Observational Study Information

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type/Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☐ NO
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Medicinal product	Xarelto, Pradaxa, and Eliquis
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Research question and objectives	**Primary Objective** • To provide baseline characteristics of NVAF patients who are prescribed with any of the three DOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention, and contrast with the corresponding characteristics of patients in clinical trials. • To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of rivaroxaban, dabigatran and apixaban in UK for stroke prevention in NVAF patients • To assess the proportion of NVAF patients with renal impairment who are prescribed with rivaroxaban, dabigatran, and apixaban at index date including their treatment characteristics (daily dose, dose posology, duration). **Secondary Objective**

	• To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in NVAF patients.
Country(-ies) of study	United Kingdom
Author	Dr Luis A Garcia Rodriguez Spanish Centre for Pharmacoepidemiologic Research (CEIFE) Almirante, 28, 2 28004 Madrid, Spain Phone: +34-91-531 3404 Email:lagarcia@ceife.es

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	Dr. Gunnar Brobert Epidemiology Bayer AG 13353 Berlin Phone: +49-30 468 193 129 Email: gunnar.brobert@bayer.com

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

AF Atrial fibrillation
ACR Albumin to Creatinine Ratio
ATC Anatomical Therapeutic Chemical (Classification System)
BMI Body Mass Index
CEIFE Centro Español de Investigación Farmacoepidemiológica
CI Confidence Interval
CKD Chronic Kidney Disease
CKD-EPI Chronic Kidney Disease Epidemiology Collaboration
DVT Deep Vein Thrombosis
eGFR estimated Glomerular Filtration Rate
EMA European Medicine Agency
ENCePP European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
CPRD Clinical Practice Reaseach Datalink
GCP Good Clinical Practice
HR Hazard Ratio
IHD Ischemic Heart Diseases
INR International Normalized Ratio
LMWH Low molecular weight heparins
MAH Marketing Authorization Holder
MDRD Modification of Diet in Renal Disease Study
MREC Multicenter Research Ethics Committee
N/A Not Applicable
DOACs new oral anticoagulants
NVAF Non valvular Atrial Fibrillation
OTC over the counter medications
PAD Peripheral Artery Disease
PAS Post-Authorization Study
PASS Post-Authorization Safety Study
PCPs Primary Care Physicians
SRC Scientific Research Committee
STROBE Strengthening the Reporting of Observational Studies in Epidemiology
THIN The Health Improvement Network
UK United Kingdom
VKAs Vitamin K antagonists

3. Responsible parties

Study initiator and funder / MAH

Function: Study conduct responsible and Study Epidemiologist
Name: Gunnar Brobert
Email: Gunnar.Brobert@Bayer.com

Function: Study Medical Expert
Name: Isabelle Ling Meng

Function: Study Safety Lead
Name: Tomasz Dyszynski

Function: Study Statistician
Name: Marin Homering

Function: Real Life Evidence Strategy and Outcomes Data Generation
Name: Daniel Eriksson

Function: Bayer UK – Local Study Unit, Medical Affairs
Name: Samuel Fatoba

Function: Bayer UK – Medical Advisor
Name: Luke Roberts

Collaborators / Committees

Principal Investigator: Dr Luis A Garcia Rodriguez

Co-investigator: Ana Ruigomez

Spanish Centre for Pharmacoepidemiologic Research (CEIFE)

Almirante, 28, 2

28004

Madrid, Spain

Phone: +34-91-531 3404

Email:lagarcia@ceife.es

4. Abstract

Title

Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices

v 1.0, 24 February 2017

Dr Luis A Garcia Rodriguez
Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain

Rationale and background

Individualized anticoagulant treatment should be based on patients' age, renal function, comorbidities, and concomitant treatments. The DOACs are new agents with several advantages including use of fixed-dosing with no need for INR monitoring, few interactions etc. The lack of effective antidote for some of them, their cost, or uncertainties in patients with kidney disease, and associated risk of bleeding may explain reservations in their widespread use (Hinojar et al. 2015).

There is a limited data on prescription and usage patterns of DOACs in routine care for stroke prevention in non-valvular atrial fibrillation (NVAF). Monitoring the usage patterns of DOACs is essential to study compliance with labelling information.

Research question and objectives

This population-based descriptive study will characterize first-time users of three DOACs in NVAF patients for stroke prevention including those renal impaired. Additionally, it will assess patterns of drug utilization in routine general practice in the UK, using the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN).

Primary Objective

- To provide baseline characteristics of NVAF patients who are prescribed with any of the three DOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention, and contrast with the corresponding characteristics of patients in clinical trials.
- To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of rivaroxaban, dabigatran and apixaban in UK for stroke prevention in NVAF patients
- To assess the proportion of NVAF patients with renal impairment who are prescribed with rivaroxaban, dabigatran, and apixaban at index date including their treatment characteristics (daily dose, dose posology, duration).

Secondary Objective

- To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in NVAF patients.

Study design

This is a population-based retrospective cohort study designed to assess the characteristics of patients and patterns of drug utilization in new users of DOACs in the UK by merging the CPRD and THIN databases.

The study enrollment period extends from 1st January 2011 up to last available database extraction (at time of writing, May 2016 in THIN and in CPRD).

Among the source population resulting from the combination of THIN and CPRD databases, we will ascertain three separate cohorts of first-time users of rivaroxaban, apixaban and dabigatran using the date of first prescription (index date) of the respective drug (index drug).

This study will apply a new-users (initiators) design (Ray, 2003). New users are individuals starting a study medication for the first time ever recorded in the database. Yet, they may have used the other study medications before index date and therefore classified as non-naïve. New-users without any history of any oral anticoagulant would be classified as naïve.

Population

All patients aged 18 and above and who have been enrolled in the databases for at least 1 year and had their first prescription recorded in the databases at least 1 year ago will be included in source population. A patient will be considered eligible to enter a study cohort as a first-time user of one the study drugs when he or she has a first prescription of the drug recorded during the enrolment period. Among the three study cohorts, we will further identify patients with Non-valvular Atrial Fibrillation (NVAF).

Variables

Detailed descriptive variables incuding baseline characteristics will be captured for the population, including co-medications and comorbidities. Dose, posology, duration of study drug and other anticoagulant before index date including naïve/non-naïve status. Renal disease using estimated glomerular filtration rate (eGFR) as well as ACR (Albumin/Creatinine Ratio) where available. Also, risk scores, lifestyle factors and healthcare utilization.

Data sources

THIN - The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution. THIN now collects data from 570 practices, covering 6% of the general population of the UK population.

CPRD – It contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The CPRD has information on 5.4 million individuals (active contributors), which represents approximately 9% of the UK population.

Study size

THIN version1605: The prevalence of NVAF among patients 18+ and register with GP for at least a year is 1.89% (N= 74319).

CPRD GOLD 2014: The prevalence of AF in all ages was 2.47% in men and 1.56 % in women.

Data analysis

Describe the three study cohorts i.e. patients prescribed with rivaroxaban, dabigatran, apixaban by baseline characteristics, use of medications, comorbidities and healthcare utilization services among the three study cohorts and contrast them with the baseline characteristics of patients in clinical trials.

Use of study medications: Dose at first Rx, dose posology, duration of treatment (time on index medication), discontinuation, switch to another study drug.

To assess the proportion of patients that are dosed in accordance and non-accordance to label, in study population and in subset of patients with renal impairment

Milestones

The project is planned to begin in February 2017 and will end in April 2017

5. Amendments and updates

None

6. Milestones

This study will be conducted between January 2017 and April 2017

Milestone	Project timeline
Protocol development and submission for review and comment	By end December 2016
Ethics Submission & Approval	By end January 2017
Data Extraction	March 2017
Data Analysis and reporting	April-May 2017

7. Rationale and Background

Vitamin K antagonists (VKAs) have been the standard treatment for antithrombotic prevention in atrial fibrillation (AF) in the last 60 years (NICE, 2016). Direct oral anticoagulants (DOACs) have shown to have a favourable balance between efficacy and safety compared with VKAs, and three (rivaroxaban, dabigatran, and apixaban) are now available and approved in the United Kingdom (UK) for the prevention of stroke in non-valvular AF (NVAF) patients.

Two classes of DOACs are currently available, the oral direct thrombin inhibitors (DTIs; e.g. dabigatran) and oral direct factor Xa inhibitors (e.g. rivaroxaban, apixaban, and edoxaban). Unlike VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in the coagulation cascade.

Individualized anticoagulant treatment should be based on patients' age, renal function, comorbidities, and concomitant treatments. The DOACs are new agents with several advantages including use of fixed-dosing with no need for INR monitoring, few interactions etc. The lack of effective antidote for some of them, their cost, or uncertainties in patients with kidney disease, and associated risk of bleeding may explain reservations in their widespread use (Hinojar et al. 2015).

There is a limited data on prescription and usage patterns of DOACs in routine care for stroke prevention in non-valvular atrial fibrillation (NVAF). Monitoring the usage patterns of DOACs is essential to study compliance with labelling information.

8. Research question and objectives

This population-based descriptive study will characterize first-time users of three DOACs in NVAF patients for stroke prevention including those renal impaired. Additionally, it will assess patterns of drug utilization in routine general practice in the UK, using the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN).

8.1 Primary Objective

- To provide baseline characteristics of NVAF patients who are prescribed with any of the three DOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention, and contrast with the corresponding characteristics of patients in clinical trials.
- To assess the pattern of use (daily dose, dose posology, treatment duration, naïve status) of rivaroxaban, dabigatran and apixaban in UK for stroke prevention in NVAF patients
- To assess the proportion of NVAF patients with renal impairment who are prescribed with rivaroxaban, dabigatran, and apixaban at index date including their treatment characteristics (daily dose, dose posology, duration).

8.2 Secondary Objective

To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in NVAF patients.

9. Research methods

9.1 Study design

This is a population-based retrospective cohort study designed to assess the characteristics of patients and patterns of drug utilization in new users of DOACs in the UK.

The study enrollement period extends from 1st January 2011 up to last available database extraction (at time of writing, May 2016 in THIN and in CPRD).

Among the source population resulting from the combination of THIN and CPRD databases, we will ascertain three separate cohorts of first-time users of rivaroxaban, apixaban and dabigatran using the date of first prescription (index date) of the respective drug (index drug).

This study will apply a new-users (initiators) design (Ray et al, 2003). New users are individuals starting a study medication for the first time ever recorded in the database. Yet, they may have used the other study medications before index date and therefore classified as non-naïve. New-users without any history of any oral anticoagulant would be classified as naïve.

All patients aged 18 and above and who have been enrolled in the databases for at least 1 year and had their first prescription recorded in the databases at least 1 year ago will be included in source population. A patient will be considered eligible to enter a study cohort as a first-time user of one the study drugs when he or she has a first prescription of the drug recorded during the enrolment period.

Patients who have any record of being prescribed their index drug prior to the enrolment period or who qualify as members of more than one cohort on the same day, will be excluded. If a patient qualifies as first-time user of more than one study drug during the enrolment period, with different index dates, she/he will be assigned to the cohort of study drug first prescribed during the enrolment period, with the date of this prescription being the index date. (eg mutually exclusive cohorts)

Among the three study cohorts, we will further identify patients with NVAF defined as:-

Patients with a record of Atrial fibrillation (AF) any time prior index date or within the 2 weeks after the index date, and free of valvular replacement or mitral stenosis prior to index date or 2 weeks after index-date

9.1.1 Primary end-points

1. Baseline characteristics of NVAF patients in the UK prescribed any of the three direct oral anticoagulants (DOACs) (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention
2. Daily dose, dose posology, naïve status, treatment duration of DOACs for stroke prevention in NVAF patients including those with renal impairment

9.1.2 Secondary end-point

1. Time-trends in the characteristics of first-time use of DOACs in NVAF patients

9.2 Setting

All patients aged >= 18 years with at least one year of enrollment with the PCP and one year since first health contact recorded in the database (THIN or CPRD) prior to index prescription date.

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records, grouped in databases that are available for research projects. The CPRD and THIN are two similarly structured, de-identified electronic medical record databases in the UK. To increase the number of patients available, both data sources would be pooled. Combining CPRD and THIN data will increase the size relative to the CPRD alone by approximately 25 to 30%. However, some practices provide data to both databases, therefore duplicate patients would be identified to avoid double-counting patients.

Among duplicate practices, it is anticipated that due to availability of free-text, the information from THIN will be retained. Therefore, we will use all THIN practices and only the information from CPRD practices that do not contribute to THIN. To identify and exclude duplicated practices between THIN and CPRD, and matching of anonymized patient characteristics will be applied (Cai et al., 2012, Garc á-Rodr íguez et al., 2014).

9.3 Variables

The following variables will be collected among the three study cohorts of DOACs:

- age and sex distribution at index date;
- dose of index drug at index date, dose posology, and duration of treatment (including pack size);
- type and duration of other anticoagulant use before the index date
- prior anticoagulation (DOACs, warfarin and LMWH) before index date: proportion of na ïve patients (defined as those with no use of any anticoagulant ever prior to index date)
- use of specifically prescribed medications both in the year before the index date and year after the index date: antiplatelet drugs (low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor); anticoagulants (including rivaroxaban, dabigatran, apixaban, warfarin, and LMWH), antiarrhythmic drugs, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs, oral steroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, antipsychotic drugs, oral contraceptives, hormone-replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole.
- Renal disease (estimated glomerular filtration rate (eGFR) before index date as well as ACR (Albumin/Creatinine Ratio) where available.
- Comorbidity: haemorrhagic disease and history of intracranial haemorrhage, urogenital bleeding and gastrointestinal bleeding. Liver disease, pancreatic disease, cancer, cardiovascular disease (acute MI, coronary artery disease, congestive heart failure, ventricular arrhythmia, peripheral arterial disease) cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), stroke/TIA, respiratory disease (asthma and chronic obstructive pulmonary disease), rheumatoid arthritis, osteoarthritis, gastrointestinal disease, liver disease and pancreatic, alcohol-related disorders.
- CHADS2 and CHA_2DS_2Vasc scores will be calculated based on the presence/ history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or transient ischaemic attack. HAS-BLED score for major bleeding risk (hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age > 65, medication usage predisposing to bleeding, alcohol usage history), will also be calculated .

- smoking status, body mass index (BMI) and Townsend score: most recently recorded value before the index date.
- healthcare utilization in the year prior to the index date and the year after (e.g. PCP visits, outpatient visits and hospital admissions).

Parameter	Description/ Definition
Demographic Characteristics at index date	• Age • Sex • Smoking status (previous 6 months) • Body mass index (previous 6 months) • Blood pressure history (previous 12 months) • Number of patients that are naïve vs non-naïve • For non-naïve: type and duration of anticoagulant used before index date
Risk factor categories	• $CHADS_2$ score • CHA_2DS_2 VASC • HASBLED score • INR measurement
Previous medical history (12 months prior to index date)	• Acute MI • Stroke or TIA • Systemic peripheral arterial embolism • Coronary artery disease • Congestive heart disease • Hypertension • Diabetes • Renal disease (eGFR) or ACR (Albumin/Creatinine Ratio)
Previous medication history (within previous 12 months of index date)	• Anti-arrhythmics • Statins • Anti-platelets • Beta-blockers • ACE inhibitors • Anti-diabetic agents • Non-steroidal anti-inflammatory drugs (NSAIDs) • Antacids • Histamine receptor antagonists • Proton pump inhibitors (PPIs) • Disease-modifying anti-rheumatic drugs (DMARDs) • Antidepressants • Antipsychotic agents • Oral contraceptives

	• Hormone replacement therapy (HRT) • Strong inhibitors of Cytochrome P450 or P-GP • Strong inducers of CYP3A4
Previous use of VKA (ever prior to index date)	• Warfarin • Other Vitamin K antagonist(s)
Concurrent (from index date) co-medication	• Anti-coagulants • Aspirin • Clopidogrel • Other

9.4 Data sources

THIN

Established in 2002, THIN now collects data from 570 practices, covering 6% of the general population, with more than 65 million patient-years of experience (CSD Medical Research, 2012). Eleven million individual patients are represented in the data; of those, approximately one-third are active at any one time. THIN records information on all services provided by the PCP, and information on specialist visits and hospitalizations are routinely forwarded to the PCP, who enters that information into the medical record. The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution (Bourke, Dattani et al. 2004; Blak, Thompson et al. 2011). THIN has been extensively validated for use in pharmacoepidemiology (Lewis, Schinnar et al. 2007).

The Read classification is used to code specific diagnoses as reasons for each consultation (O'Neil, Payne et al. 1995; Stuart-Buttle, Read et al. 1996), and a drug dictionary based on data from the MULTILEX classification is used to record prescriptions (First Data Bank 2014).

CPRD

The CPRD (http://www.cprd.com/intro.asp) contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The CPRD has information on 5.4 million individuals (active contributors), which represents approximately 9% of the UK population. These data are linkable, at least partially, with other health care data sets (e.g., hospitalization and national mortality data). Updated, valid, linked data are available through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency.

As in THIN, The CPRD also includes information recorded by GPs on patient demographics and lifestyle factors and detailed information on prescriptions written by the PCP. Free text comments are not available in CPRD.

The CPRD patients are representative of the UK population in terms of age and sex; it has been validated previously for use in pharmacoepidemiology to address a wide range of study questions in the European population (Herrett et al. 2015). Research at the CPRD requires approval from the CPRD Independent Scientific Advisory Committee (ISAC).

9.5 Study size

THIN version1605: The prevalence of AF (2011-2016), among patients 18+ and register with GP for at least a year 1.92% (No. of patients with AF= 75784). The prevalence of AF excluding patients with prior Mitral Stenosis or Valvular replacement = 1.89% (N= 74319).

CPRD GOLD database in 2014: authors reported a prevalence AF in all ages was 2.47% in men and 1.56 % in women. (Bhatnagar et al, 2015).

A study conducted using CPRD by Johnson et al, 2016, identified 541 naïve apixaban users, 1589 naïve rivaroxaban users, and 741 naïve dabigatran users up to October 2014.

9.6 Data Management

For each study project, all material including: study protocol, copy of Scientific Review Committee approval, algorithms and data collections, datasets, STATA programs, results from validation exercises and questionnaires, final STATA programs, and final report and publications are kept in one folder cross-shared by the CEIFE team. Monthly back-ups are performed and kept in a secure location, and all material is kept for a minimum of 10 years.

As a standard process, one researcher prepares the list of codes, test the computer algorithms to be used and runs statistical analysis after agreement on all phases of analyses with the rest of the team. As one measure of quality control, another researcher independently performs several checks in reviewing commands and analyses performed in order to minimise data errors.

9.6.1 Strategy for handling missing data

As a general strategy, no data imputation strategies will be applied to supplement missing data. The requirement for inclusion is complete data for critical variables; otherwise this individual is not eligible to be a member of the study population. However, missing values may occur in a small proportion. 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.

9.7 Data analysis

The analysis will be based on descriptive statistics: frequencies and percentages will be calculated to the variables of interests, continuous and count variables will be described using mean (±standard deviation), proportions, median (quartiles) and minimum and maximum values. 95% confidence intercals will be computed for descriptive varaibles. The following outcomes will be assessed:

- Describe the three study cohorts i.e. patients prescribed with rivaroxaban, dabigatran, apixaban by baseline characteristics, use of medications, comorbidities and healthcare utilization services

(see all the variables in section 9.3) among the three study cohorts and contrast them with the baseline characteristics of patients in clinical trials.

- Use of study medications: Dose at first Rx, dose posology, duration of treatment (time on index medication), discontinuation, switch to another study drug .
- To assess the proportion of patients that are dosed in accordance and non-accordance to label, in study population and in subset of patients with renal impairment
- Contrasting patient characteristics of those prescribed DOACs with the corresponding characteristics in patients participating in clinical trials.

Table 1: Dosing of each study drug in the study population.

	Rivaroxaban	Apixaban	Dabigatran
Low dose **Renal impairment** **Other indication to reduce the dose** **Non- accordance to label**			
Standard dose incl.documented renal impairment			
All			

- Use of medication before index date will be categorized as:
    - Concurrent use (when the drug supply lasts until index date or is prescribed at index-date)
    - Recent (when the drug supply ends 1-30 days before index date)
    - Past use (when the drug supply ends 31-365 days before index date)
    - Non-use: no use in year before index date

9.8 Quality control

Standard operating procedures at research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as study reports, will undergo quality control and senior scientific review.

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. The Company will not receive any patient or

provider identifiable information from CEIFE at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices. The study protocol is dependent on approval by a Scientific Research Committee (SRC) that review studies performed in THIN

9.9 Limitations

- Given the nature of real-world data, missing data are likely to be present in a minority of instances.
- Only prescriptions captured in the CPRD and THIN dataset will be available. Medications prescribed at hospital will not be captured nor will over the counter medications (OTC).
- Incomplete data concerning medication compliance: drug use is based on prescriptions written by the treating physician, but no information is available to confirm if the drug was actually taken by the patient (common to virtually any computerized clinical database).
- There may be some missing data if GPs may not enter the hospitalization data however we expect that the vast majority of GPs will record information on hospitalization into THIN or CPRD (in practices not linked to HES).
- Some lifestyle variables such as smoking, BMI and alcohol consumption is not consistently recorded for all patients.
- The results from the three study cohorts should be interpreted with care, as in the presence of confounding, any findings cannot simply be attributed to the treatments defining the cohorts.

9.10 Other aspects

None

10. Protection of human subjects

This study protocol will be approved by a Research Ethics Committee (REC), and the study will be conducted in accordance with Good Pharmacoepidemiology Practices. We will send the study protocol to the Multicenter Research Ethics Committee (MREC). 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.

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. We will abide by the Guidelines for Good Pharmacoepidemiology Practices(31). The study protocol is dependent on approval by a Scientific Research Committee (SRC) for studies performed in THIN

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 (European Medicines Agency 2012).

12. Plans for disseminating and communicating study results

At least one manuscript based on the findings from this project will be submitted for publication to a peer-review journal.

Study results will be published following guidelines of the International Committee of Medical Journal Editors (ICMJE, 2013), and communication in appropriate scientific venues will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE, 2007) will be followed.

13. List of references

- Atrial fibrillation: the management of atrial fibrillation NICE Clinical Guidelines (CG180) 2014 available at https://www.nice.org.uk/guidance/cg180/evidence/atrial-fibrillation-update-full-guideline-243739981 accessed 15th Feb 2016. Page 15
- Bhatnagar, P et al, The epidemiology of cardiovascular disease in the UK 2014. Heart doi:10.1136/heartjnl-2015-307516
- Blak, B. T., M. Thompson, et al. (2011). "Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates." Inform Prim Care 19(4): 251-255.
- Bourke, A., H. Dattani, et al. (2004). "Feasibility study and methodology to create a quality-evaluated database of primary care data." Inform Prim Care **12**(3): 171–177
- Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36.

- Hinojar R, Jimenez-Natcher JJ, Fernandez-Golfin C, and Zamorano JJ: New oral anticoagulants: a practical guide for physicians. European Heart Journal – Cardiovascular Pharmacotherapy (2015) 1, 134–145 doi:10.1093/ehjcvp/pvv002
- Lewis, J. D., R. Schinnar, et al. (2007). "Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research." Pharmacoepidemiol Drug Saf **16**(4): 393–401
- Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003 Nov 1;158(9):915-20.
- Strobe. Strobe statement - strengthening the reporting of observational studies in epidemiology. 2007 [[accessed 5 October 2016]. Available from: http://www.strobe-statement.org.
- ISPE. (2007). "Guidelines for good pharmacoepidemiology practices (second revision)." Retrieved 10 Oct, 2010, from http://www.pharmacoepi.org/resources/guidelines_08027.cfm
- European Medicines Agency (2012) "Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products."
- Johnson ME, Lefèvre C, Collings SL, Evans D, Kloss S, Ridha E, Maguire A. Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. BMJ Open. 2016 Sep 26;6(9):e011471.

Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title:
Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8
1.1.2 End of data collection[2]	☒	☐	☐	8
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	8

Comments:

The study is not yet registered in the EU PAS register however will be registered soon.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	9
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10

[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 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.4 Which formal 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**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	10-11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10-11
4.2.2 Age and sex?	☒	☐	☐	10-11
4.2.3 Country of origin?	☒	☐	☐	10-11
4.2.4 Disease/indication?	☒	☐	☐	10-11
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	10-11

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	10-11
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	15
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	11-13
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	11-14
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	11-14
8.1.3 Covariates?	☒	☐	☐	11-14
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	13-14
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13-14
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	13-14
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	13-14
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	13-14
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10-11

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	14-15
10.3 Are descriptive analyses included?	☒	☐	☐	11-15
10.4 Are stratified analyses included?	☒	☐	☐	11-15
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	15
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	14-15
11.3 Are methods of quality assurance described?	☒	☐	☐	14-15
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	14-15
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	15-16
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	15-16

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	15-16

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	16
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	16

Comments:

The application to the ethics approval is still pending

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	8

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☒	☐	☐	17

Comments:

Name of the main author of the protocol: Gunnar Brobert

Date: 24/01/2017

Signature: _____

Annex 3. Additional information

List of Read Codes

Table S1.

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

Table S2:
Operational definitions for subpopulations:

Non-valvular Atrial Fibrillation (NVAF)	Patients with a record of Atrial fibrillation (AF) any time prior index date or within the 2 weeks after the index date, and free of valvular replacement or mitral stenosis (see table codes below) prior to index date or 2 weeks after index-date
Renal Impairment	We will obtain eGFR values from creatinine values using the MDMR (1) or CDK-EPI (2) formula. Furthermore we will define four levels of decreasing severity of - severe renal impairment (defined as eGFR < 30 ml/min/1.73m ²) or READ code indicating renal dialysis or kidney transplant - moderate renal impairment (defined as eGFR 30–44 ml/min/1.73m^2 - mild renal disease (45–59 ml/min/1.73m^2

(1)Modification of Diet in Renal Disease equation (MDMR) formula *to calculated the eGFR, expressed in ml per minute*
eGFR =186 x (Creat / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female)
(2)CDK-EPI Formula:*eGFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 [if female] * 1.159 [if black]*

Scr: serum creatinine (mg/dL)
κ : 0.7 for females and 0.9 for males
α: 0.329 for females and 0.411 for males
min : the minimum of Scr/κ or 1
max : the maximum of Scr/κ or 1.

Table S3- AF READ codes

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 READ Codes for mitral stenosis (to exclude from AF patients)

READ	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

Table S5 READ Codes for valvular replacement- to exclude from AF patients)

READ	Description
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 of Dialysis (renal Impairment)

Read	Description
14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7A60600	Creation of graft fistula for dialysis
7A61900	Ligation of arteriovenous dialysis fistula
7A61A00	Ligation of arteriovenous dialysis graft
7L1A.11	Dialysis for renal failure

7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
8882.00	Intestinal dialysis
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis
TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U611200	[X]Foreign obj accid left body dur kidney dialys/oth perfus
U612200	[X]Failure sterile precautions dur kidney dialys/other perf
U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines
Z919300	Reversing haemodialysis lines
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV45100	[V]Renal dialysis status

ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
SP01500	Mechanical complication of dialysis catheter
Z131400	Warming patient by dialysis therapy
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training
Z919400	Recirculation of the dialysis machine
ZVu3G00	[X]Other dialysis

Table S7. Read codes of Kidney transplant (renal Impairment)

Read	Description
7B00.00	Transplantation of kidney
7B00000	Autotransplant of kidney
7B00100	Transplantation of kidney from live donor
7B00111	Allotransplantation of kidney from live donor
7B00200	Transplantation of kidney from cadaver
7B00211	Allotransplantation of kidney from cadaver
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00500	Allotransplantation of kidney from cadaver NEC
7B00y00	Other specified transplantation of kidney
7B00z00	Transplantation of kidney NOS
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B06300	Exploration of renal transplant
7B0F.00	Interventions associated with transplantation of kidney
7B0F100	Pre-transplantation of kidney work-up, recipient
7B0F200	Pre-transplantation of kidney work-up, live donor
7B0F300	Post-transplantation of kidney examination, recipient
7B0F400	Post-transplantation of kidney examination, live donor

7B0Fy00	OS interventions associated with transplantation of kidney
7B0Fz00	Interventions associated with transplantation of kidney NOS
8L50.00	Renal transplant planned
SP08011	13.1.1.1.1.1.1 Det.ren.func.after ren.transpl
SP08300	Kidney transplant failure and rejection
TB00100	Kidney transplant with complication, without blame
ZV42000	[V]Kidney transplanted
14S2.00	H/O: kidney recipient

CKD stage 1

1Z10.00	Chronic kidney disease stage 1
1Z17.00	Chronic kidney disease stage 1 with proteinuria
1Z17.11	CKD stage 1 with proteinuria
1Z18.00	Chronic kidney disease stage 1 without proteinuria

CKD Stage 2

1Z11.00	Chronic kidney disease stage 2
1Z19.00	Chronic kidney disease stage 2 with proteinuria
1Z19.11	CKD stage 2 with proteinuria
1Z1A.00	Chronic kidney disease stage 2 without proteinuria
1Z1A.11	CKD stage 2 without proteinuria

CKD stage 3

1Z12.00	Chronic kidney disease stage 3
1Z15.00	Chronic kidney disease stage 3A
1Z16.00	Chronic kidney disease stage 3B
1Z1B.00	Chronic kidney disease stage 3 with proteinuria
1Z1B.11	CKD stage 3 with proteinuria
1Z1C.00	Chronic kidney disease stage 3 without proteinuria
1Z1C.11	CKD stage 3 without proteinuria
1Z1D.00	Chronic kidney disease stage 3A with proteinuria
1Z1D.11	CKD stage 3A with proteinuria
1Z1E.00	Chronic kidney disease stage 3A without proteinuria
1Z1E.11	CKD stage 3A without proteinuria
1Z1F.00	Chronic kidney disease stage 3B with proteinuria
1Z1F.11	CKD stage 3B with proteinuria
1Z1G.00	Chronic kidney disease stage 3B without proteinuria

1Z1G.11	CKD stage 3B without proteinuria

CKD stage 4

1Z13.00	Chronic kidney disease stage 4
1Z1H.00	Chronic kidney disease stage 4 with proteinuria
1Z1H.11	CKD stage 4 with proteinuria
1Z1J.00	Chronic kidney disease stage 4 without proteinuria
1Z1J.11	CKD stage 4 without proteinuria

Dialysis Stage 4

14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7A60600	Creation of graft fistula for dialysis
7A61900	Ligation of arteriovenous dialysis fistula
7A61A00	Ligation of arteriovenous dialysis graft
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
8882.00	Intestinal dialysis
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis

TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis
TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U611200	[X]Foreign obj accid left body dur kidney dialys/oth perfus
U612200	[X]Failure sterile precautions dur kidney dialys/other perf
U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines
Z919300	Reversing haemodialysis lines
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV45100	[V]Renal dialysis status
ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
SP01500	Mechanical complication of dialysis catheter
Z131400	Warming patient by dialysis therapy
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training

Z919400	Recirculation of the dialysis machine
7B00.00	Transplantation of kidney
7B00000	Autotransplant of kidney
7B00100	Transplantation of kidney from live donor
7B00111	Allotransplantation of kidney from live donor
7B00200	Transplantation of kidney from cadaver
7B00211	Allotransplantation of kidney from cadaver
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00500	Allotransplantation of kidney from cadaver NEC
7B00y00	Other specified transplantation of kidney
7B00z00	Transplantation of kidney NOS
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B06300	Exploration of renal transplant
7B0F.00	Interventions associated with transplantation of kidney
7B0F100	Pre-transplantation of kidney work-up, recipient
7B0F200	Pre-transplantation of kidney work-up, live donor
7B0F300	Post-transplantation of kidney examination, recipient
7B0F400	Post-transplantation of kidney examination, live donor
7B0Fy00	OS interventions associated with transplantation of kidney
7B0Fz00	Interventions associated with transplantation of kidney NOS
8L50.00	Renal transplant planned
SP08011	Det.ren.func.after ren.transpl
SP08300	Kidney transplant failure and rejection
TB00100	Kidney transplant with complication, without blame
ZV42000	[V]Kidney transplanted
14S2.00	H/O: kidney recipient

Annex 4. Signature pages

Signature Page - Study Conduct Responsible and Study Epidemiologist

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Epidemiology
Name	Gunnar Brobert

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Study Medical Expert

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Global Medical Affairs Thrombosis
Name	Isabelle Ling Meng

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Study Safety Lead

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Pharmacovigilance
Name	Tomasz Dyszynski

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Study Statistician

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Statistics
Name	Martin Homering

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Study Health Economist

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Patient Access
Name	Kevin Bowrin

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Real Life Evidence Strategy and Outcomes Data Generation

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Real Life Evidence Strategy and Outcomes Data Generation
Name	Daniel Eriksson

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page - Local Study Unit - Medical Affairs (Bayer UK)

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Local Study Unit - Medical Affairs (Bayer UK)
Name	Samuel Fatoba

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page – Medical Advisor (Bayer UK)

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
Function	Medical Advisor (Bayer UK)
Name	Luke Roberts

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page – Principal Investigator

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen

Function	Principal Investigator
Name	Dr Luis A Garcia Rodriguez
	Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante, 28, 2, 28004 Madrid, Spain

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____

Signature Page – Co-investigator

Title	Pattern of use of Direct Oral Anticoagulants in Non-valvular Atrial Fibrillation patients in UK general practices
Protocol version identifier	1.0
Date of last version of protocol	24.02.2017
IMPACT study number	19330
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not yet registered
Active substance (medicinal product)	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen

Function	Co-investigator
Name	Ana Ruigomez
	Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante, 28, 2, 28004 Madrid, Spain

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: _____,_____