Observational Study Information

Acronym/Title	**TRE**atment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia
Protocol version and date	v1.1, 06 Feb 2018
IMPACT study number	20104
Study type / Study phase	Observational, Phase IV PASS: Yes Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN) and B01A E07 DABIGATRAN
Medicinal product	Xarelto, Pradaxa, and Eliquis
Product reference	EU/1/08/472/001-041
Procedure number	EMEA/H/C/00944
Comparator / Reference therapy	Dabigatran and Apixaban
Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	This population-based descriptive study will characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in NVAF patients and will assess the patterns of drug utilization in routine general practice in Colombia.
Country of study	Colombia
Author	Dr, Luis A Garcia Rodriguez, Spanish Centre for Pharmacoepidemiologic Research (CEIFE) Jenny Lee, Bayer AG Pareen Vora, Bayer AG

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
MAH contact person	Christine Tarenz Gunnar Brobert

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

EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
MAH	Marketing Authorization Holder
N/A	Not Applicable
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
QPPV	Qualified Person Responsible For Pharmacovigilance
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO DD	World Health Organization Drug Dictionary
OACs	Oral Anticoagulants
NOACs	Non-vitamin K antagonist Oral Anticoagulants
NVAF	Non valvular Atrial Fibrillation
SPAF	Stroke prevention for Atiral Fibrillation
AF	Atrial Fibrillation
GIFF	Grupo de Investigación en Farmacoepidemiológica y Farmacovigilancia
MI	Myocardial Infarction
TIA	Transient Ischaemic Attack
PCP	Primary Care Physicians
eGFR	estimated Glomerular Filtration Rate
SGSSS	General Health Social Security System of Colombia
POS	Obligatory Health Plan
EPS	Health Promoting Entities
CEIFE	Centro Español de Investigación Farmacoepidemiológica

3. Responsible parties

3.1 Study initiator and funder

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

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

- Dr Luis A Garcia Rodriguez
  Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
- Jorge Machado
  Faculty of Health Sciences, Universidad Tecnológica de Pereira,
  Pereira, Colombia

4. Abstract

Acronym/Title	**TRE**atment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia
Protocol version and date	v1.1, 28 JAN 2018
IMPACT study number	20104
Study type / Study phase	Observational, Phase IV PASS: Yes Joint PASS: ☐ YES ☒ NO
Author	Jenny Lee, Bayer AG Pareen Vora, Bayer AG Dr, Luis A Garcia Rodriguez, Spanish Centre for Pharmacoepidemiologic Research (CEIFE)
Rationale and background	Three NOACs (rivaroxaban, dabigatran and apixaban) are now available and approved in Colombia for the prevention of stroke in non-valvular atrial fibrillation (SPAF). This population-based study will characterize first-users of NOACs and assess patterns of drug utilization in routine general practice using the Audifarma database in Colombia. The results of this study will address the shortage of real-world data on prescription and usage patterns of NOACs in routine care. This study is a collaboration with Grupo de Investigación en Farmacoepidemiológica y Farmacovigilancia. This initiative will allow us to expand our reach to Latin American countries and increase knowledge about data sources in Latin America.
Research question and objectives	This population-based descriptive study will characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in SPAF patients and will assess the patterns of drug utilization in routine general practice in Colombia. • To provide a detailed description of SPAF patients who are prescribed NOACs (rivaroxaban, dabigatran and apixaban) for first time use in an outpatient setting • To assess the pattern of outpatient use of NOACs in SPAF

	patients • To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF patients
Study design	Population-based retrospective cohort study
Population	Using the population from the Audifarma database, the study will be comprised of three separate cohorts of first time users of rivaroxaban, dabigatran and apixaban using the first prescription date (index date) of the respective drug (index drug). All patients aged ≥18 years with at least one year of enrollment in the databases and one year since first encounter with healthcare provider will be included in the study. The study period is from July 2009 to May 2017.
Variables	Descriptive variables, including baseline demographic characteristics such as age and sex distribution, will be captured for the study population. Co-morbidity and healthcare utilization information will also be collected. Additional variables include type and duration of other anticoagulant used before the index date and proportion of naïve to non- naïve patients.
Data sources	The study will be performed using Audifarma, the largest drug dispenser in Colombia. Audifarma outpatient database is comprised of about 4.8 million people affiliated to five insurers of the Colombian Health System.
Study size	As this is a drug utilization study, all users of the three NOACs in the Audifarma database will be included.
Data analysis	The analysis will be based on descriptive statistics. • Description of the study cohorts in use of medications, comorbidity and healthcare utilization. • Usage of study medications: dose at first prescription, duration of treatment (time on index medication), discontinuation and switch to another study drug • The above mentioned characteristics per year – Time trends
Milestones	The study starts 26th February 2018 and the final results will be available by April 2018

5. Amendments

None

6. Milestones

Table 1: Milestones

Milestone	Planned date
Start of study	26 February 2018
End of study	20 March 2018
Registration in the EU PAS register	28 February 2018
Final report of study results	30 April 2018

7. Rationale and background

The use of prescription oral anticoagulants (OACs) such as Vitamin K antagonists (VKAs) can be effective for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and is recommended for persons at increased risk [1]. However, certain food and drug interactions require more frequent monitoring and dosage adjustments, making it arduous for many patients to properly adhere to VKAs in clinical practice [2].

VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX and X), have been the standard treatment for antithrombotic prevention in atrial fibrillation (AF) and other indications for the past 60 years. However, new oral anticoagulants, which block the activity of one single step in the coagulation cascade, have shown to have a more favorable balance between efficacy and safety compared to VKAs. Currently, three non-vitamin K oral anticoagulants (NOACs), rivaroxaban (2012), dabigatran (2011) and apixaban (2013), are available and approved in Colombia for the stroke prevention in atrial fibrillation (SPAF) patients.

This population-based study will characterize first-time users of NOACs and assess patterns of drug utilization in routine general practice using the Audifarma database in Colombia. In a letter to the editor for a meta-analysis published by Bai et al [18], Machado-Alba et al reported that in Colombia in 2016, 63% of the patients receiving oral anticoagulants had at least 1 dispensing delay of ≥15 days, meaning that ≈2 of 3 of anticoagulant users could remain for >2 weeks without medication. In the case of oral anticoagulants, patients with anticoagulation because of atrial fibrillation will be unprotected from thromboembolic complications that could be effectively prevented considering adherence to therapy is fundamental to achieve adequate drug effectiveness. This should motivate further real-world studies in populations with cultural, social, economic, and health services differences. [7] The results of this study will address the shortage of real-world data on prescription and usage patterns of NOACs in routine care. Currently, there is no information available.

This study is a collaboration with Grupo de Investigación en Farmacoepidemiológica y Farmacovigilancia (GIFF). This would be the first analysis of NOACs in SPAF patients using a

database in Latin America. This is the only database identified and accessible in collaboration with GIFF for research purposes. This initiative will also allow us to expand our reach to Colombia, open other opportunities in Latin American countries, and increasing knowledge about new data sources in Latin America.

8. Research questions and objectives

This population-based descriptive study will characterize first-time users of three NOACs (rivaroxaban, dabigatran and apixaban) in SPAF patients and will assess the patterns of drug utilization in routine general practice in Colombia.

8.1 Primary objective

- To provide a detailed description of SPAF patients who are prescribed NOACs (rivaroxaban, dabigatran and apixaban) for first time use in an outpatient setting
- To assess the pattern of outpatient use of NOACs in SPAF patients

8.2 Secondary objective

- To determine time-trends in the characteristics of first-time use of rivaroxaban, dabigatran and apixaban in outpatient SPAF 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 first-users of three NOACs in Colombia using Audifarma database.

Data will be extracted from July 2009 to the last available database extraction (currently May 2017):

- The index date will be the first prescription date of rivaroxaban, dabigatran or apixaban for the first time users without any previous dispensation of the three above mentioned NOACs.
- The enrollment period will be from the date of first marketing of one of the 3 study NOACs until May 2017
- The study follow-up period will start on the study index date and will end on the last available database extraction (currently May 2017).

9.1.1 Primary end-point

- Baseline patient characteristics of SPAF patients in Colombia prescribed any of the three NOACs (rivaroxaban, dabigatran and apixaban) for the first time for stroke prevention

- Outpatient patterns (daily dose, dose posology, naïve status and treatment duration) of rivaroxaban, dabigatran and apixaban use in SPAF patients

9.1.2 Secondary end-point

- Time-trends in the characteristics of first-time use of NOACs in SPAF patients. The primary endpoints like patient characteristics, medical history, medication history, characteristics of index prescription, stratified per year (wherever possible).

9.2 Setting

Audifarma, the largest drug dispenser in Colombia [3], is a private company which delivers medication to approximately 6.5 million people in the country which constitutes approximately 13.8% of the country's population [4]. Using the population from this database, the study will be comprised of three separate cohorts of first time users of rivaroxaban, dabigatran and apixaban using the first prescription date (index date) of the respective drug (index drug).

The study will apply the new-users (first-time) design [5], where first-time users are defined as individuals starting a study medication for the first time ever in the database. Yet, they may have used the other study medications or oral anticoagulants before index date and therefore classified as non-naïve. First-time users without any history of any oral anticoagulant would be classified as naïve. A patient is eligible to enter a study cohort as a first-time user of one of the study drugs when s/he has a first prescription of the drug recorded during the enrolment period.

If a patient qualifies as a first-time user of more than one study drug during the enrolment period, with different index dates, s/he will be assigned to the cohort of the first prescribed study drug, with the date of this prescription as the index date.

Among the three study cohorts, we will further identify NVAF patients defined as patients with record of AF any time prior to the index date or within two weeks after the index date with no history of valvular replacement or mitral stenosis prior to index date or up to two weeks after the index date. There is no ICD-10 code specifically for NVAF.

The study period is from July 2009 to May 2017 (current last available database extraction).

9.2.1 Inclusion Criteria

- First prescription of NOACs (rivaroxaban, dabigatran and apixaban) in the outpatient setting.
- NVAF Patients
- aged ≥18 years
- at least one year of enrollment in the Audifarma database
- one year since first encounter with healthcare provider will be included in the study.

9.2.2 Exclusion criteria

- Patients with any record of index drug prescription prior to the enrolment period.
- Patients who qualify as members of more than one cohort study on the same day.

9.3 Variables

The following variables will be collected among the three study cohorts of first-time users of NOACs:

- Age and sex distribution at index date
- Use of specific 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); 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.
- 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 and/or alcohol-related disorders
- Healthcare utilization in the year prior to the index date and the year after (e.g. PCP visits, outpatient visits and hospital admissions)
- 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
- Proportion of naïve patients (defined as those with no outpatient use of any anticoagulant ever prior to index date)

Parameter	**Description/Definition**
Demographic Characteristics (at index date)	Age Sex Proportion of naïve vs non- naïve patients

	For non-naïve: type and duration of anticoagulant used before index date
Previous Medication History (within past 12 months of index date)	Antiplatelets Antiarrhythmic drugs Antihypertensives Statins Anti-diabetic agents Non-steroidal anti-inflammatory drugs (NSAIDs) 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 Strong CYP3A4 inducers Fluconazole
Previous Medical History (12 months prior to index date)	Haemorrhagic disease and history of intracranial haemorrhage Urogenital bleeding and gastrointestinal bleeding Liver disease Pancreatic disease Cancer Cardiovascular disease Cardiovascular risk factors Stroke/TIA VTE Respiratory disease Rheumatoid arthritis Osteoarthritis

	Gastrointestinal disease Alcohol-related disorders Renal disease (eGFR)
Healthcare Utilization (year prior to index date and year after)	PCP visits Outpatient visits Hospital admissions

9.4 Data sources

Upon issuance of Law 100 of 1993, a basic package of services, processes, and drugs for all persons affiliated to the General Health Social Security System of Colombia (SGSSS) was created, known as the Obligatory Health Plan (POS) (1). The SGSSS is a universal insurance for 47 million inhabitants divided into a contributory regime and one subsidized by the state where the services are offered by Health Promoting Entities (EPS / insurance companies). [17] The Health System of Colombia offers universal coverage through 2 regimes, one payment for the worker and employer and another subsidized by the state.

Drug dispensing records for this study were collected from Audifarma S.A., the largest drug dispenser in Colombia [3]. This private company delivers medication to approximately 6.5 million people insured by the Colombian Health Care System (SGSSS, in Spanish), corresponding to 28% of the population affiliated to the payment (contributory) regime, which constitutes approximately 13.8% of the country's population [4].

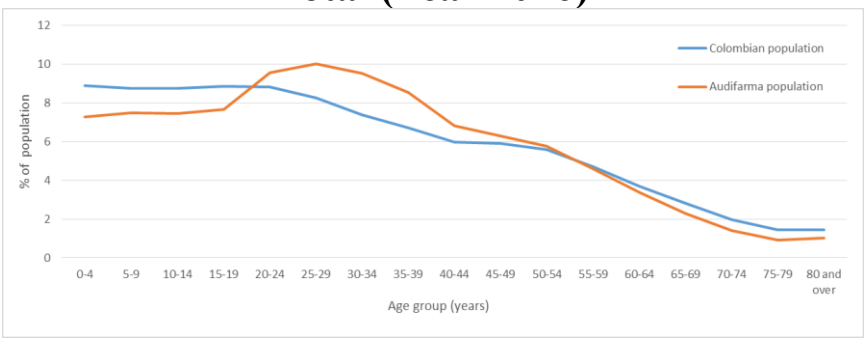
Audifarma is comprised of both an outpatient and inpatient database. The outpatient database consists of about 4.8 million people affiliated to five health insurance companies called Entidades Promotoras de Salud (EPS) of the Colombian Health System in >150 cities. These cities are the most important and representative cities of the country with populations between 7000 and 8 million inhabitants. Information about medications purchased outside of the insurance system and over-the-counter medications are not included. A database designed by Audifarma's pharmacoepidemiology division allows collection of variables about the consumption of medications. The database records the date, quantity, strength and dose instructions for each drug dispensed, disease, prescribing doctor's specialty. Other information included in the prescription are age and sex of the patients and up to two recorded diagnoses (International Classification of Diseases, 10th Revision). Daily drug dispensation information is stored on a server, which produces approximately 2.8 formulas per month, with data available from January 1, 2006 to present. Lot of studies have been looking in to prescription patterns have been conducted using this data source [10-16]

The distribution by age and sex of the persons affiliated to the insurers of the contributory system of the Colombian Health System, to which Audifarma dispenses drugs, is the same as that of the general population of the country, with the exception of one of these insurers, which has 40% of the adult population over 45 years old versus the others whose percentage varies between 23 and 29%, which is that of Colombia.

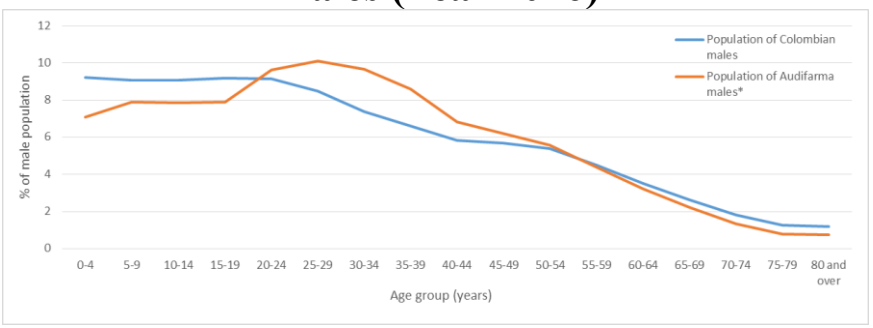
The age distribution of Colombian population and the population of the 2 out of the 5 main insurers in Audifarma Database population (the ones that have the age and sex distribution of all enrollees in

2016, N = ~3.2 million; Total Audifarma population in 2016 was 4.5 million) presented in the figure below. There are a few less young people and a few more people in productive age in Audifarma however, the population of interest for our study is Atrial fibrillation patients and the majority of the AF patients generally are >45 years of age which shows a very good agreement with the Colombian Population.

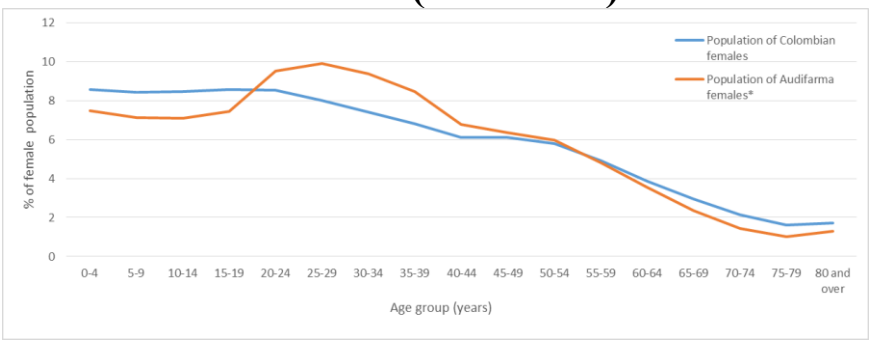
Total (Year 2016)



Males (Year 2016)



Females (Year 2016)



9.5 Study size

As this is a drug utilization study, all users of the three NOACs in the Audifarma database will be included. However, we do not have an estimate of the number of users in the database, which is one of the objectives of the study.

An estimated 2.7 million people in the Latin American region had AF in 2015. The estimated prevalence of AF in Colombia was 0.8% in 2015. [8] Based on the 6-7 years of data, we expect approximately ≤15,000 to 20,000 patients.

9.6 Data management

Grupo de Investigación en Farmacoepidemiológica y Farmacovigilancia (GIFF) in collaboration with 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. GIFF and 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. GIFF and CEIFE will store the Database used to perform this study at the premises of CEIFE. For each study project, all material including: study protocol, copy of Scientific Review Committee approval, algorithms and data collections, datasets, 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 10 years.

9.7 Data analysis

The analysis will be based on descriptive statistics. For variables of interest, the frequency and percentage will be calculated. Continuous and count variables will be described using mean (± standard deviation), proportions, median (quartiles) and minimum and maximum values. 95% confidence intervals will be computed for all descriptive variables.

The following outcomes will be assessed:

- Description of the study cohorts in use of medications, comorbidity and healthcare utilization.
- Usage of study medications: dose at first prescription, duration of treatment (time on index medication), discontinuation and switch to another study drug
- The above mentioned characteristics per year – Time trends
- Usage of medication before index date will be categorized as:
    - Concurrent use: when the drug supply lasts until the index date or ends 1-30 days before the index date
    - Past use: when the drug supply ends 31-365 days before the index date
    - Non-use: no use in the year before the index date

9.8 Quality control

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 the statistical analysis plan and 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 at any time. We will abide by the Guidelines for Good Pharmacoepidemiology Practices (GPP, 2007). The study protocol is dependent on approval by ethics committee in research that review studies performed in Pereira University.

9.9 Limitations of the research methods

- Some variables to calculate CHA_2DS_2Vasc score and HAS-BLED are not available in the outpatient database and the linkage is still in process with the inpatient database to obtain that information, and therefore cannot be calculated for this study.
- 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).
- The database could have some missing information regarding hospitalizations.
- There is no formal assessment available on the representativeness of the Audifarma database. However, the patients registered in the database correspond to more than 150 cities including the most important and representative of the country with populations between 7000 and 8 million inhabitants. The distribution by age and sex of the persons affiliated to the insurers of the contributory system of the Colombian Health System, to which Audifarma dispenses drugs, is the same as that of the general population of the country with exception of one insurer which has 40% of the adult population over 45 years old versus the others whose percentage varies between 23 and 29%, which is that of Colombia.

9.10 Other aspects

Not Applicable

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. In this investigation we will use an automated database where the information of patients is anonymized and there is no need to obtain informed consent from patients.

CEIFE and GIFF 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 and GIFF 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. 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 (GPP, 2007).

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 [Revision 1]), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2014).

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.

The study results will be published following the 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. References

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Annex 1: List of stand-alone documents

None

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

Study title:
TREatment Pattern of **N**OACs (non-vitamin K oral anticoagulants) in Outpatient Users in Colombian **D**atabases – TREND Colombia

Study reference number: Not yet registered

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

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)	☒	☐	☐	
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)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative 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. incidence rate, absolute risk)	☒	☐	☐	9.1.1, 9.1.2
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1, 9.2
	4.2.2 Age and sex?	☐	☐	☒	
	4.2.3 Country of origin?	☒	☐	☐	
	4.2.4 Disease/indication?	☒	☐	☐	
	4.2.5 Duration of follow-up?	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1,9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

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

Comments:

This is only a descriptive drug utilisation study

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

This is a pilot study to evaluate the performance of the database and hence to understand the available information in the database

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				9.4
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)	☐	☐	☒	
9.1.3 Covariates?	☒	☐	☐	9.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☒	☐	☐	9.4
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 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6, 9.8

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?	☒	☐	☐	9.4, 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, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1, 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Dr. Luis A Garcia Rodriguez

Date: 28/Jan/2018

Signature: _____

Annex 3: Additional information

Not applicable