 2021.

5. Amendments

On November 9, 2020 the following secondary outcomes were added due to medical insights (sections 8.2 and 9.3.2)

- Composite of stroke, systemic embolism, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Composite of stroke, systemic embolism, myocardial infarction, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Major adverse cardiovascular event (stroke, myocardial infarction, vascular death) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Diabetic retinopathy (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Vascular mortality (a primary diagnosis/procedure code indicating cardiovascular condition(s) associated with a hospital admission or emergency room visit within 365 days of death, see Annex 1, .xlxs file for specific billing codes)
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy or all-cause death

6. Milestones

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	August 2020
End of data collection	February 2021
Final report of study results	August 2021

7. Rationale and background

Non-valvular atrial fibrillation (NVAF) is a common cardiac arrhythmia with one in four middle-aged adults in the United States (US) and Europe likely to be diagnosed. NVAF substantially increases patients' risk of stroke by five-fold and mortality by two-fold [1-2].

Oral anticoagulation (OAC) with either a warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), such as apixaban, dabigatran, edoxaban or rivaroxaban, significantly decreases the risk of clot formation and is used to prevent ischemic stroke in NVAF population [1-2], reducing thus morbidity, mortality and economic burden for patients and healthcare systems worldwide.

Data from randomized controlled trials (RCTs) [3-4] and administrative claims database analyses [5-6] show that the oral factor Xa inhibitor, rivaroxaban, is safe and effective in patients with NVAF and diabetes mellitus (DM); however, electronic health record (EHR)-based evaluations of such patients (which provide more detailed patient data) are scarce.

Patients with diabetes are at a 49% greater risk of developing NVAF [7]. Comorbid diabetes and NVAF increases the risk of stroke and systemic embolism (SSE) compared with those without diabetes [4,8]. Patients with NVAF and diabetes are at increased risk of death due to vascular causes. Data suggest that NOACs may be associated with reduced risk of vascular death compared to VKA in the diabetic NVAF patient population[4,26]. Diabetes also increases patients' risk of lower extremity arterial disease by two- to four-fold compared with absence of diabetes; this includes major adverse limb events such as need for amputation and revascularization procedures of the lower limbs [9]. Finally, vascular calcification is common in diabetic patients and warfarin (when used to treat NVAF) has been associated with increased renovascular calcification and worsening renal function and need for dialysis [10-11].

8. Research questions and objectives

What is the comparative effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and comorbid type 2 diabetes managed in routine practice using Optum® De-Identified electronic health record (EHR) data?

8.1 Primary objective

The primary objective of this study will be:

- To compare the effectiveness and safety of rivaroxaban versus warfarin in NVAF patients with comorbid type 2 diabetes using the Optum® De-Identified EHR dataset, including:
    - The composite outcome of stroke or systemic embolism (SSE) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
    - Any major or clinically-relevant nonmajor bleed resulting in hospitalization [15] (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)

8.2 Secondary objective(s)

Secondary objectives will compare rivaroxaban versus warfarin in NVAF patients with comorbid type 2 diabetes for the risk of :

- Ischemic stroke (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Systemic embolism (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Need for revascularization or major amputation of the lower limb (i.e., MALE) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Intracranial hemorrhage (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Critical organ bleeding per ISTH categories (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Any extracranial bleeding (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- New-onset vascular dementia (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Doubling of the serum creatinine level from baseline (per laboratory value)
- Decrease in eGFR>30% or 40% (per laboratory values)

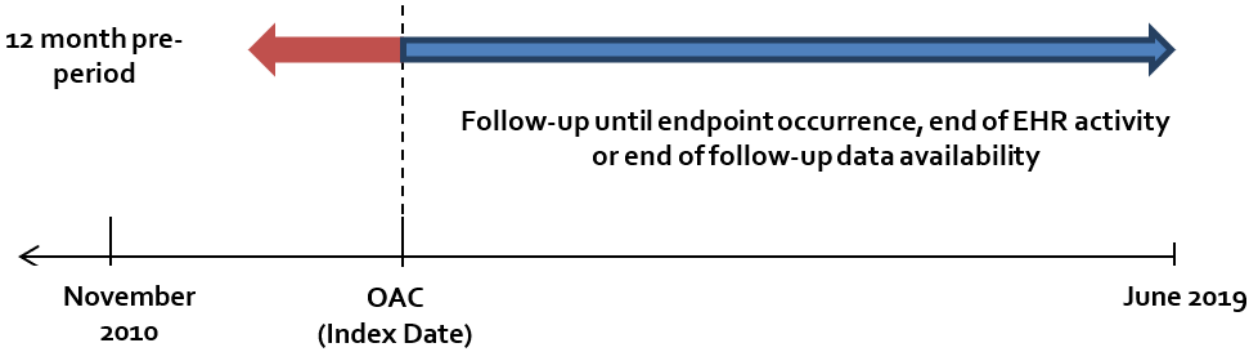
- Development of an eGFR<15 mL/min or initiation of dialysis (per laboratory values and billing codes) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of end-stage renal disease per billing codes only (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types) [14]
- Development of urine albumin-to-creatinine ratio (UACR) of 30-300 or >300 (per laboratory measurement and/or billing codes) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of serum potassium > 5.6 or >6 mg/dL (per laboratory values)
- Composite stroke, systemic embolism, need for lower limb revascularization or major amputation (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Myocardial infarction (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of diabetic retinopathy (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Vascular mortality (a primary diagnosis/procedure code indicating cardiovascular condition(s) associated with a hospital admission or emergency room visit within 365 days of death, see Annex 1, .xlxs file for specific billing codes)
- Composite of stroke, systemic embolism, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Composite of stroke, systemic embolism, myocardial infarction, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Major adverse cardiovascular event (stroke, myocardial infarction, vascular death) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy or all-cause death
- All-cause mortality

9. Research methods

9.1 Study design

We will perform a retrospective cohort analysis using US Optum® De-Identified EHR data. We will use Optum EHR data from November 1, 2010 through latest available data (currently December 31, 2019). Patient identification and flow is depicted in **Figure 1.** Rivaroxaban was approved in the United States (US) for use in NVAF patients in November 2011 (thus data back to November 2010 is required to provide a full 12-month pre-period for all patients). Included patients will have to be OAC-naïve, newly-initiated on rivaroxaban or warfarin (defined as the index date), be active in the data set for at least 12 months prior to the index event (based on the "First Month Active" field provided in the Optum data set) and have received care documented in the EHR database from at least one provider in the 12-months prior to the index date.

Figure 1: Schematic of RIVA-DM analysis



9.2 Setting

The Optum EHR database [12] includes longitudinal patient-level medical record data for 97 million patients seen at ~700 hospitals and ~7,000 clinics across the US. The database includes records of prescriptions and over-the-counter medications as prescribed, administered or self-reported by patients, laboratory results, vital signs, body measurements, other clinical observations, diagnose (ICD-9 and ICD-10) and procedures codes (ICD-9, ICD-10, CPT-4, HCPCS, Revenue codes).

9.2.1 Study population

The Optum EHR database [12] contains data on insured and uninsured patients of all ages to provide a representative sample of US patients with NVAF. The study population of interest will be those with NVAF and comorbid type 2 diabetes, OAC-naïve and newly-initiated on rivaroxaban or warfarin (defined as the index date), be active in the data set for at least 12 months prior to the index event (based on the "First Month Active" field provided in the Optum data set) and have received care documented in the EHR database from at least one provider in the 12-months prior to the index date.

9.2.2 Study time frame

We will use Optum EHR data from November 1, 2010 through latest available data (currently December 31, 2019). Rivaroxaban was approved for use in NVAF patients in November 2011 (thus data back to November 2010 is required to provide a full 1-year pre-period for all patients).

9.2.3 Selection criteria

To be included in the study patients will have to:

- Be ≥18 years of age at the time of anticoagulation initiation
- Have diagnoses of type 2 diabetes and NVAF (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
    - Given the high specificity (>98%) of billing codes for identifying diabetes, a code for diabetes will be considered sufficient to indicate diabetes in our study, regardless of A1c value (which is also a treatment goal)
    - Due to the moderate sensitivity of billing codes for diabetes (~60-70%), patients without a billing code for diabetes, but having an A1c>6.5% AND receiving an antihyperglycemic medication (oral medications, GLP1-antagonists) will be considered diabetics as well

- Have no record of prior OAC use in the prior 12-months (see Annex 1, .xlxs file for listing of oral anticoagulants by generic name)
- Newly initiated on rivaroxaban or warfarin (index date, see **Figure 1**)
- Have ≥12-months of EHR activity prior to the index date and received care documented in the EHR database from at least one provider in the 12-months prior.

We will exclude patients with:

- Evidence of valvular heart disease defined as any rheumatic heart disease, mitral stenosis or mitral valve repair/replacement (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Pregnancy (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Use of rivaroxaban doses other than 15 mg once daily or 20 mg once daily or the presence of other indication(s) for OAC use
- Any prior OAC utilization per written prescription or patient self-report at baseline.

9.2.4 Representativeness

The Optum EHR database [12] includes longitudinal patient-level medical record data for 97 million patients seen at ~700 hospitals and ~7,000 clinics across the US. This database contains data on insured and uninsured patients of all ages to provide a representative sample of US patients with NVAF.

9.3 Variables

9.3.1 Exposure definition

Newly-initiated on rivaroxaban or warfarin per written prescription, medication administration or patient self-report of medication use (including over-the-counter medications) at baseline.

9.3.2 Outcomes definition

The study outcomes will be defined based on ICD-9/10-CM diagnosis codes, CPT-4, HCPCS, ICD-9/10-PCS procedure codes or laboratory, vital sign and other patient observation results (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types for each outcome).

Primary outcomes

- Composite of stroke or systemic embolism (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Any major or clinical-relevant nonmajor bleed resulting in hospitalization (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)

Secondary outcomes

- Composite of stroke, systemic embolism, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Composite of stroke, systemic embolism, myocardial infarction, vascular death (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Major adverse cardiovascular event (stroke, myocardial infarction, vascular death) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Ischemic stroke (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)

- Systemic embolism (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Need for revascularization or major amputation of the lower limb (i.e., MALE) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Intracranial hemorrhage (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Critical organ bleeding (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Any extracranial bleeding (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Doubling of the serum creatinine level from baseline (per laboratory value)
- Decrease in eGFR>30% or 40% (per laboratory values)
- Development of an eGFR<15 mL/min or initiation of dialysis (per laboratory values and billing codes) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of end-stage renal disease per billing codes only (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types) [14]
- Development of urine albumin-to-creatinine ratio (UACR) of 30-300 or >300 (per laboratory measurement and/or billing codes) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of diabetic retinopathy (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Development of serum potassium > 5.6 or >6 mg/dL (per laboratory values)
- Myocardial infarction (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- All-cause mortality
- Vascular mortality (a primary diagnosis/procedure code indicating cardiovascular condition(s) associated with a hospital admission or emergency room visit within 365 days of death, see Annex 1, .xlxs file for specific billing codes)
- Composite stroke, systemic embolism, need for lower limb revascularization or major amputation (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types)
- Composite of >40% decrease in eGFR from baseline, eGFR<15 mL/minute, need for dialysis, renal transplant, major adverse limb event, retinopathy or all-cause death

9.3.3 Covariate definition

Patient baseline characteristics such as age, gender, comorbidities and comedications, stroke and bleeding scores will be collected at the index date or from the last recorded value within the baseline period.

Number of patients, total

Demographic characteristics

- Sex
- Age
    - Age group: <45, 45–64, 65-74, 75–79, 80+
- Race

Clinical characteristics

- Presence of the following clinical characteristics will be assessed from patients' medical and pharmacy data in the baseline period (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types):
  - **Comorbidities/prior history/risk scores:**
    - Atrial fibrillation type (starting in 2016)
    - Ischemic stroke
    - Intracranial bleeding
    - Systemic embolism
    - Deep vein thrombosis
    - Pulmonary embolism
    - Mitral stenosis
    - Heart valve/complications
    - Aortic valve replacement
    - Transcatheter aortic valve replacement
    - Pulmonary valve replacement
    - Mitral valve replacement
    - Tricuspid valve replacement
    - Valvotomy/valvuloplasty for mitral stenosis
    - Heart failure
    - Hypertension
    - Prior Ischemic stroke
      - Recent ischemic stroke within 30-days prior of index event
    - Transient ischemic attack
    - Bariatric surgery
    - Peripheral vascular disease
    - Myocardial infarction
    - Percutaneous coronary intervention
    - Coronary artery bypass grafting
    - Any major bleed
    - Major adverse limb events
    - Major amputation
    - Gastrointestinal bleeding
    - Active cancer treatment
    - Aortic plaque

- Central venous catheter
- Acute kidney injury
- Chronic kidney disease
- End-stage renal disease or hemodialysis
- Liver disease
- Coagulopathy
- Gastroesophageal reflux disease/heartburn
- Anemia
- Asthma
- Chronic obstructive pulmonary disease
- Sleep apnea
- Smoker
- Hemorrhoids
- Alcohol abuse
- Anxiety
- Depression
- Lower extremity paralysis
- Psychosis
- Osteoarthritis
- Headache
- Diverticulitis
- Crohns or ulcerative colitis
- Helicobacter pylori
- Hypothyroidism
- Solid tumor
- Lymphoma
- Metastatic cancer
- Recent major surgery within 6-12 weeks of index event
- Dementia
- Vascular dementia
- Trauma
- Hypercoagulable state
- Prior history of VTE
- Obesity

- Morbid obesity
- Varicose veins
- Chronic venous insufficiency
- Acute coronary syndrome
- Carotid stenosis
- Pneumonia
- Osteoporosis
- Orthopedic surgery
- Rheumatoid arthritis/collagen vascular disease
- Proteinuria
- Ischemic (coronary) heart disease
- Number of hospitalizations for any cause during the baseline period
- Hospital Frailty Risk Score [17]
- $CHADS_2$ score
- CHA_2DS_2-VASc score
- Modified HAS-BLED score

- **Comedications**
  - Aspirin
  - P2Y12 Inhibitors
  - Other antiplatelet agents
  - NSAIDs
  - COX-2-specific NSAIDs
  - ACE inhibitors or ARBs
  - β-blockers
  - Diltiazem
  - Verapamil
  - Dihydropyridine calcium channel blockers
  - Loop diuretic
  - Thiazide diuretic
  - Digoxin
  - Amiodarone
  - Dronedarone
  - Other antiarrhythmic drugs
  - Statins

- Other cholesterol lowering drugs
- Metformin
- Sulfonylureas or glinides
- Thiazolidinediones
- Dipeptidyl peptidase-4 inhibitors
- Glucagon-like peptide-1 agonists
- Insulin
- Benzodiazepines
- SSRIs or SNRIs
- Other antidepressants
- Proton pump inhibitors
- Histamine-2 receptor antagonists
- Systemic corticosteroids
- Estrogens
- Strong CYP3A4 inhibitors
- Strong CYP3A4 inducers

- Laboratory values and vital signs
  - SBP
  - DBP
  - HR
  - LVEF
  - D-Dimer
  - Potassium
  - Serum creatinine
  - Reported eGFR
  - Glycosylated hemoglobin (A1c)
  - Height
  - Weight
  - Body mass index (BMI)
  - Urine albumin-to-creatinine ratio (UACR)
  - AST
  - ALT
  - Total bilirubin
  - Platelet count

- Blood urea nitrogen (BUN)
- Total cholesterol
- LDL cholesterol

See Annex 1, Supplemental coding files (.xlxs) for the corresponding diagnosis and procedure codes and medication names.

9.4 Data sources

The Optum EHR database includes longitudinal patient-level medical record data for ~97 million patients seen at ~700 hospitals and ~7,000 clinics across the United States. The database includes records of prescriptions as prescribed and administered, laboratory results, vital signs, body measurements, diagnose and procedures. This database contains data on insured and uninsured patients of all ages to provide a representative sample of US patients with NVAF.

As with any secondary data source, Optum EHR claims databases have limitations [12, 19] including misclassification and sampling bias. Optum EHR only representative of patients within the US that contribute data to this specific EHR. Patients may have received care at institutions that are not included in Optum EHR, allowing for potential incompleteness of data in the follow-up period. It will also not be possible to assess time since diabetes diagnosis. The risk of many cardiovascular and renal outcomes increases with increasing time since diabetes diagnosis (regardless of other comorbidities). The EHR database lacks information on prescription fills as only written prescriptions or self-reported medications are captured. Given the lack of prescription fill data, it will not be possible to assess adherence/persistence to treatment exposure. In a database analysis setting, (where randomization is not possible) propensity score methods (matching or weighting) serve to harmonize comparison groups with respect to patient characteristics; however, residual confounding caused by unmeasured factors, missing data, miscoding or tactical coding issues, etc. may be present.

Strengths of the data set include the ability to use clinical data as opposed to relying solely on billing codes disease classification/severity. Both prescribed and self-reported medication use is tracked, allowing for assessment of important over the counter medication use (e.g., aspirin, proton pump inhibitors St John's Wort). Importantly, this EHR database includes patients from different geographical areas of the US and captures commercially insured, Medicare, Medicaid, and uninsured patients which are likely to provide a more accurate reflection of the general population than a traditional administrative claims data set.

9.5 Study size

Based on preliminary review of the Optum® EHR dataset, we anticipate their being >217,000 NVAF patients receiving either rivaroxaban (~40%) or warfarin (~60%), of which, ~35% will have comorbid diabetes at baseline. Consequently, we anticipate having 75,000+ patients eligible for analysis of our primary effectiveness (i.e., composite of stroke or systemic embolism) and safety (i.e., any major or clinical-relevant nonmajor bleed resulting in hospitalization) outcomes. Given the sample sizes seen in ROCKET AF (N=14,264) which had similar primary efficacy and safety outcomes, we believe sample available to use for the present study should provide sufficient power. We will include all available patients qualifying for study inclusion.

9.6 Data management

Database management will be performed using SAS Enterprise Guide version 8.1 (SAS Inc., Cary, NC, USA). MetaEvidence LLC has meet all data maintenance and security requirements of Optum Inc (the data

owners). The required data (de-identified and HIPAA-compliant) will be provided by Optum Inc to MetaEvidence LLC via a secure, password protected, temporary SharePoint link. Raw and processed data files will be maintained by MetaEvidence LLC on a secured, password protected (2 step verification required) network assessable server and made available only to members of the research team via unique logins and passwords.

9.7 Data analysis

Patients receiving rivaroxaban will be *1:n* matched to warfarin patients based on propensity scores calculated via multivariable logistic regression where the probability of exposure (here: receiving rivaroxaban) given patient characteristics will be calculated [13]. Propensity scores will be estimated based upon commonly used variables and accepted risk factors for differential oral anticoagulation exposure identified during the baseline period including demographics, comorbidities, laboratory and vital signs and concurrent outpatient co-medication use. All clinical characteristics listed in section 9.3.3 of this protocol will be included in the propensity score model. Given the retrospective nature of the data analysis, the presence of a comorbid disease diagnosis will be made based upon billing codes and/or supporting laboratory/observation data. The absence of data suggesting a comorbidity exists will be assumed to represent the absence of the disease (no missing data for binary comorbidity disease diagnoses). For continuous laboratory and observation data (e.g., eGFR, BMI, etc.) missing data will be imputed using a "multiple imputation" approach based on a fully conditional specification linear regression model with all other available variables included in the model [24]. No imputation will be performed for potentially missing outcomes/endpoint data. Separate propensity score models will be fit once for the primary analysis and for each subgroup analysis. The presence of residual differences in measured covariates following cohort matching (using a caliper ≤0.5 standard deviations of the logit of the propensity score) will be assessed by calculating standardized differences (with a difference <0.1 considered well-balanced for each covariate) [13]. Propensity score matching will be performed using the **'MatchIT'** package and R statistical software (version 3.4.3, The R Project for Statistical Computing).

All methods for confounder adjustment have potential limitations related to selecting a clinically relevant target population, covariate balance and precision. Propensity score matching operates by taking each treated study participant and finding the closest propensity score match among controls within a calliper (or bound). Conventional IPTW assigns a weight of 1/PS for treated and 1/(1 − PS) for untreated patients, allowing individuals with underrepresented characteristics to count more in the analysis. IPTW can produce inflated variance estimates which can be addressed through a simple stabilization of weights (multiplying propensity scores of each participant by the relative proportion of the specific cohort makes up of the total study population). In observational data, in which the initial differences in treatment groups may be large, these methods can modify the target population, fail to achieve good balance or substantially worsen precision. Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group. Specifically, treated patients are weighted by the probability of not receiving treatment (1 − PS) and untreated patients are weighted by the probability of receiving the treatment (PS). These weights are smaller for extreme PS values so that outliers who are nearly always treated (PS near 1) or never treated (PS near 0) do not dominate results and worsen precision, as occurs with IPTW. These outliers contribute relatively less to the result, while patients whose characteristics are compatible with either treatment contribute relatively more. The resulting target population mimics the characteristics. Overlap weighting also leads to exact balance on the mean of every measured covariate when the PS is estimated by a logistic regression. Like all PS-based methods, overlap weighting cannot adjust for patient characteristics that are not measured and included in the model for the PS. When initial imbalances in patient characteristics between treatment groups are modest, overlap weighting yields similar results to IPTW. The advantages of overlap weighting are greatest when comparator groups are initially very different.

Visual inspection of plots of propensity score distributions can aid in the determination of the best method to utilize. To test the robustness of our conclusions to various methods for confounding adjustment, we will perform sensitivity analyses in which each analysis/outcome will be assessed using a stabilized-IPTW [20],

overlap weighting [18] and a competing risk model assessing the effect of covariates (in this case, anticoagulant choice) on the cause-specific hazard of outcome (death, stroke/systemic embolism or major bleeding) [21, 25].approach. Because a competing risk scenario in which different event types including nonfatal outcomes (stroke/systemic embolism, major bleeding) and death is anticipated in our study, we will seek to determine which event type occurred first. Therefore, for this study, we will fit a cause-specific hazard model [25]. Competing risk regression will be performed using 'cmprsk' and 'riskRegression' in R. Results of the competing risk regression will be reported as incidences over time for the cohorts and as hazard ratios (HRs) with 95% confidence intervals (CIs). Finally, to assess the magnitude of confounding as well as the consistency and robustness of the results with the different analytical methods, also unadjusted analyses will be reported.

Cox regression (or proportional hazards regression) is a method for investigating the effect of variables upon the time a specified event takes to happen. We will fit Cox proportional hazards regression models to compare event rates over time for the rivaroxaban and warfarin cohorts. As propensity score based methods will be assumed to balance key characteristics of the treatment cohorts, the only independent variable that will be included into Cox regression model will be OAC received (rivaroxaban or warfarin); this means that the analysis, adjusted for treatment only, will be performed on already matched population to keep baseline characteristics in balance. Results of Cox regression will be reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Cox proportional hazards regression analysis will be performed using R statistical software (version 3.4.3, The R Project for Statistical Computing). The proportional hazard assumption will be tested based on Schoenfeld residuals. Patients will be censored in the Cox models at the first incidence a patient experiences end-of-EHR activity (based on "Last Month Active" data available in the Optum EHR) or reaches the end of data availability in the Optum data set (June 30, 2019). As the EHR dataset does not allow to calculate exposure times (prescriptions are not captures with all the relevant details for such an analysis), patients will be analyzed using an intention-to-treat approach, where patients will be evaluated based on their initial OAC prescription Time from treatment initiation to end of follow-up will then be considered the time under risk.

Based on prior NVAF analyses, It is estimated the median follow-up for available patients using this approach will exceed 2.5 years (similar to that of RCTs). We will perform an additional sensitivity analyses in which we cap the maximum follow-up of patients at 2-years and analyze data using logistic regression instead of Cox proportional hazards regression.

Baseline characteristics will be analyzed using descriptive statistics. Categorical data will be reported as percentages and continuous data as medians with accompanying 25%, 75% ranges or means ± standard deviations (SDs). The incidence rate of each outcome of interest will be reported as events per 100 person-years (%/year).

Subgroup analyses

The primary effectiveness and primary safety outcomes will be analyzed in the entire study cohort as well as stratified by the following subgroups:

- Hemoglobin A1c value closest and prior to baseline, <7%, 7% to <8%, ≥8% (Diabetes severity)
- Age≥75 years or <75 years
- Age ≥80 years or <80 years
- Sex
- Body mass index (BMI) ≥40 kg/m2 and/or body weight ≥120 kg
- eGFR (value closest and prior to baseline, <15 ml, 15 to 30 ml, 30 to <45 ml, 45 to <60 ml (and < 50 ml), 60 to <90 ml, >=90 ml per minute per 1.73 m2) or chronic kidney disease (CKD)[14]

- Frailty risk using the Hospital Frailty Risk Score[17] (score <5 is low risk, 5-15 intermediate risk, >15 high risk) (see Annex 1, .xlxs file for specific billing codes, code positions and encounter types for the Hospital Frailty Risk Score)
- Presence or absence of the following comorbid conditions (in addition to NVAF and type 2 diabetes):
    - Peripheral artery disease
    - Coronary artery disease
    - Heart failure
    - Active cancer (e.g., active treatment in prior 6-months or metastatic disease)
    - Prior ischemic stroke
    - Concomitant antiplatelet utilization (aspirin, P2Y12 platelet inhibitor, dual antiplatelet therapy)
    - Initial rivaroxaban dose (20 mg or 15 mg)

To limit the number of analyses performed (and the impact of multiple hypothesis testing), subgroup analyses will only be performed on the primary effectiveness and primary safety endpoints.

9.8 Quality control

When dependence on billing codes is required to identify covariates or outcomes, we will utilize endorsed and/or validated coding algorithms (e.g., CMS, AHRQ, Elixhauser or Charlson comorbidity indices, Cunningham bleeding algorithm), whenever possible. All database coding will be performed in SAS Enterprise Guide version 8.1 (SAS Inc., Cary, NC, USA). All coding will be reviewed by a second trained investigator to assure its accuracy. Billing codes, generic drug names, laboratory values and observation data used for this study are detailed in the supplied Annex 1, .xlxs file.

9.9 Limitations of the research methods

As with any secondary data source, Optum EHR claims databases have limitations [12, 19]. Key limitations include:

- Misclassification bias can negatively impact the internal validity of database analyses.
- Optum EHR data patient sampling is not random, it may contain biases or fail to generalize well to other populations.
    - Optum EHR only representative of patients within the US that contribute data to this specific EHR.
- Patients may have received care at institutions that are not included in Optum EHR, allowing for potential incompleteness of data in the follow-up period.
- The EHR database lacks information on prescription fills as only written prescriptions are captured. The study was conducted as an intent to treat approach, and given the lack of prescription fills, it is difficult to ascertain treatment exposure.
- Data on time since diabetes diagnosis cannot be assessed in this data set.
- New onset neurologic impairment will be assessed based on the presence of new billing codes for vascular dementia which may miss less severe cases of neurologic impairment.
- An EHR entry to initiate an oral anticoagulation does not necessarily mean a patient filled their prescription and/or took it. Moreover, as the Optum® EHR does not provide data on adjudicated

prescription claims from pharmacies, traditional methods for assessing adherence and persistence in large observational studies cannot be implemented. As a result, we will only analyze our results using an intention-to-treat approach.

- In the database analysis where randomization is not possible, such PS based methods as matching serve to harmonize comparison groups with respect to patient characteristics. However, residual confounding caused by e.g. unmeasured factors, missing data, miscoding or tactical coding issues, etc. may be present.

9.10 Other aspects

None.

10. Protection of human subjects

The use of Optum clinical EHR database was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research [12].

11. Management and reporting of adverse events/adverse reactions

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

12. Plans for disseminating and communicating study results

The results of the study are intended for publication and will follow the International Committee of Medical Journal Editors guidelines [22]. In addition, communication in appropriate scientific meetings will be considered. 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”.

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Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	Final version and date (if available)*
ICD_optum_coding.xlxs	19 October 2020

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

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9.1
1.1.2 End of data collection[2]	☒	☐	☐	9.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	12
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:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
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	☒	☐	☐	9.2.3
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

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?	☒	☐	☐	9.7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
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

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
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)	☒	☐	☐	9.7 and 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7 and 9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3 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)	☒	☐	☐	9.3 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3 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)	☐	☐	☐	9.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☐	9.2
9.3.3 Covariates and other characteristics?	☐	☐	☐	9.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	9.4

Comments:

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

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3: Additional information

Annex 4: Signature pages

Signature Page – Study External Partner

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
Medicinal product / Active substance / Medical Device / Combination Product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®/ Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG

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

Print Name: PPD

Date, Signature _____

Signature Page – OS Conduct Responsible

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
Medicinal product / Active substance / Medical Device / Combination Product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®/ Direct factor XA inhibitor, Rivaroxaban (B01AF01)
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Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
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Signature Page – OS Safety Lead

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
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Date, Signature _____

Signature Page – OS Medical Expert

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
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Study Initiator and Funder	Bayer AG

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Date, Signature _____

Signature Page – OS Statistician

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
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Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG

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Date, Signature _____

Signature Page – OS Epidemiologist

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
Study type / Study phase	Observational, Phase IV PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
Medicinal product / Active substance / Medical Device / Combination Product	BAY 59-7939; 1912, Rivaroxaban, Xarelto®/ Direct factor XA inhibitor, Rivaroxaban (B01AF01)
Comparator / Reference therapy	Warfarin, Coumadin®
Study Initiator and Funder	Bayer AG

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Signature Page – OS Outcomes Data Generation

Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Protocol version and date	2.0, 09 November 2020
IMPACT study number	21449
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