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Non-interventional Study Protocol

Document Number:	**c28106106-01**
BI Study Number:	1160-0297
BI drug in the scope of this NIS:	Dabigatran etexilate (Pradaxa®)
Title:	Non-Interventional, cross-sectional study to describe NOACs management in elderly patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-BELD Study
Brief lay title	This study observes the usage of non-vitamin K antagonist oral anticoagulants (NOACs) in elderly patients with a heart rhythm disorder in Spain
Protocol version identifier:	1
Date of last version of protocol:	*Not applicable*
PASS:	No
EU PAS register number:	Study will be registered in EU PAS register
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):	MAH: [redacted] This study is initiated, managed and sponsored by: [redacted]
Joint PASS:	No

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Research question and objectives:	This study has been designed in order to describe the current non-vitamin K antagonist oral anticoagulants (NOACs) management in elderly patients in Spain. **Primary objective**: To describe the pattern of usage of NOACs prescribed according to their Summary of Product Characteristics (SmPC), by current NOAC type and dose, in elderly patients (≥75 years-old) with non-valvular atrial fibrillation (NVAF) at the time of the study visit. **Secondary objectives:** To describe patients characteristics at the time of the study visit by current NOAC type stratified by duration since first NOAC initiation. To describe OAC treatment management since first NOAC initiation until the study visit by duration since first NOAC initiation: previous vitamin K antagonists (VKA) treatment, first NOAC treatment duration, dose changes, switch between NOACs and reasons for switch, total NOAC treatment duration and additional antiplatelet treatment. To describe the Clinical Frailty Scale grading, CFS at the time of the study visit, by current NOAC type. To describe first NOAC usage by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation. [redacted]
Country(-ies) of study:	Spain
Author:	[redacted] Mobile: [redacted]
Marketing authorisation holder(s):	MAH: [redacted] This study is initiated, managed and sponsored by: [redacted]

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	[redacted]
MAH contact person:	*Not applicable*
EU-QPPV:	*Not applicable*
Signature of EU-QPPV:	*Not applicable*
Date:	24 May 2019

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical, Therapeutic, Chemical classification system
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CFS	Clinical Frailty Scale
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age (> 75),Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, SexCategory
CI	Confidence Interval
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
DMP	Data Management Plan
DVP	Data Validation Plan
EHRA	European Heart Rhythm Association
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol.
ICH	Intracranial hemorrhage
ICH-GCP	Harmonized Tripartite Guideline for Good Clinical Practice
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder Activities
NIS	Non-Interventional Study
NYHA	New York Heart Association
NOAC	Non-vitamin K antagonist oral anticoagulant
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
SAHS	Sleep apnoea-hypopnoea syndrome
SAP	Statistical Analysis Plan

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SMF	Study Master File
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
TIA	Transitory ischemic attack
TTR	Time in Therapeutic range
VKA	Vitamin K Antagonist

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3. RESPONSIBLE PARTIES

Sponsor representatives:

Medical Advisor cardiovascular	[redacted]
Medical Project [redacted]	
Trial Statistician	
GPV Study coordination	

Coordinating Investigators:

[redacted]	[redacted]

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: B01AE07 - Dabigatran etexilate			
Protocol date: 24 May 2019	**Study number:** 1160-0297	**Version/Revision:** N/A	**Version/Revision date:** N/A
Title of study:	Non-Interventional, cross-sectional study to describe NOACs management in elderly patients with non-valvular atrial fibrillation (NVAF) in Spain.		
Rationale and background:	Atrial fibrillation (AF) is the most frequent cardiac arrhythmia in clinical practice. AF affects between 1-2% of general population, but especially in patients aged ≥80 years prevalence can reach between 9-10% up to 17% of these patients (1-4). It is known that older age is an important risk factor for patients with AF and it is associated with a four to five fold increased risk of embolic stroke and with an estimated increased stroke risk of 1.45-fold per decade in aging (4). Additionally, aging is also associated with an increased risk of major bleeding with oral anticoagulant therapy (5). The current clinical guidelines on the usage of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation EHRA 2018 (6) recommend that patients with an embolic risk factor receive preventive anticoagulant therapy, with special emphasis in the frail and older patients. The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocumarol. The management of these agents remains problematic because they require frequent routine coagulation monitoring and dose adjustment to maintain the intensity of anticoagulation within a safe and effective range. In elderly patients (≥70 years) with NVAF and treated with VKA, TTR should be maintained ≥60% to prevent thromboembolism and all-cause death and TTR <40% should be avoided to prevent major hemorrhage (7). NOACs, with a similar benefit as warfarin but with greater safety, even in a very old population, offers a new possibility of therapeutic strategy in clinical practice. In patients 75 years and older, randomized trials have shown NOAC to be as effective as warfarin, or in some cases superior, with an overall better safety profile, consistently reducing rates of intracranial hemorrhages (4). The non-vitamin K antagonist oral anticoagulants (NOAC) maintain the benefits of anticoagulant therapy and may increase perception of quality of life and satisfaction among patients because they not necessitate the strict monitoring required for VKA.		

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However, the usage of NOACs in the elderly population in routine clinical practice show deficiencies and can be optimized, showing that under-dosing of NOACs is common in this population (8). Other studies suggest that as many as 34% of elderly patients on NOACs were on an incorrect dose or were prescribed the medication despite a contraindication (9) and more than half were found to be on an inappropriately low dose (10). These errors could lead to increased bleeding risk and/or increased risk of treatment failure (11). In general, oral anticoagulants (OAC) remain underutilized in older age groups.

The benefit / risk balance of anticoagulation in elderly patients and AF has already been analyzed in different studies. The risk of hemorrhagic stroke was lower in the NOAC group than in the warfarin group (12). In another study, the rates of hemorrhagic and thromboembolic events in patients older than 90 years under treatment with NOACs at VKAs were comparable (13). Elderly patients treated with high doses of NOACs had a statistically similar incidence of stroke, a lower statistical incidence of intracranial hemorrhage (ICH) and a higher net clinical benefit, compared with those treated with low doses (14).

In addition to age, other characteristics of the patient should be considered at the time of selecting an appropriate anticoagulant treatment. The female sex as a risk factor for stroke and thromboembolism in patients with atrial fibrillation should also be considered. Thromboembolic risk related to atrial fibrillation (AF) may differ between men and women, and this may affect the response to anticoagulant therapy and warrant a sex-specific management of patients with AF. Bleeding risk seems to be higher in women mainly related with the women's lower body weight (15) and women with AF are at increased risk of stroke, particularly elderly women (16). Comprehensive stroke risk assessment, including sex as a risk factor, should be undertaken in all AF patients.

In conclusion, challenges remain about NOACs usage in NVAF in elderly patients and effective strategies should be developed to improve the outcomes in elderly patients in clinical practice. An integral geriatric assessment (17) and patient profile (18) should be considered, including the age, sex, frailty (19) and comorbidities, before initiating oral anticoagulation. Based on these assumptions, it's considered interesting to describe the current the anticoagulation management in elderly patients in Spain.

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Study design:	This is an observational, multicenter and cross-sectional study in NVAF elderly patients currently on NOAC treatment for their stroke prevention. It will be conducted in approximately 50 sites in Spain, by investigators from the following specialties: cardiologists, hematologists and geriatricians. It is planned to have a 9-month recruitment period from first site initiated, or until the sample size is achieved. The design of the study impose a single visit to be performed for the		

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	informed consent signature and data collection that will coincide with one of those performed by the patients as part of the routine follow-up of their disease, without interfering with the usual clinical practice of the investigator. A specific therapeutic strategy has already been assigned to each included patient, 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.		

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Population:	Approximately 500 elderly patients with NVAF currently on NOAC treatment 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 number of patients per site to be included in the study will be initially set up to a maximum of 10 patients per site. Once the 50% of the participating sites have been initiated, the recruitment will become competitive until the end of the study and the limitation of 10 patients per site will be removed to allow sites to continue with the recruitment, until overall sample size is achieved. Patients will be included in the study if all of the following criteria are met: 1. Patients are willing and provide written informed consent prior to participate in this study 2. Patients ≥ 75 years-old at the time of the study visit. 3. Patients with a diagnosis of non-valvular atrial fibrillation (NVAF). 4. Patients who are being treated with NOAC treatment according to the indication approved in the SmPC: 5. Patients who have started the NOAC treatment at least 3 months prior to the study visit. Patients will be excluded from participating in this study if the following criterion is met: 1. Current participation in any clinical trial of a drug or device. 2. Patients who have any contraindication for NOAC treatment, according to the SmPC.		
Variables:	For the primary and secondary objectives, the following variables will be obtained, if available, at the time of study visit (enrolment) and at the time of first NOAC initiation. <u>Variables collected for the primary objective:</u> - Current NOAC (active substance, dose, start date). <u>Additional variables collected for the secondary objectives:</u> - Demographic characteristics: Age, sex, height, weight, BMI, caregiver (yes/no), place where patient is living.		

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- Smoking and alcohol consumption.
- Analytical results (from last available blood sample analysis):
  - Kidney function.
  - Liver function.
  - Hemoglobin and platelet levels.
- NVAF diagnosis date, type, Modified EHRA scale for AF related symptoms (23).
- Procedures and interventions: Cardioversion / Ablation; Coronary interventions: Percutaneous coronary intervention (PCI)/Coronary Artery Bypass Grafting (CABG); Pacemaker carrier.
- History of thromboembolic and bleeding events.
- History and current antiplatelet treatment.
- Other concomitant treatments (total number of current concomitant treatments; Type).
- Comorbidities and Clinical Risk Factors: Heart failure NYHA classification (24), LVEF %); Coronary artery disease, diabetes, peripheral vascular disease, diabetes, chronic kidney disease, liver disease, cancer, Sleep apnoea-hypopnoea syndrome (SAHS) (yes/no), hypertension, previous stroke, transitory ischemic attack (TIA) or thromboembolism, vascular disease, ischemic cardiomyopathy, vascular disease, comorbidity Charlson index (25).
- CHA_2DS_2-VASc score.
- HAS-BLED score.
- Clinical Frailty Scale (CFS) grading – modified Rockwood scale (19).
- In case of previous treatment with VKA: treatment duration and reasons for VKA treatment switch.
- NOAC treatment management (since first NOAC until study visit):
  - NOAC dose changes.
  - NOAC switch.
  - First NOAC start date, for primary or secondary prevention.

No specific safety outcome has been defined in this study.

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Data sources:	Data will be collected through an eCRF which will include all the study variables. Investigator will enter patient data in eCRF. Variables collected at the time of the study visit (including those related to the first NOAC initiation) will be obtained based on and limited to those available in the medical records of the selected patients. Demographic characteristics, smoking habit and alcohol consumption may be asked to the patient at the study visit if not available in the medical records. LVEF measurement will be obtained from the last images available for the patient. Clinical Frailty Scale (19), Modified EHRA scale for AF related symptoms (23), NYHA classification for heart failure (24), CHA2DS2-VASc and HAS-BLED scores will be assessed by the investigators at the study visit by evaluating the patient's functional status and medical records and the values will be directly included in the eCRF. Final score for the Comorbidities Charlson Index (25) will be automatically calculated based on the answers individually entered by the investigator in the eCRF for each index item. Any required missing data to calculate the score for the scales or the Comorbidities Charlson Index may be asked to the patient at the study visit if not available in the medical records and should be documented, however the final score number obtained by the investigator from this information will not need to be included in medical records.		
Study size:	It is planned that a total of approximately 500 patients will be recruited for the study.		
Data Analysis	A Data Management Plan (DMP) and Statistical Analysis Plan (SAP) will be prepared to describe all processes, treatment and specifications for data collection, cleaning, validation and analysis. Since the study is essentially descriptive, the variables included in the study objectives will be analyzed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges. 95% confidence intervals will be provided as appropriate. All eligible patients (all enrolled patients fulfilling all inclusion criteria and no exclusion criteria) will be included in the analysis. Missing data		

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will not be imputed. Number of missing values will be presented for each outcome.

For the primary objective, the pattern of usage of NOAC will be described as the percentage of patients by NOAC type and dose.

[redacted]

For the secondary objectives, the following descriptive analyses are planned:

1. Patient's characteristics at the time of the study visit will be summarized descriptively by current NOAC type. [redacted]
2. For OAC treatment management, descriptive analysis of previous VKA treatment (yes/no), VKA treatment duration in years, reason for switch to NOAC, first NOAC treatment duration, first NOAC dose and dose changes, switch to new NOAC, new NOAC treatment duration, new NOAC dose and dose changes, reason for switch will be done. Duration since NVAF diagnosis until first NOAC initiation, duration of first NOAC treatment and total time in NOAC treatment will be described. Also, the number of patients that switched their first NOAC and mean number of switches will be presented. Antiplatelet treatment description will be also considered for this outcome.

   [redacted]
3. Clinical Frailty Scale (19) grading at the time of the study visit by current NOAC type will be described as the number of patients on each category of frailty, and summarized descriptively in the following two categories: Frailty patients (CFS scoring >4) and Non-frailty patients (CFS scoring ≤4).
4. First NOAC usage will be described by NOAC type, for primary or secondary prevention, at the time of first NOAC initiation.

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Milestones:	The times described below may be modified by the administrative processing periods for study initiation - *EU PAS Register*: May 2019 - *Final Protocol:* May 2019 - *Start of data collection:* July 2019 - *End of data collection:* April 2020 - *Final study report:* November 2020		

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5. AMENDMENTS AND UPDATES

None

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6. MILESTONES

Table 1 Milestones

Milestone	**Planned Date**
EU PAS Register	30 May2019
EC approval	31 June 2019
Start of data collection	25 July 2019
End of data collection	27 April 2020
Final report of study results:	25 November 2020

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7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia in clinical practice. AF affects between 1-2% of general population, but especially in patients aged ≥80 years prevalence can reach between 9-10% up to 17% of these patients (1-4). It is known that older age is an important risk factor for patients with AF and it is associated with a four to five fold increased risk of embolic stroke and with an estimated increased stroke risk of 1.45-fold per decade in aging (4). Additionally, aging is also associated with an increased risk of major bleeding with oral anticoagulant therapy (5).

The current clinical guidelines on the usage of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation EHRA 2018 (6) recommend that patients with an embolic risk factor receive preventive anticoagulant therapy, with special emphasis in the frail and older patients.

The first oral anticoagulants to prevent the risk of thromboembolic events in AF were the vitamin K antagonists (VKA) warfarin and acenocumarol. The management of these agents remains problematic because they require frequent routine coagulation monitoring and dose adjustment to maintain the intensity of anticoagulation within a safe and effective range. In elderly patients (≥70 years) with NVAF and treated with VKA, TTR should be maintained ≥60% to prevent thromboembolism and all-cause death and TTR <40% should be avoided to prevent major hemorrhage (7). NOACs, with a similar benefit as warfarin but with greater safety, even in a very old population, offers a new possibility of therapeutic strategy in clinical practice. In patients 75 years and older, randomized trials have shown NOAC to be as effective as warfarin, or in some cases superior, with an overall better safety profile, consistently reducing rates of intracranial haemorrhages (4). The non-vitamin K antagonist oral anticoagulants (NOAC) maintain the benefits of anticoagulant therapy and may increase perception of quality of life and satisfaction among patients because they not necessitate the strict monitoring required for VKA.

However, the usage of NOACs in the elderly population in routine clinical practice show deficiencies and can be optimized, showing that under-dosing of NOACs is common in this population (8). Other studies suggest that as many as 34% of elderly patients on NOACs were on an incorrect dose or were prescribed the medication despite a contraindication (9) and more than half were found to be on an inappropriately low dose (10). These errors could lead to increased bleeding risk and/or increased risk of treatment failure (11). In general, OAC remains underutilized in older age groups.

The benefit / risk balance of anticoagulation in elderly patients and AF has already been analyzed in different studies. The risk of hemorrhagic stroke was lower in the NOAC group than in the warfarin group (12). In another study, the rates of hemorrhagic and thromboembolic events in patients older than 90 years under treatment with NOACs at VKAs were comparable (13). Elderly patients treated with high doses of NOACs had a statistically similar incidence of stroke, a lower statistical incidence of ICH and a higher net clinical benefit, compared with those treated with low doses (14).

In addition to age, other characteristics of the patient should be considered at the time of selecting an appropriate anticoagulant treatment. The female sex as a risk factor for stroke and thromboembolism in patients with atrial fibrillation should also be considered.

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Thromboembolic risk related to atrial fibrillation (AF) may differ between men and women, and this may affect the response to anticoagulant therapy and warrant a sex-specific management of patients with AF. Bleeding risk seems to be higher in women mainly related with the women's lower body weight (15) and women with AF are at increased risk of stroke, particularly elderly women (16). Comprehensive stroke risk assessment, including sex as a risk factor, should be undertaken in all AF patients.

In conclusion, challenges remain about NOACs usage in NVAF in elderly patients and effective strategies should be developed to improve the outcomes in elderly patients in clinical practice. An integral geriatric assessment (17) and patient profile (18) should be considered, including the age, sex, frailty (19) and comorbidities, before initiating oral anticoagulation. Based on these assumptions, it's considered interesting to describe the current the anticoagulation management in elderly patients in Spain.

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8. RESEARCH QUESTION AND OBJECTIVES

This study has been designed in order to describe the current non-vitamin K antagonist oral anticoagulants (NOACs) management in elderly patients in Spain.

Primary objective: To describe the pattern of usage of NOACs prescribed according to their Summary of Product Characteristics (SmPC), by current NOAC type and dose, in elderly patients (≥75 years-old) with non-valvular atrial fibrillation (NVAF) at the time of the study visit.

Secondary objectives:

1. To describe patients characteristics at the time of the study visit by current NOAC type stratified by duration since first NOAC initiation.
2. To describe OAC treatment management since first NOAC initiation until the study visit by duration since first NOAC initiation: previous vitamin K antagonists (VKA) treatment, first NOAC treatment duration, dose changes, switch between NOACs and reasons for switch, total NOAC treatment duration and additional antiplatelet treatment.
3. To describe the Clinical Frailty Scale grading, CFS (19), at the time of the study visit, by current NOAC type.
4. To describe first NOAC usage by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.

[redacted]

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9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational, multicenter and cross-sectional study in NVAF elderly patients currently on NOAC treatment for their stroke prevention.

AF is classified as non-valvular AF in the absence of mitral stenosis or cardiac valvular prosthesis, since NOACs are not recommended for patients with mechanical heart valve (level of evidence B) or moderate to severe mitral stenosis (level of evidence C) (22).

The study will be conducted in approximately 50 sites in Spain. Investigators from different specialties are planned to be included as follows: 35 cardiologists, 10 hematologists and 5 geriatricians.
The design of the study impose a single visit to be performed for the informed consent signature and data collection 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 to each included patient, 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.

9.2 SETTING

Approximately 500 elderly patients with NVAF currently on NOAC treatment 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. It is planned to have a 9-month recruitment period from first site initiated, or until the sample size is achieved.

The number of patients per site to be included in the study will be initially set up to a maximum of 10 patients per site. Once the 50% of the participating sites have been initiated, the recruitment will become competitive until the end of the study and the limitation of 10 patients per site will be removed to allow sites to continue with the recruitment.

9.2.1 Study sites

Cardiology, hematology, geriatric services at a hospital setting, specialty medical offices and nursing homes, who regularly prescribe NOACs for stroke prevention in NVAF patients may be invited to participate.

It is necessary to ensure that study population is representative of the entire national territory. Therefore, patients may be recruited from sites with different level of medical care (e.g, primary hospital, secondary hospital, private care) in several geographical areas according to

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the distribution of the overall population in this area. Site selection will be performed in order to secure representativeness of the NVAF population treated with NOAC.

As a pre-study activity, sites will need to answer a site feasibility questionnaire in order to determine that the site has adequate facilities and investigator is qualified and meets the needs of the study, recruitment targets, quality and timelines in compliance with the applicable regulatory requirements.

9.2.2 Study population

To be eligible to participate in the study, patients must meet the following selection criteria. The patient will be considered included when he/she agrees to participate in the study by signing the informed consent.

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

1. Patients are willing and provide written informed consent prior to participate in this study
2. Patients ≥ 75 years-old at the time of the study visit.
3. Patients with a diagnosis of non-valvular atrial fibrillation (NVAF).
4. Patients who are being treated with NOAC treatment according to the indication approved in the SmPC.
5. Patients who have started the NOAC treatment at least 3 months prior to the study visit.

Patients will be excluded from participating in this study if the following criterion is met:

1. Current participation in any clinical trial of a drug or device.
2. Patients who have any contraindication for NOAC treatment, according to the SmPC.

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

9.2.3 Study visits

Patients will be invited to participate in this study during a routine medical visit for any purpose with their physician. Investigator will provide to patients the "patient information and informed consent form" and will explain the study to the patient. If patients agree to participate, after signing the informed consent, investigator will assess the Clinical Frailty Scale (19), the Modified EHRA scale for AF related symptoms (23), the NYHA classification of heart failure (24) (refer to Annex 3) and the CHA2DS2-VASc and HAS-BLED scales, and include the scores directly in eCRF after evaluating the patient's functional status and patient's medical records. The investigator will review the medical records in order to complete other variables needed to address study objectives that will mainly be obtained

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directly from patient medical records or requested to the patient at the study visit if not available in medical records (refer to Section 9.4). The end of the single study visit is the end of the study for each patient.

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. Administrative reasons (i.e. study rejected by the hospital director)
3. Violation of GxP (as applicable), 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

9.3.1 Exposures

Patients in this study will be currently on treatment with NOAC for their NVAF, according to the indication approved in their SmPC, and initiated it at least 3 months before the study visit. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before considering the participation in the study.

As this is an observational study, designed to reflect as faithfully as possible real-life clinical practice, the decision to start treatment with NOAC 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 outcome

The primary outcome is the pattern of usage of non-vitamin K oral anticoagulants (NOACs) prescribed according to their Summary of Product Characteristics (SmPC), based on the percentage of patients by NOAC type and dose the patient is taking at the time of the study visit. Timeframe to complete data collection for this outcome is one day, the study visit day.

Table 2 Primary variable collected at the time of the study visit

Variable	Obtained from medical records
Current NOAC active substance and dose	x

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9.3.2.2 Secondary outcomes

Secondary outcomes are:

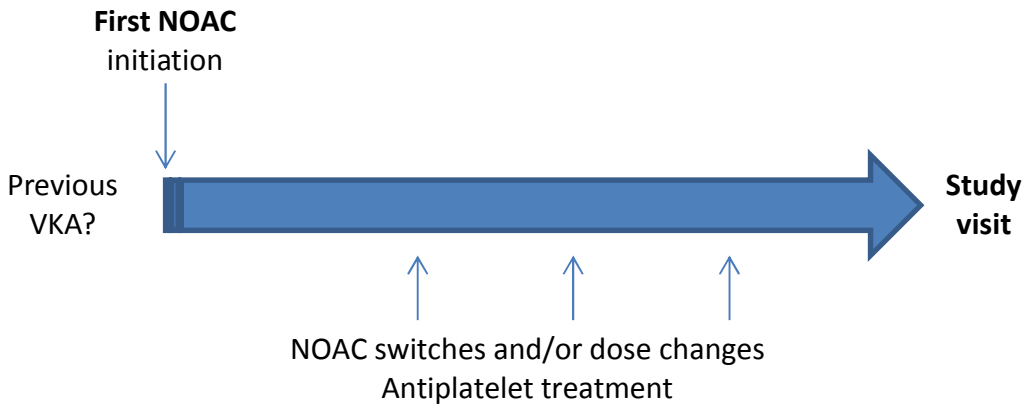
1. Patient's characteristics at the time of the study visit by the NOAC type that the patient is taking at the time of the study visit. Patients will be also stratified by the duration since the first NOAC initiation date until the study visit date (> 4months / ≤4 months). (see Related patient's characteristics covariates: refer to Section 9.3.3, Table 3).

2. OAC treatment management (since first NOAC initiation until the study visit date), based on the following variables:

   - Previous vitamin K antagonist (VKA) treatment (yes/no), VKA treatment duration in years, reason for switch to NOAC,
   - Duration since NVAF diagnosis until first NOAC initiation,
   - Duration of first NOAC treatment (first NOAC active substance, start and stop date, first NOAC dose and its dose changes),
   - Switch to new NOAC (active substance, start/stop date, dose and dose changes, reason for switch to new NOAC): number of patients that switch their first or further NOAC and mean number of switches.
   - Total time in NOAC treatment
   - History and current antiplatelet treatment (yes/no, start date, end date, active substance).

[redacted]

Figure 1 OAC treatment management



3. Clinical Frailty Scale grading, CFS, (19) at the time of the study visit, by current NOAC type.

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4. The first NOAC usage by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.

Timeframe to complete data collection for the secondary outcomes is one day, the study visit day.

9.3.3 Covariates

The following covariates, related to the secondary outcome, will be collected from medical records or at the study visit (refer to section 9.4) to describe the patient's characteristics:

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Table 3 Patient characteristics at the time of the study visit

Variable*	Obtained from medical records	Obtained at the study visit
Demographic characteristics: Age, sex, height, weight, BMI, caregiver (Yes/No), place where patient is living (Home alone; At home with partner/other family member/a friend; Other's home (e.g family member's); Nursing home)	x	x
Smoking habit (past/current/non-smoker) and alcohol consumption (casual/habitual/abuse/dependence)	x	x
Analytical lab results (from last available blood sample analysis): - Kidney function: serum creatinine (mg/dl), creatinine clearance (Cockcroft-Gault calculation) - Liver function: AST/ALT, total bilirubin - Hemoglobin and platelet levels	x	
NVAF: - Diagnosis date (month and year) - Type (persistent, long standing persistent, permanent, paroxysmal) - Modified EHRA scale for AF related symptoms (23) (Refer to Annex 3).	x	x (mEHRA scale)
Procedures and interventions: - Cardioversion/Ablation (Yes/No) - Coronary interventions (Yes/No): Percutaneous coronary intervention (PCI)/Coronary Artery Bypass Grafting (CABG) - Pacemaker carrier (Yes/No)	x	
History of thromboembolic events (Yes/No, number): TIA, ischemic stroke, hemorrhagic stroke, embolism systemic, deep vein thrombosis, pulmonary embolism, stable angina, unstable angina, myocardial infarction with/without ST segment elevation; and bleeding events (Yes/No): intracranial, digestive, genitourinary, gingival, nasal, pulmonary, articular-muscular, conjunctival.	x	
Other concomitant treatments (Total number of current concomitant drugs; Type (Yes/No, number): ARB or ACE inhibitor, Beta-blocker, Calcium channel blockers, Diuretics, Amiodarone, Statin, Proton pump inhibitor, H2-	x	

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Variable*	Obtained from medical records	Obtained at the study visit
receptor antagonist, , Digoxin, NSAIDs, Verapamil / Dronedarone, Other antiarrhythmics, ketoconazole systemic), ciclosporine, itraconazol)		
Comorbidities and Clinical Risk Factors: - Heart Failure (Yes/No, New York Heart Association (NYHA) classification (24) (Refer to Annex 3); Left Ventricular Ejection Fraction, LVEF, %) - Coronary artery disease (Yes/No) - Sleep apnoea-hypopnoea syndrome (SAHS) (Yes/No) - Hypertension (Yes/No) - Comorbidity Charlson index (25) (Refer to Annex 3) (Yes/No; total score): myocardial infarction (already collected for history of thromboembolic events), congestive heart failure (already collected for the NHYA scale scoring), cerebral and peripheral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild/moderate/severe liver disease, diabetes, diabetes with end-organ damage, hemiplegia, moderate/severe renal disease, any solid tumor, metastatic solid tumor, leukemia, lymphoma AIDs, age (already collected as a demographic characteristic).	x	x (NYHA classification, Charlson Index)
CHA2DS2-VAS (total score)		x
HAS-BLED(total score)		x

* Refer to section 9.4 for more details about how these variables will be collected.

9.4 DATA SOURCES

Variables collected at the time of the study visit (including those related to the time of the first NOAC initiation) will be obtained based on and limited to those available in the medical records of the selected patients.

Demographic characteristics, smoking habit and alcohol consumption may be asked to the patient at the study visit if not available in the medical records.

The variables used to determine the kidney and liver function, as well as the hemoglobin and platelet levels can be obtained from the last analytical results available in the medical charts. Creatinine clearance will be automatically determined with the serum creatinine if the Cockcroft-Gault calculation is not available in medical charts. LVEF measurement will be obtained from the last images available for the patient.

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Clinical Frailty Scale (19), Modified EHRA scale for AF related symptoms (23) and NYHA classification (24) (Refer to Annex 3 for these scales), CHA2DS2-VASc, HAS-BLED scores, will be assessed by the investigators at the study visit by evaluating the patient's functional status and medical records and the values will be directly included in the eCRF.
Final score for the Comorbidities Charlson Index (25) will be automatically calculated based on the answers individually entered by the investigator in the eCRF for each index item.

Any required missing data to calculate the score for the scales or the Comorbidities Charlson Index may be asked to the patient at the study visit if not available in the medical records and should be documented, however the final score number obtained by the investigator from this information will not need to be included in medical records.

9.5 STUDY SIZE

It is planned that a total of approximately 500 patients will be recruited for the study. Based on such a sample size estimate, categorical variables of binomial proportions (e.g. sex) will be estimated with the precision (i.e. width of descriptive 95% confidence interval) described in the following Table 4. Calculations of the confidence intervals (CI) are based on the Clopper-Pearson method:

Table 4 Width of 95% confidence interval by prevalence of attribute:

Prevalence of attribute		Sample size 500
10%	Expected n	50
	95% CI width	5.46%
20%	Expected n	100
	95% CI width	7.20%
30%	Expected n	150
	95% CI width	8.22%
40%	Expected n	200
	95% CI width	8.76%
50%	Expected n	250
	95% CI width	8.94%

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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 the method and procedure for each data management step for the study, from electronic Case Report Form (eCRF) design up to final database delivery.

The eCRFs will include programmable edit checks to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. The Edit Checks Specifications (Data Validation Plan (DVP)) is included in the eCRF specification documentation. These checks will be performed once data is entered into the eCRF. Thus the data entered into 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.

AE reconciliation will be performed quarterly from study initiation date.

Data quality reviews are planned to be performed in the study with the purpose of data cleaning and to detect possible quality issues in advance. Details will be explained in the NIS Monitoring Manual.

When data management is outsourced, the designated contract organization will be responsible for the development and implementation of the data management and validation plans.
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.

In this non-interventional study, retrospective data from medical charts and data at the study visit will be collected for non-valvular AF patients. 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.

Since the study is descriptive, the variables included in the study objectives will be summarized overall and by factors of interest. All results will be summarized with measures

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of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges.

A Statistical Analysis Plan (SAP), will be prepared to describe all processes, treatment and specifications for the planned statistical analysis.

9.7.1 Main analysis

All eligible patients (all enrolled patients fulfilling all inclusion criteria and no exclusion criteria) will be included in the analysis. Missing data will not be imputed. Number of missing values will be presented for each outcome.

For the primary objective, the pattern of usage of NOAC will be described as the percentage of patients by NOAC type and dose.

[redacted]

For the secondary objectives, the following descriptive analyses are planned:

1. Patient's characteristics at the time of the study visit will be summarized descriptively by current NOAC type. [redacted] All covariates related to patient's characteristics (refer to Section 9.3.3, Table 3) will be analyzed descriptively by NOAC type and by the duration since the first NOAC initiation. Standardized differences between Pradaxa® and other NOACs will be estimated for these covariates. For this, a minimum of 50 patients is required for each group.

2. For OAC treatment management, descriptive analysis of previous VKA treatment (yes/no), VKA treatment duration in years, reason for switch to NOAC, first NOAC treatment duration, first NOAC dose and dose changes, new NOAC treatment duration, new NOAC dose and dose changes. Duration since NVAF diagnosis until first NOAC initiation and total time in NOAC treatment will be described. Also, the reason for switches, the number of patients that switched their first or further NOAC and mean number of switches will be presented. Antiplatelet use will be also summarized.

[redacted]

3. Clinical Frailty Scale grading at the time of the study visit by current NOAC type will be described as the number of patients on each category of frailty (19) as evaluated by the investigator according to patient's records. In addition, CFS score will be summarized in

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the following two categories: Frailty patients (CFS scoring >4) and Non-frailty patients (CFS scoring ≤4).

4. First NOAC usage will be described by NOAC type, for primary prevention or secondary prevention, at the time of first NOAC initiation.

[redacted]

9.8 QUALITY CONTROL

The NIS monitoring manual will define all aspects related to the monitoring activities for the study, to ensure that it is performed in a manner that will provide meaningful data, the rights and well-being of the study patients are protected, and the conduct of the study is compliant with protocol and all applicable regulation.

All relevant issues, including protocol deviations, detected during the study will be handled and followed-up until their resolution or closure. A register of the issues and related actions will be kept.

On-site and remote monitoring will be performed by a Contract Research Organisation (CRO) appointed by BI.

Source data verification in a sample of sites is planned for this study and detailed in the monitoring manual.

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 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 document of this study.

All study relevant documentation will be stored in the study master file (SMF). In addition, each site will have an Investigator Site File (ISF) containing all study documents relevant for the site. Relevant documentation on the participating investigators, including their curricula vitae, will be filed in ISF.

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9.9 LIMITATIONS OF THE RESEARCH METHODS

A NIS is the most suitable design to obtain information about the use of medicines in everyday therapeutic practice and thus for investigating questions in everyday therapeutic practice. However, there are some limitations inherent to this design.

Variables collected at the time of the study visit will be obtained based on and limited to those available in the medical records of the selected patients (refer to section 9.4)

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are less restrictive than the ones of a randomized clinical trial, which will permit the enrolment of a broader patient population.

The choice of NOAC was done before the study visit and it is done at the discretion of the investigator. However, patients seen by their physician less than twice per year are therefore less likely to be included in the study. Patients with higher frequency of visits are more likely to be included in the study and could be over-represented in the sample.

Due to regulatory requirements, patients are not allowed to start the NOAC treatment on the study visit date. For this, a minimum of three months of NOAC treatment before study participation has been stablished, which limits the NOAC population.

As patients are included after first NOAC initiation and need to be treated by a NOAC at the time of enrolment, any patient having prematurely discontinued any NOAC treatment between the time of first NOAC initiation and the start of the enrolment period will not be included in the study. The sample may therefore not be representative of all patients having initiated a NOAC. Besides, sample size may be limited for some of the planned subgroup analyses, resulting in decreased precision.

Channeling bias is a form of confounding that occurs when a drug is preferentially prescribed to patients with different baseline characteristics. Standardized differences will be applied when assessing channeling bias.

9.10 OTHER ASPECTS

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 Institutional Review Board (IRBs) / 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

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor (eCRF will be outsourced to a designated contract organization), via remote data capture.

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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 reported on 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, except the value of the score in CFS, CHA2DS2-VASc, HAS-BLED that will be included in the eCRF directly by the investigators.

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 (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1

9.10.3 Completion of study

In Spain, the Sponsor will send the final report to competent authorities and national authority between 3 and six months after the completion of the study that is defined as the database lock date.

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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) and BI local study documents. 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 of the participating country. 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 authorized monitors (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.

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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 authority.

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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.

No AESIs have been defined for this study.

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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 authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the BI drug in the scope of this NIS. For this reason the following AE collection and reporting requirements have been defined.

Once informed consent is signed the following must be collected in the eCRF by the investigator if identified during chart review and study visit data collection until the end of the study visit:

- all adverse drug reaction (ADRs) (serious and non-serious) associated with Pradaxa®,
- all AEs with fatal outcome in patients exposed to Pradaxa®,

All ADRs may 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).

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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.

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:

Table 5 Expedited reporting of AEs and Drug Exposure during pregnancy

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 in patients or partner exposed to Pradaxa®	7 calendar days

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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 eCRF 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 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.

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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 finalization of the Study Report.
The summary study results will be distributed to national health authority and ethics committees. They will be also made public in CT.gov and EUPAS Register.
The results of this study will be published in a national journal and/or presented in regional or national congresses.

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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 Jan;65(1):47-53.
2. Cea-Calvo L, Redon J, Lozano JV, Fernandez-Perez C, Marti-Canales JC, Llisterri JL, et al. [Prevalence of atrial fibrillation in the Spanish population aged 60 years or more. The PREV-ICTUS study]. Rev Esp Cardiol 2007 Jun;60(6):616-24.
3. Gomez-Doblas JJ, Muniz J, Martin JJ, Rodriguez-Roca G, Lobos JM, Awamleh P, et al. Prevalence of atrial fibrillation in Spain. OFRECE study results. Rev Esp Cardiol (Engl Ed) 2014 Apr;67(4):259-69
4. Petidier Torregrossa R, Abizanda Soler P, Noguerón García A, et al. Oral anticoagulation therapy in the elderly population with atrial fibrillation. A review article. Rev Esp Geriatr Gerontol. 2018 Jul 30.
5. Lip G.Y.H., Clementy N., Pericart L., Banerjee A. and Fauchier L. Stroke and Major Bleeding Risk in Elderly Patients Aged ≥75 Years With Atrial Fibrillation. The Loire Valley Atrial Fibrillation Project. Stroke. 2014;46:143–150
6. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Georg Haeusler K, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. EP Europace, Volume 20, Issue 8, 1 August 2018, Pages 1231–1242,
7. Inoue H, Kodani E, Atarashi H et al. Time in Therapeutic Range and Disease Outcomes in Elderly Japanese Patients With Nonvalvular Atrial Fibrillation. Circ J. 2018 Aug 28.
8. Grant SJ, Kothari S, Gimotty PA, Gooneratne NS, Cuker A. Quality of direct oral anticoagulant prescribing in elderly patients with non-valvular atrial fibrillation: results from a large urban health system. J Thromb Thrombolysis. 2018 Jul;46(1):1-6.
9. Pattullo CS, Barras M, Tai B, McKean M, Donovan P. New oral anticoagulants (NOACs)—appropriateness of prescribing in real-world setting. Intern Med J 2016, 46: 812–818
10. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. Am J Med 2016, 129: 1198–1204

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11. Stöllberger C, Brooks R, Finsterer J, Pachofszky T. Use of direct-acting oral anticoagulants in nonagenarians: a call for more data. Drugs Aging 2016, 33:315–320
12. Chao TF, Liu CJ, Lin YJ et al. Oral Anticoagulation in Very Elderly Patients With Atrial Fibrillation: A Nationwide Cohort Study.Circulation. 2018, Jul 3;138(1):37-47
13. Giustozzi, M.G., Vedovati M.C., Verso M. et al. Effectiveness and safety of oral anticoagulants in patients aged 90 years or older with Atrial Fibrillation. European Heart Journal, Volume 39, Issue suppl_1, August 2018.
14. Alnsasra H, Haim M, Senderey AB, et al. Net Clinical Benefit of Anticoagulant Treatments in Elderly Patients with Non-Valvular Atrial Fibrillation: Experience From the Real World. Heart Rhythm 2018 Aug 18. pii: S1547-5271(18)30816-6.
15. Law SWY, Lau WCY, Wong ICK, Lip GYH, Mok MT, Siu CW, Chan EW. Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018 Jul 17;72(3):271-282. doi: 10.1016/j.jacc.2018.04.066. Epub 2018 Jul 9.
16. Wagstaff AJ, Overvad TF, Lip GYH, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM: An International Journal of Medicine, Volume 107, Issue 12, 1 December 2014, Pages 955–967
17. Roberto Martín-Asenjo, Héctor Bueno, María Teresa Vidán. Anticoagulación en el anciano: ¿son suficientes guías y algoritmos para ejercer bien la medicina o todavía queda lugar para el arte? Rev Esp Geriatr Gerontol. 2018 Aug 8
18. Tayaa S, Berrut G, de Decker L, Chevalet P. Direct oral anticoagulants in non-valvular atrial fibrillation in elderly: for a treatment adapted to patient profile. Geriatr Psychol Neuropsychiatr Vieil. 2018 Sep 1;16(3):229-240.
19. Pablo Díez-Villanueva, Albert Arizá -Solé, María Teresa Vidán et al. Recommendations of the Geriatric Cardiology Section of the Spanish Society of Cardiology for the Assessment of Frailty in Elderly Patients With Heart Disease. Rev Esp Cardiol. 2019;72(1):63–71.

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20. General criteria and recommendations for the use of direct oral anticoagulants (NOAC) in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Spanish Health Authority Therapeutic Positioning Report.Version 5 (2016). Available at: https://aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm#anticoagulantes-orales.
21. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005; 173:489-495
22. Camm AJ, Lip GYH, de Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation developed with the special contribution of the European Heart Rhythm Association Authors/Task Force Members. Eur Heart J. 2012;33:2719-47.
23. Kirchhof et al 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal (2016) 37, 2893–2962.
24. Villar R, Meijide H, Castelo L, Mema A, Serrano J, Vares Mª, Ramos V. Escalas en práctica clínica: cardiología. Galicia Clin 2010; 71 (1): 31-36.
25. Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. J Clin Epidemiol 47: 1245–1251.

13.2 UNPUBLISHED REFERENCES

Not applicable.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Title
Data Management Plan
Statistical Analysis Plan
Monitoring Manual
Study Master File Plan

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (revision 4)
Adopted by the ENCePP Steering Committee on 15/10/2018

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

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

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

Study title: Non-Interventional, cross-sectional study to describe NOACs management in elderly patients with non-valvular atrial fibrillation (NVAF) in Spain. RE-BELD Study.

EU PAS Register® number: Study will be registered in the EU Pass Register.
Study reference number (if applicable): 1160-0297

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 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[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.

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Comments:

Study progress reports for EC and authorities will be performed annually

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

No hypothesis testing is planned in this descriptive study in section 9.7

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
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?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2

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Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	
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)	☒	☐	☐	9.2.2

Comments:

No follow-up is foreseen.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	

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Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Descriptive outcomes

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

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

Comments:

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)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3

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Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.2

Comments:

Unique patient identification code numbers will be used.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Only descriptive summaries will be done.

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:

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Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
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

Comments:

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ANNEX 3. ADDITIONAL INFORMATION

Clinical Frailty Scale- Spanish Translation (19)

1. **En muy buena forma.** Personas que están fuertes, activas, vigorosas y motivadas. Son personas que suelen practicar ejercicio con regularidad. Son de los que están en mejor forma para su edad.

2. **En forma.** Personas **sin síntomas de enfermedad activa,** pero que están menos en forma que las de la categoría 1. Suele ocurrir que se ejercitan o están **muy activas por temporadas,** por ejemplo, según la estación.

3. **En buen estado.** Personas que tienen **bien controlados sus problemas médicos,** pero que **no llevan actividad física regular** más allá de los paseos habituales.

4. **Vulnerables.** Aunque **no dependen de otros** que les ayuden en la vida diaria, a menudo **los síntomas limitan sus actividades.** Suelen quejarse de estar «lentos» o cansados durante el día.

5. **Levemente frágiles.** Estas personas a menudo tienen un **enlentecimiento más evidente** y necesitan ayuda para las **actividades de la vida diaria importantes** (economía, transporte, labores domésticas, medicación). Es típico que la fragilidad leve vaya dificultando salir solos de compras o a pasear y hacer la comida o las tareas del hogar.

6. **Moderadamente frágiles.** Personas que necesitan ayuda para **todas las actividades en el exterior** y para realizar las **tareas domésticas.** En casa, suelen tener problemas con las escaleras y necesitan **ayuda con el baño,** y pueden requerir alguna asistencia para vestirse (guía y acompañamiento).

7. **Con fragilidad grave. Dependen totalmente para el cuidado personal,** sea cual fuere la causa (física o cognitiva). Aun así, parecen estables y sin riesgo de muerte (en los siguientes ~6 meses).

8. **Con fragilidad muy grave.** Totalmente dependientes, se acercan al final de la vida. Es típico que ni siquiera se recuperen de afecciones menores.

9. **Enfermo terminal.** Se aproximan al final de la vida. Esta categoría se aplica a personas con **esperanza de vida < 6 meses y sin otros signos de fragilidad.**

En personas con demencia, el grado de fragilidad se corresponde con el grado de demencia. **Son síntomas comunes de demencia leve** olvidar los detalles de un acontecimiento reciente aun recordando el evento en sí, la repetición de una misma pregunta o relato y el aislamiento social. En la **demencia moderada,** la memoria reciente está muy afectada, aunque parezca que recuerdan bien los acontecimientos de su pasado. Con pautas, pueden cuidarse solos. En la **demencia grave,** no son posibles los cuidados personales sin ayuda.

P. Díez-Villanueva et al/Rev Esp Cardiol. 2019;72(1):63-71(Clinical Frailty Scale. Reproduced with permission of Rockwood et al (21)

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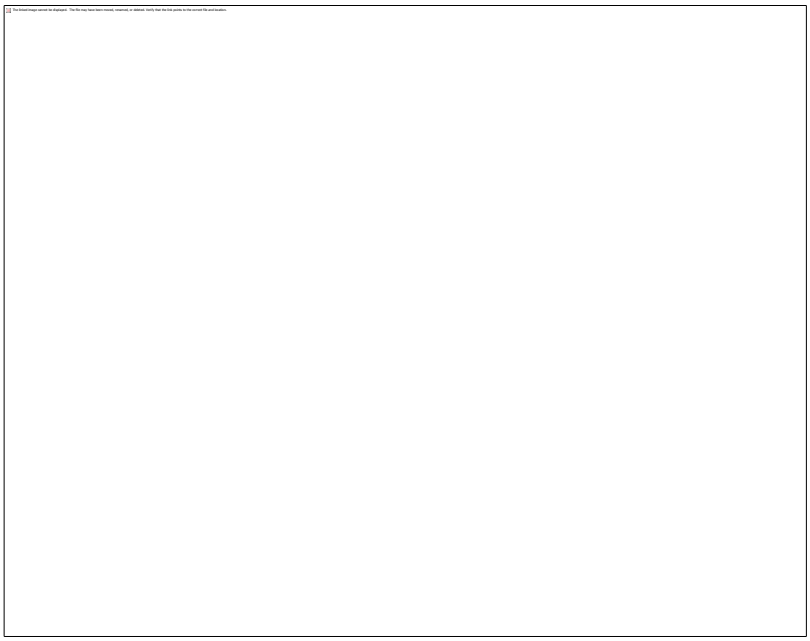
EHRA scoring related-symptoms (23)



Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. Guías ESC 2016 sobre el diagnóstico y tratamiento de la fibrilación auricular, desarrollada en colaboración con la EACTS. Rev Esp Cardiol 2017;70(1):43.e1-e84 (23)

NYHA classification of heart failure (24)

Villar R, Meijide H, Castelo L, Mema A, Serrano J, Vares Mª, Ramos V. Escalas en práctica clínica: cardiología. Galicia Clin 2010; 71 (1): 31-36 (24)

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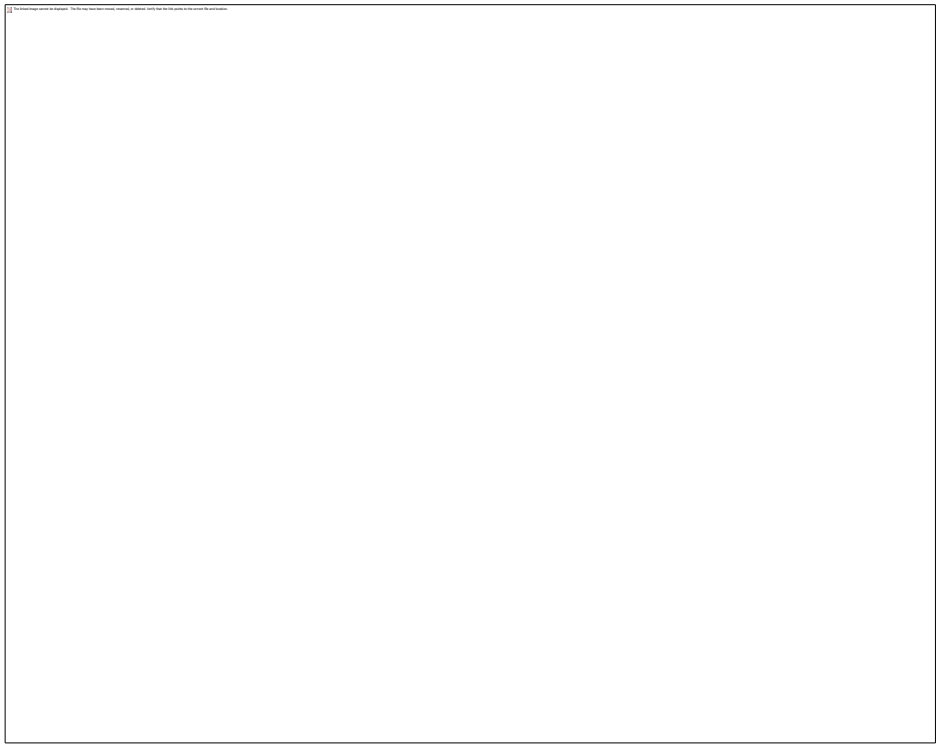
Comorbidities Charlson Index (25)



Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. J Clin Epidemiol 47: 1245–1251 (25)