Boehringer Ingelheim

Non-interventional Study Protocol

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BI Investigational Product(s):	Dabigatran etexilate (Pradaxa®)
Title:	Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants. RE-QUOL study.
Brief lay title	Health related quality of life in patients on anticoagulants
Protocol version identifier:	1.0
Date of last version of protocol:	05 January 2017
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EU PAS register number:	EU PAS 16988
Active substance:	B01AE07 - Dabigatran etexilate
Medicinal product:	Dabigatran etexilate
Product reference:	EU/1/08/442
Procedure number:	EMEA/H/C/829
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein Germany
Joint PASS:	No
Research question and objectives:	There is a dearth of evidence regarding Health Related Quality of Life (HRQoL) in controlled and uncontrolled patients on oral anticoagulants. The present study has been designed to describe the HRQoL in patients with non valvular atrial fibrillation (NVAF) receiving conventional vitamin K antagonist (VKA) but no controlled and those controlled who received VKA or direct oral anticoagulant

	(DOAC). Primary objective: The primary objective of the study is to describe the HRQoL in uncontrolled patients treated with VKA and controlled patients treated with VKA or DOAC. Secondary objective: The secondary objective is to describe the profile of uncontrolled patients
Country(-ies) of study:	Spain
Author:	(Outsourced Trial Clinical Monitor) Mobile:
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein Germany
Date:	05 January 2017
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
AF	Atrial Fibrillation
CA	Competent Authority
!"# $%&'	!+./-*012- 3-4,0 54167,-89:-,0-.*1+.8 #/- ;< =>?8
(#&) *)+,-	%14@-0-A-66107*80,+B-CDE(#8*)764, F1*-4*-8#/- G>=H8&-I !40-/+,9
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
DMP	%404J4.4/-A-.0 K64.
DOAC	%1,-)0L,46 #.01)+4/764.0
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
MK(!D!	M6+@46 K34,A4)+21/164.)- !61.1)46 D,146 !++,F1.40+,
"#& 'NOP%	"9:-,0-.*1+.8 #@.+,A46,-.46 4.F 612-,57.)01+.8&0,+B;Q:+1.0?8 N6--F1./ 31*0+,9 +, :,-F1*:+*101+.8 O4@16- ERS8 P6,F<6?99-4,*?8 %,7/* 4.F #6)+3+6T
"SU+O	"-4603 ,-640-FU746109+5O15-
E!&S	E.F121F746*- &45-09S-:+,0
EP!	E.F-:-.F-.0 P031)*!+AA100--
ERS	E.0-,.401+.46R+,A461V-S401+
E&W	E.2-*01/40+,&10-W16-
OK(J	O+)46K34,A4)+21/164.)- J4.4/-,
O(PW	Left Ventricular Ejection Fraction
J#"	J4,B-01./ #703+,1V401+".+6F-,
R(#W	R+. '(462764, #0,146W1@,166401+.
L#!	L,46 4.01)+4/76401+.
&#P	&-,1+7*#F2-,*- P2-.0
&%	&04.F4,F%-21401+.
&#K	&0401*01#4669*1*K64.
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3. RESPONSIBLE PARTIES

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D-4A J-A@-, J-F1)46 #5541,*	
D,146161.1)46J+.10+,	;L70*+7,)-F?
D,146&0401*01)14.	
OK(J	
!++,F1.40+, E.2-*01/40+,	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Protocol date: 05 Jan 2017	**Study number:** 1160-0280	**Version/Revision:**	**Version/Revision date:**
Title of study:	Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants. RE-QUOL study		
Rationale and background:	The present study has been designed to describe the HRQoL in patients with non valvular AF receiving conventional VKA but no controlled and those controlled who received VKA or DOAC. The type of patients to be included in this study are those seen in Internal Medicine, i.e. elderly patients, chronically ill, mostly hospitalized, polymedicated, and at high thromboembolic and bleeding risk. The present study will provide valuable data about the HRQoL of these patients regarding their anticoagulation status (controlled or non-controlled).		
Research question and objectives:	There is a dearth of evidence regarding HRQoL in controlled and uncontrolled patients on oral anticoagulants. The present study has been designed to describe the HRQoL in patients with non valvular AF receiving conventional VKA but no controlled and those controlled who received VKA or DOAC. Primary objective: to describe the HRQoL in uncontrolled patients treated with VKA and controlled patients treated with VKA or DOAC. Secondary objective: to describe the profile of uncontrolled patients		
Study design:	This observational multicenter and cross-sectional study will be conducted in Departments of Internal Medicine from approximately 50 centers in Spain Approximately 500 patients seen in internal medicine are planned to be included in the study. To minimize selection bias at the patient level, consecutive patients from each site who meet entry criteria will be enrolled. The 3 participating autonomous communities planned are Madrid, Valencia and Andalucía. Patients should be included in a ratio 2:1, 2 patients controlled (VKA patients with a Time in Therapeutic range TTR ≥ 65% and all DOAC patients) per 1 patient uncontrolled (VKA patients with a TTR < 65%), due to the controlled patients comprise more treatments. Control will be considered when INR values are between 2 and 3. The design of the study impose an only visit to be performed that will		

	coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator. A specific therapeutic strategy has already been assigned based on routine practice, and without interference with the physician's prescription habits. The observational nature of the study is ensured as no diagnostic or therapeutic intervention outside of routine clinical practice will be applied.
Population:	Patients with non-valvular atrial fibrillation who are on the same anticoagulant therapy (VKA or DOAC) during at least 6 months and maximum 2 years will be included. The patient will be considered included when he/she agrees to participate in the study by signing the informed consent. The patient will be classified between controlled or uncontrolled group depending on the %TTR if VKA patients. If the %TTR collected from the analytical records was obtained by the Rosendaal method, VKA patients with a TTR < 65% will be allocated to the uncontrolled group and VKA patients with a TTR ≥ 65% will be allocated to the controlled group). If the %TTR was obtained by the direct method, the patient will be considered uncontrolled or controlled depending on whether the TTR value is < 60%. All DOAC patients will be allocated to the controlled group.
Variables:	Quality of life: HRQoL will be based on the patients' ratings on Sawicki questionnaire completed during the only study visit. This questionnaire includes 32 items grouped in 5 dimensions – treatment satisfaction, self-efficacy, strained social network, daily hassles and distress. Higher scores indicate lower HRQoL. Uncontrolled patient profile: demographic characteristics (age, gender, work status, life status, etc), CHA2DS2-VASc, HAS-BLED, AF diagnosis date, VKA treatment, time since treatment initiation, time since patient is uncontrolled (if assessable) left ventricular ejection fraction, Kidney function (creatinine clearance), concomitant diseases, concomitant treatments, frequency of visits to the physician, and history of thromboembolic and bleeding events
Data sources:	Data collection will be limited to those available in the medical records of selected patients and the questionnaire necessary to evaluate the primary objective of the study, of patients in whom a specific therapeutic strategy has already been assigned based on routine practice, and without interference with the physician's prescription habits
Study size:	It is planned that a total of approximately 330 patients will be recruited for the controlled group and 170 patients will be recruited for the uncontrolled group. Based on such sample size estimates, categorical variables of binomial proportions (e.g. gender) will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in Table 9.5: 1, according to the prevalence of the attribute.
Data analysis:	To describe the quality of life among patients controlled and uncontrolled: The primary outcome of the study is the health-related

	quality of life as measured by the Sawicki questionnaire. The scores of each individual question will be summarized descriptively in the controlled and uncontrolled patients. In addition, the summary score for each dimension of the questionnaire will be calculated for each patient by dividing the total score by the number of items included in that dimension and summarized in the same way as the individual questions. To describe the profile of uncontrolled patients treated with vitamin K antagonists: The specified variables in Section 9.3.2.2 [demographic characteristics (age, gender, work status, life status, etc), CHA2DS2-VASc, HAS-BLED, AF diagnosis date, VKA treatment, time since treatment initiation, time since patient is uncontrolled (if assessable) left ventricular ejection fraction, Kidney function (creatinine clearance), concomitant diseases, concomitant treatments, frequency of visits to the physician, and history of thromboembolic and bleeding events] will be summarized descriptively. Missing data will not be imputed and will be left as lost.
Milestones:	Note that the times described below may be modified by the administrative processing periods for study initiation - Final Protocol: January 2017 - start of data collection: March 2017 - end of data collection: September 2017 - final study report: December 2017

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
IEC approval	January 2017
Start of data collection	March 2017
End of data collection	September 2017
Registration in the EU PAS register	December 2016
Final report of study results:	December 2017

7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) affects 1-2% of general population, but specially persons between 80 - 85 years, in whom the prevalence can reach 16% [1-3]. The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocoumarol. The management of these agents remains problematic because they need routine coagulation monitoring, clinical surveillance and continuous patient education, affecting to their daily habits and in consequence to their quality of life [4]. Also, data show that 80% of patients continue receiving acenocoumarol in Spain, with a percentage of International Normalized Ratio (INRs) in therapeutic range between 44%-59% [5,6], and mean time in therapeutic range (TTR) of 64% [5].

The direct oral anticoagulants (DOAC) maintain the benefits of anticoagulant therapy and may increase perception of quality of life among patients because they not necessitate the strict monitoring required for VKA. On the other hand maintaining a stable level of anticoagulation with DOACs prevents uncontrolled patients as well as the increased number of monitoring visits for this reason. Theoretically, this fact would have positive implications in quality of life. However, the available evidence from the study of quality of life, does not suggest that patients have large decrements in their quality of life because of suffering from FA. In this sense, the study of Roalfe et al., cross sectional in 1762 patients over 75 years and suffering AF, concluded that in absence of comorbidity, chronic AF has little impact on generic QoL [7]. This suggests that treatment strategies should focus on the prevention of complications such as stroke, so it is necessary to go depth in the study of the anticoagulant therapy and the impact in QoL.

HRQoL was assessed in a sub-group of the overall RE-LY population to measure the effect of the choice of anticoagulant during a stable phase of treatment in the first year of the study, in patients without outcome events, such as strokes or major bleedings [8] . HRQoL was assessed using the EQ-5D, a generic measure of health outcome. Over the course of one year, all anticoagulated patients without outcome events had stable HRQoL. Scores between dabigatran and warfarin were comparable. There is a dearth of evidence regarding HRQoL in controlled and uncontrolled patients on oral anticoagulants.

The present study has been designed to describe the HRQoL in patients with non valvular AF receiving conventional VKA but no controlled and those controlled who received VKA or DOAC.

Since the type of patients to be included in this study is that seen in Internal Medicine, i.e. elderly patients, chronically ill, mostly hospitalized, polymedicated, and at high thromboembolic and bleeding risk, the present study will provide valuable data about the HRQoL of these patients regarding their anticoagulation status (controlled or non-controlled).

8. RESEARCH QUESTION AND OBJECTIVES

The present study has been designed to describe the HRQoL in patients with non valvular AF receiving conventional VKA but no controlled and those controlled who received VKA or DOAC.

The primary objective of the study is to describe the HRQoL in uncontrolled patients treated with VKA and controlled patients treated with VKA or DOAC.

The secondary objective is to describe the profile of uncontrolled patients

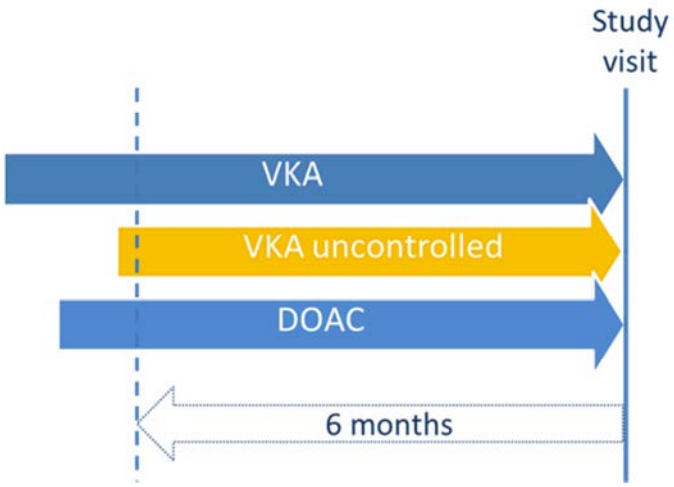
9. RESEARCH METHODS

9.1 STUDY DESIGN

This observational multicenter and cross-sectional study will be conducted in Departments of Internal Medicine from approximately 50 centers in Spain.

The design of the study impose an only visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator. A specific therapeutic strategy has already been assigned based on routine practice, and without interference with the physician's prescription habits. The observational nature of the study is ensured as no diagnostic or therapeutic intervention outside of routine clinical practice will be applied. Figure 1 shows the design of the study.

Figure 1. Design of the study

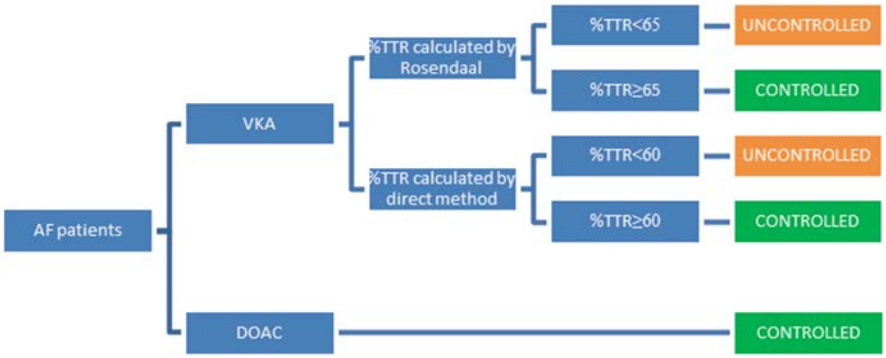


9.2 SETTING

Approximately 500 patients seen in internal medicine are planned to be included in the study. To minimize selection bias at the patient level, consecutive patients from each site who meet entry criteria will be enrolled. Patients should be included in a ratio 2:1, 2 patients controlled (VKA patients with a TTR ≥ 65% and all DOAC patients) per 1 patient uncontrolled (VKA patients with a TTR < 65%), due to the controlled patients comprise more treatments.

The patient will be classified between controlled or uncontrolled group depending on the %TTR if VKA patients. If the %TTR collected from the analytical records was obtained by the Rosendaal method, VKA patients with a TTR < 65% will be allocated to the uncontrolled group and VKA patients with a TTR ≥ 65% will be allocated to the controlled group. If the %TTR was obtained by the direct method, the patient will be considered uncontrolled or controlled depending on whether the TTR value is < 60%. All DOAC patients will be allocated to the controlled group. See figure 2 below.

Figure 2. Patient allocation



If %TTR is not available on analytical records, investigator will calculate it using the last 6 months INR values (at least 4 INR values during the last 6 months). To perform the calculation, it is recommended to avoid periods of anticoagulation initiation and periods with treatment interruptions due to surgery or bleedings.

9.2.1 Study sites

Internal medicine specialists from Hospital sites regularly prescribing DOACs and VKA for stroke prevention in non-valvular atrial fibrillation according to the respective Summary of Product Characteristics will participate.
The study will be performed among 3 autonomous communities in Spain: Madrid, Comunidad Valenciana and Andalucía.

9.2.2 Study population

To be eligible to participate in the study, patients must meet the following selection criteria:

Inclusion criteria

Patients will be included in the study if all of the following criteria are met:

1. The patient is willing and provides written informed consent to participate in this study.
2. The patient is at least 18 years of age
3. The patient has a diagnosis of non-valvular atrial fibrillation
4. The patient is on the same anticoagulant therapy (VKA or DOAC) during at least 6 months and maximum 2 years.
5. If treated with VKA, availability of %TTR in past analytical records or enough amount of INR measures to calculate it.

Exclusion criteria:

Patients will be excluded from participating in this study if 1 or more of the following criteria are met:

1. Current participation in any clinical trial of a drug or device
2. Contraindication to the use of DOAC or VKA as described in the Summary of Product Characteristics (SmPC).

A log of all patients included into the study (having given informed consent) will be maintained in the study file at the study site.

9.2.3 Study visits

The design of the study impose an only visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator. A specific therapeutic strategy has already been assigned based on routine practice, and without interference with the physician's prescription habits.

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study
3. Violation of the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

The following variables will be obtained at the unique study visit if available in patient medical records:

Variables	Study visit
Informed consent	X
Selection criteria	X
Date of visit	X
Demographic data: age, sex, race, work status, life status, weight, height	X

Variables	Study visit
Non Valvular Atrial Fibrilation (NVAF) history: age at diagnosis, disease duration	X
Concomitant diseases	X
Physical examination: height, weight and BMI	X
Creatinine clearance calculated via Cockcroft-Gault Formula / Creatinine values if available from already existing lab report (to be calculated in eCRF)	X
Left Ventricular Ejection Fraction (LVEF)-quantitative	X
LVEF-qualitative Normal (≥50%), slightly depressed (49-31%), moderately (40-31%), severely (≤30%)	X
TTR	X
CHA_2DS_2VASc score (to be calculated in the eCRF)	X
HAS-BLED score (to be calculated in the eCRF)	X
VKA treatment	X
Time since treatment initiation	X
Time since patient is uncontrolled	X
Concomitant treatments	X
Frequency of visits to the physician	X
History of thromboembolic and bleeding events	X
HRQoL questionnaire (Sawicki)	X

9.3.1 Exposures

Patients in this study will have been prescribed a specific anticoagulant treatment for their NVAF at least 6 months prior to study initiation. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional. The study population will be treated with VKA or DOAC according to the approved local Summary of Product Characteristics (SmPC).

As this is a non-interventional observational study, designed to reflect as faithfully as possible real-life clinical practice, the decision to start treatment with VKA or DOAC is prior

to and independent of the participation of the patient in the study and based on medical judgment criteria and routine clinical practice. In addition, no intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome is the health-related quality of life and will be obtained with the results of the sawicki questionnaire at study visit. The questionnaire to be used is the validated spanish adaptation [9] of the original questionnaire [10]. The questionnaire includes 32 items grouped in 5 dimensions. Patients will estimate the impact of each item on their self-perceived treatment-related quality of life on a scale of 1 (total disagreement) to 6 (total agreement). The 5 dimensions are general treatment satisfaction, self-efficacy, strained social network, daily hassles and distress. A lower score indicates greater higher quality of life and a higher score indicates lower quality of life. The questionnaire is self-completed (see annex no 3).

9.3.2.2 Secondary outcomes

The secondary outcome is the uncontrolled patient profile and will be defined by the following variables collected from patient medical records: demographic characteristics (age, gender, work status, life status, etc), CHA2DS2-VASc, HAS-BLED, AF diagnosis date, VKA treatment, time since treatment initiation, time since patient is uncontrolled (if assessable) left ventricular ejection fraction, Kidney function (creatinine clearance), concomitant diseases, concomitant treatments, frequency of visits to the physician, and history of thromboembolic and bleeding events.

9.3.3 Covariates

Not applicable.

9.4 DATA SOURCES

Data collection will be limited to those available in the medical records of selected patients. Patients will be asked to answer the questionnaire necessary to evaluate the primary objective of the study at the unique study visit.
Patient demographic data, concomitant therapies and concomitant diseases will be completed based on patient's medical records. Creatinine clearance for assessment of kidney function will be calculated within the electronic Case Report Form (eCRF), by entering creatinine values from existing lab reports, if available.

9.5 STUDY SIZE

It is planned that a total of approximately 330 patients will be recruited for the controlled group and 170 patients will be recruited for the uncontrolled group.

Based on such sample size estimates, categorical variables of binomial proportions (e.g. gender) will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in Table 9.5: 1, according to the prevalence of the attribute.

Table 9.5: 1 Width of 95% confidence interval by prevalence of attribute

Prevalence of attribute		Sample size	
		170	330
10%	Expected n	17	33
	95% CI width	9.60	6.78
20%	Expected n	34	66
	95% CI width	12.54	8.91
30%	Expected n	51	99
	95% CI width	14.27	10.16
40%	Expected n	68	132
	95% CI width	15.20	10.84
50%	Expected n	85	166
	95% CI width	15.50	11.05

* Calculations are based on the Clopper-Pearson method.

9.6 DATA MANAGEMENT

The data will be entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous.

When data management is outsourced, the designated contract organization will be responsible for the development and implementation of the data management plan and preparation of the data handling report according to the sponsor´s standards.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

Analyses will be performed by Boehringer Ingelheim's designees. The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria).

In this non-interventional study, cross-sectional data at study visit will be collected for non-valvular AF patients with a VKA or DOAC therapy. Once the study has been completed and all data from the last patient have been recorded, the database will be closed and statistical analysis will be performed.

The proposed methods for statistical analysis presented below are a summary of the methods that will be applied in the study to analyze the data collected and to answer the study objectives. Missing data will not be imputed and will be left as lost.

Summary statistics for continuous variables will include the N, mean, standard deviation, minimum, Q1 (lower quartile), median, Q2 (upper quartile), and maximum value; tabulations of categorical variables will present all possible categories and will display the number of observations per category as well as percentages. Estimates will be presented with 95% confidence intervals for the variables of interest. Additional details of the planned analysis will be provided in the statistical analysis plan (SAP).

9.7.1 Main analysis

The primary outcome of the study is the health-related quality of life as measured by the Sawicki questionnaire. The scores of each individual question will be summarized descriptively in the controlled and uncontrolled patients. In addition, the summary score for each dimension of the questionnaire will be calculated for each patient by dividing the total score by the number of items included in that dimension and summarized in the same way as the individual questions.

9.7.2 Further analysis

To describe the profile of uncontrolled patients treated with vitamin K antagonists, the specified variables in Section 9.3.2.2 will be summarized descriptively.

9.8 QUALITY CONTROL

The eCRF will include programmable edit checks to obtain feedback if data is missing, out of range, illogical or potentially erroneous. These checks will be performed once data is entered into the eCRF. Thus the data entered in to the eCRF will be validated within the system and

the physician will receive alerts for missing or inconsistent data. In case any changes of already entered data will be required, an audit trail will be available.

Strict and continuous quality control will be maintained to ensure the accuracy and scientific rigor of the data obtained, maintaining uniform conditions for collecting the information. Quality control will be carried out by qualified personnel designated for this purpose.
A quality assurance audit/inspection of his study may be conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent document of this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study is only descriptive and is not designed to allow for causal inference regarding the impact of OAC control on HRQoL.
Apart from inherent limitations of observational studies, a criticism could be the use of a specific questionnaire of HRQoL originally designed for patients receiving oral anticoagulation with vitamin K and that could ignore other aspects related to quality of life in atrial fibrillation as previously reported

9.10 OTHER ASPECTS

Not applicable

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all eCRFs, and written informed consents. The accuracy of the data may be verified by reviewing source documents.

9.10.3 Completion of study

The EC/competent authority in Spain needs to be notified about the end of the study (last patient out) or early termination of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the

study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the competent authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

All ADRs , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug

- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 4.0, in the (e)CRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Pradaxa, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **serious ADRs** associated with Pradaxa®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Pradaxa®	immediately within 24 hours
All **non-serious ADRs** associated with Pradaxa®	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Pradaxa according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the Study Report.
The results of this study may be published in a national journal and presented in regional or national congresses.

13. REFERENCES

13.1 PUBLISHED REFERENCES

[1] Barrios V, Calderon A, Escobar C, de la Figuera M. Patients with atrial fibrillation in a primary care setting: Val-FAAP study. Rev Esp Cardiol (Engl Ed) 2012;65:47-53.

[2] Cea-Calvo L, Redon J, Lozano JV, et al. [Prevalence of atrial fibrillation in the Spanish population aged 60 years or more. The PREV-ICTUS study]. Rev Esp Cardiol 2007;60:616-24.

[3] Gomez-Doblas JJ, Muniz J, Martin JJ, et al. Prevalence of atrial fibrillation in Spain. OFRECE study results. Rev Esp Cardiol (Engl Ed) 2014;67:259-69.

[4] Alegret JM, Vinolas X, Arias MA, et al. New oral anticoagulants vs vitamin K antagonists: benefits for health-related quality of life in patients with atrial fibrillation. Int J Med Sci 2014;11:680-4.

[5] Ansell J, Hollowell J, Pengo V, Martinez-Brotons F, Caro J, Drouet L. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). J Thromb Thrombolysis 2007;23:83-91.

[6] Clua Espuny JL, Dalmau Llorca MR, Aguilar MC. [Characteristics of oral anti-coagulation treatment in high-risk chronic auricular fibrillation]. Aten Primaria 2004;34:414-9.

[7] Roalfe AK, Bryant TL, Davies MH, et al. A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. Europace 2012;14:1420-7.

[8] Monz BU, Connolly SJ, Korhonen M, Noack H, Pooley J. Assessing the impact of dabigatran and warfarin on health-related quality of life: results from an RE-LY sub-study. Int J Cardiol 2013;168:2540-7.

[9] Sanchez GR, Yanes BM, Cabrera MA, Ferrer Garcia-Borras JM, Alvarez NR, Barrera LE. [Cross-cultural adaptation of a questionnaire for measuring the quality of life of patients taking oral anticoagulants]. Aten Primaria 2004;34:353-9.

[10] Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. Working group for the Study of Patient Self-Management of Oral Anticoagulation. JAMA 1999; 281: 145-50.

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Title
<1>	Patient information and Informed Consent Form
<2>	Investigator List
<3>	Statistical Analysis Plan (SAP)
<4>	Data Management Plan (DMP)
<5>	Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
<6>	Pregnancy Monitoring Form

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants. RE-QUOL study.

Study reference number:
1160-0280

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Study progress reports to Ethics committee and health authorities will be done annually according to spanish regulations.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Exploratory study

[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?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
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:

Descriptive study. No measures of occurrence or measures of association are performed

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
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2
	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

Comments:

Cross-sectional study. No follow-up is carried out

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Observational study. Patients treated as per routine clinical practice.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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)	☒	☐	☐	9.3

Comments:

Descriptive outcomes

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:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

This study is only descriptive

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:

This study is only descriptive

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates?	☐	☐	☒	
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)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.2

Comments:

Coding system for exposure and outcomes will be described in SAP

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?	☐	☐	☒	

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?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

This study is only descriptive

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

Comments:

Observational study of routine clinical practice.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.2
12.1.2 Information bias?	☐	☐	☒	
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)	☒	☐	☐	9.2

Comments:

This study is only descriptive

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

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

ANNEX 3. ADDITIONAL INFORMATION

Spanish adaptation of the Sawicki questionnaire:

1. Su tratamiento le hace sentir preocupado o estresado	1	2	3	4	5	6
2. El esfuerzo por controlar su coagulación sanguínea le produce molestias cuando está fuera de casa	1	2	3	4	5	6
3. Su tratamiento le limita para organizar su tiempo libre como quiere	1	2	3	4	5	6
4. Está insatisfecho con la cantidad de tiempo que invierte en controlar su coagulación	1	2	3	4	5	6
5. Cree que ha aprendido a controlar su tratamiento	1	2	3	4	5	6
6. El riesgo de hacerse heridas le limita para llevar a cabo sus tareas domésticas	1	2	3	4	5	6
7. Evita realizar ciertas actividades (p. ej. Montar en bicicleta) por el riego de accidentes	1	2	3	4	5	6
8. Su tratamiento preocupa a sus familiares	1	2	3	4	5	6
9. Puede afrontar los problemas que surgen relacionados con su tratamiento	1	2	3	4	5	6
10. Le preocupa su salud en el futuro	1	2	3	4	5	6
11. Tiene miedo de realizar ejercicio por el miedo de hacerse una herida	1	2	3	4	5	6
12. Está insatisfecho con el tiempo que le lleva conseguir los resultados	1	2	3	4	5	6
13. Le preocupa que su tratamiento pudiera acortar su vida	1	2	3	4	5	6
14. Le disgusta tener que planear sus actividades con antelación	1	2	3	4	5	6
15. Le preocupa la incertidumbre que siente mientras espera los resultados	1	2	3	4	5	6
16. Ve menos a sus amigos desde que sigue este tratamiento	1	2	3	4	5	6
17. Evita salir de vacaciones porque es incapaz de conocer los efectos negativos que tienen los diferentes alimentos en su tratamiento	1	2	3	4	5	6
18. Está bien informado de lo que debe hacer para conseguir unos resultados dentro de los límites adecuados	1	2	3	4	5	6
19. Se siente dependiente de su medicación anticoagulante	1	2	3	4	5	6
20. Evita viajar porque tiene miedo de no recibir tratamiento adecuado en el caso de que sus resultados estén demasiado altos o bajos	1	2	3	4	5	6

21. Está harto de la cantidad de tiempo que pierde en el médico	1	2	3	4	5	6
22. Practicaría más deporte si no tomara anticoagulantes	1	2	3	4	5	6
23. Tiene problemas en el trabajo por sus frecuentes faltas a causa del tratamiento	1	2	3	4	5	6
24. Está seguro de poder controlar su tratamiento	1	2	3	4	5	6
25. Tiende a preocuparse por las cosas	1	2	3	4	5	6
26. A pesar de las visitas habituales al médico, cómo se siente de limitado	1	2	3	4	5	6
27. Le molesta que mucha gente no comprenda los problemas relacionados con su tratamiento	1	2	3	4	5	6
28. Cuando va al dentista o a otros médicos. Está preocupado por si no saben lo suficiente sobre la anticoagulación	1	2	3	4	5	6
29. Su tratamiento ha afectado a su vida sexual	1	2	3	4	5	6
30. Le molesta ser tratado como un inválido	1	2	3	4	5	6
31. Está preocupado por los efectos secundarios de su tratamiento anticoagulante	1	2	3	4	5	6
32. Le preocupa la reacción de otras personas ante su tratamiento	1	2	3	4	5	6

Opciones de respuesta

1=Nada

2=Muy poco

3=Poco

4=Algo

5=Bastante

6=Mucho

Puntuación:

Satisfacción	
Autoeficacia	
Estrés	
Limitaciones diarias	
Alteraciones sociales	

APPROVAL / SIGNATURE PAGE

Document Number: c14917649 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Non-Interventional, cross-sectional study to describe health-related quality of life among controlled and uncontrolled patients with nonvalvular atrial fibrillation on anticoagulants. RE-QUOL study.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medical Affairs		10 Jan 2017 10:01 CET
Approval-Medical		10 Jan 2017 10:51 CET
Approval- Safety Evaluation Therapeutic Area		10 Jan 2017 13:37 CET
Author-Trial Statistician		10 Jan 2017 19:06 CET
Approval-Therapeutic Area		13 Jan 2017 11:18 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed