Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**c18071759-01**
BI Study Number:	1321-0022
BI Investigational Product(s):	Prazaxa (Dabigatran etexilate)
Title:	Medical Need of Non-vitamin K Oral Anti-coagulant Reversal in Japan: Epidemiological Assessment of Emergency Surgery, Major Bleeding due to Trauma and Fracture, using Large Scale Claims Database
Protocol version identifier:	Version 1.0
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EU PAS register number:	Not Applicable
Active substance:	Dabigatran, warfarin, apixaban, rivaroxaban, edoxaban
Medicinal product:	Dabigatran, warfarin, apixaban, rivaroxaban, edoxaban
Product reference:	Not applicable
Procedure number:	Not Applicable
Joint PASS:	No
Research question and objectives:	The primary objective of this study is to assess, for adult patients initiating an oral anticoagulant for non-valvular atrial fibrillation, the incidence rates of emergency surgery, major bleeding due to fracture, and major bleeding due to trauma, overlall and stratified by age (<64, 65-74, >75). The secondary objective of the study is to assess the incidence rates of cardiac tamponade or pericardiocentesis, overall and stratified by age (<64, 65-74, >75). .
Country(-ies) of study:	Japan

Author:	
Marketing authorisation holder(s):	
MAH contact person:	
In case of PASS, add: **<EU-QPPV:>**	Not Applicable
In case of PASS, add: <**Signature of EU-QPPV:>**	Not Applicable
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme inhibitors
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blockers
ATC	Anatomical Therapeutic Chemical
CCB	Calcium-Channel Blocker
DPC	Diagnosis Procedure Combination
ICD	International Classification of Diseases
MDV	Medical Data Vision
NOAC	Non-warfarin Oral Anti Coagulants
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants

3. RESPONSIBLE PARTIES

Person responsible for trial

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Biostatistics

Data and analyser
Milliman Inc.
Medical writing and claims coding
Milliman Inc.

Data Source Provider:
Medical Data Vision Co., Ltd. (MDV)

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa			
Name of active ingredient: Dabigatran etexilate			
Protocol date: 18 July 2017	**Study number:** 1321-0022	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	Medical Need of Non-vitamin K Oral Anti-coagulant Reversal in Japan: Epidemiological Assessment of Emergency Surgery, Major Bleeding due to Trauma and Fracture, using Large Scale Claims Database		
Rationale and background:	There has been no epidemiological assessment to investigate the medical need of reversal in patients undergoing emergency surgery or major bleeding from trauma or fracture receiving oral anticoagulant in Japan. The objective of this study is to assess the incidence of emergency surgery and major bleeding associated with fracture and head trauma in Japanese patients prescribed with oral anti-coagulants such as warfarin, dabigatran, apixaban, rivaroxaban and edoxaban		
Research question and objectives:	The primary objective is to assess, for adult patients initiating an oral anticoagulant for non-valvular atrial fibrillation (NVAF), the incidence rates of emergency surgery, major bleeding due to trauma, and major bleeding due to fracture, overall and stratified by age (<64, 65-74, >75). The secondary objective is to estimate the overall and age stratified incidence of cardiac tamponade and pericardiocentesis.		
Study design:	Non-interventional study based on existing health insurance claims data		
Population:	Medical Data Vision (MDV) clinical database is used Oral anticoagulants (OAC) naïve, adult patients with NVAF initiating dabigatran, warfarin, apixaban, rivaroxaban or edoxaban between March 1, 2011 and June 30, 2016 Inclusion criteria: patients aged >18 year-old with confirmed diagnosis of NVAF (International Classification of Diseases (ICD) 10 I48), having a first prescription (index date) of any one of OACs (dabigatran, warfarin, rivaroxaban, apixaban or edoxaban) having no prescription of OACs for 6 months prior to the index date (this period is defined as the baseline period). Exclusion criteria: patients having less than 6 months of enrolment prior to the index date, being dialysis or kidney transplant recipients in baseline period, having either atrial flutter, valvular atrial fibrillation (AF), mechanical valve placement, rheumatic AF, and/or mitral valve prolapse/regurge/stenosis in baseline period, and having record of deep		

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	vein thrombosis or pulmonary embolism < 6months before AF diagnosis in baseline period.		
Variables:	Outcomes of interest are emergency surgeries, major bleeding due to fracture, major bleeding due to trauma, cardiac tamponade and pericardial effusion. Co-variates are baseline characteristics of patients (age, sex, clinical history), medical history, type of OAC, concomitant medications, events related to bleeding, trauma and fracture		
Data sources:	MDV clinical database. The database is health insurance claims database. As of end of February 2016, MDV has accumulated claims records from 12.94 million patients, both in and out-patients, from more than 230 large acute, sub-acute and outpatient care DPC hospitals.		
Study size:	The previous study 1160.279 has identified the patients with confirmed 6 months of baseline period and no OAC treatment (defining "treatment naïve" new starter population). The total of these patients was 62,888. The breakdown by OAC initiated was 7,441 for dabigatran, 23,412 for warfarin, 16,026 for apixaban, 12,779 for rivaroxaban and 3,230 for edoxaban. The mean on-treatment follow-up duration for all OACs new starters combined in patients with one year of baseline period was calculated as 121 days. The mean on-treatment follow-up duration for all OACs new starters combined with 6 months of baseline period is unknown.		
Data analysis:	Baseline characteristics of patients overall and stratified by age will be provided in a tabulated format. The main analysis will be on OAC-naïve initiators and will consider outcomes until the complete discontinuation of any OAC (i.e. including the periods during which patients switched from an OAC to another OAC in less than 14 days) <u>For the primary objective</u>		

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	Incidence rate (overall and age stratified) of emergency surgery, and major bleeding due to fracture, and major bleeding due to trauma will be described with number of patients presenting the event, patient-years and 95% confidence interval overall and stratified by age. <u>For the secondary objective</u> 1. Incidence rates (overall and age stratified) of cardiac tamponade or peri-cardiocentesis, along with number of events, patient year of follow-up and 95% confidence interval.		
Milestones:	Start of Data Analysis: 1 Aug 2017 End of Data Analysis: 19 Sep 2017 Study Report: 30 Nov 2017		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
	None			

6. MILESTONES

Milestone	Planned Date
Start of data collection	1 Aug 2017
End of epidemiology analysis	19 Sep 2017
Final report of study results:	30 Nov 2017

7. RATIONALE AND BACKGROUND

Until 2002 in Japan, administrative claims data were not standardized or coded electronically. There was limited use for Health Authorities policy decision making or in health research (epidemiological, HTA). Ministry of Health, Labor and Welfare launched the Diagnosis Procedure Combination (DPC) system in 2002 linked with the reimbursement system. DPC is a Japanese version of the Diagnosis Related Groups system; such system is implemented in many countries including UK, US and Germany.

MDV provides commercial claims database consisting of medical records from more than 12.94 million in and out-patients (>80% outpatient claims) from 230 large DPC hospitals as of February 2016.

Dabigatran was the first of the non-warfarin oral anti coagulants (NOACs) to be approved and launched in March 2011 in Japan, then three additional NOACs have been launched for an indication of stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Idarucizumab, a specific reversal agent of dabigatran's coagulation effect, has been launched in November of 2016, and is indicated in dabigatran treated patients who undergo emergency operation or experience life threatening bleeding.

Buchelle et al analysed the German claims database system to calculate the incidence of traumatic brain injury in 65 years or older population, and concluded that 4.8 hospital admissions in 1000 patient year of follow-up, and was found to be higher in nursing home resident with higher morbidity and mortality [1]. Curtis et al reported that fracture annual incidence was 155.3 per 10,000 patient-year in men aged 18-24. For age above 90, the incidence was 224.8 per 10,000 patient-year[2].

There has been no epidemiological assessment to investigate the medical need of reversal in patients undergoing emergency surgery or major bleeding from trauma or fracture receiving NOACs in Japan. The objective of this study is to assess the incidence of emergency surgery and major bleeding associated with fracture and head trauma in Japanese patients prescribed with oral anti-coagulants such as warfarin, dabigatran, apixaban, rivaroxaban and edoxaban.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to assess the incidence rate (overall and age stratified) of emergency surgery and major bleeding associated with fracture and trauma among patients to characterize the incidence of relatively homogeneous population who undergo oral anticoagulants (OAC) therapy.

The secondary objective is to estimate the incidence rate (overall and age stratified) of cardiac tamponade or pericardiocentesis occurring during or within one day after conducting a PCI or cardiac ablation procedure.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Study design
- Non-interventional study based on existing health insurance claims data

Treatments Considered:
- Dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin

Strength of the study design
- Up-to-date epidemiological information can be obtained using large-scale real-world database.

9.2 SETTING

MDV clinical database is used.

Inclusion criteria
1. >18 year old non-valvular atrial fibrillation (NVAF) patients
2. Prescribed dabigatran, rivaroxaban, apixaban, edoxaban or warfarin
3. Patients with confirmed date of initiation of OACs
4. Patients with a minimum of 6 months of enrolment data prior to index date
5. Has an index date between 14th of March 2011 to 30 June, 2016

Exclusion criteria
1. Patients receiving two or more oral anti-coagulants at the same time at index date
2. Patients with prescriptions of index treatment in the 6 months prior to index date
3. Patients without enrolment period of at least six month in the database

Definition of terminology
1. Index date: the date of first oral anticoagulant prescription, namely dabigatran, apixaban, rivaroxaban, edoxaban and warfarin

2. Follow-up period: the day after index date to the earliest of treatment discontinuation, , end of continuous enrolment in the database, end of study period, first occurrence of the event of interest, or death.
3. Any OAC treatment discontinuation: treatment gap of any one of OACs for more than 14 days including the time after switch from one OAC to another OAC (primary analysis)

9.3 VARIABLES

9.3.1 Exposures

Patients prescribed with NOACS (dabigatran, rivaroxaban, apixaban, edoxaban) or warfarin will be grouped as a single exposure group and analysed as a whole.
On treatment duration will be expressed in patient year for the follow-up duration to calculate the incidence of various clinical events during the on-treatment duration.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- Outcome name: A combined endpoint of three outcomes; 1) emergency surgery, (2) major bleeding due to fracture (3) major bleeding due to trauma
- Definition: each events will be defined as following:
  (1) Emergency Surgery defined as any surgical procedure(International Classification of Diseases (ICD) 10 code K000-879) performed on the same day as hospital admission with additional claims associated with urgent fee MDV codes (114701370, 160000210, 180709110)
  (2) Major bleeding due to fracture
  Any bleeding associated with hospitalization or blood transfusion (ICD10 code E83.111) accompanied by any fracture (M484, M80, S021, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142) listed as the primary diagnosis requiring most medical resource
  (3). Major Bleeding due to trauma
  Any bleeding associated with hospitalization or blood transfusion (ICD10 code E83.111) accompanied by any trauma (S00-S09, I620, M125, M164, M165, M172, M173, M191, M483, M872, S065, S066, S081, S089, S130, S18, S230, S480, S481, S532, S533, S580, S581, S589, S633, S634, S680, S681, S684, S688, S689, S780, S789, S889, S980, S981, S982, T050, T053, T058, T059, T116, T136, T147, T794, T795, T796, T797, S271, S272, S330, S334, S382, S480, S481, S532, S580, S581, S589, S633, S634, S680, S681) listed as the primary diagnosis requiring most medical resource

9.3.2.2 Secondary outcomes

Outcome name: cardiac tamponade and pericardiocentisis

Event Definition:
(1). Cardiac tamponade diagnosis (ICD 10 code 4200001) on the same or next day as catheter ablation or PCI (MDV procedure codes 150153910, 150267810, 150263310, 150284310, 150303310, 150345710, 150374910, 150375010, 150375210, 150375310, 150375410)
(2). Pericardiocentisis (MDV procedure code 140010510) on the same or next day as catheter ablation or PCI (MDV procedure codes as above)

9.3.3 Covariates

These covariates will be used as patient characteristics for the overall population with the primary outcome events.

1. History of stroke or transient ischemic attack yes/no
2. History of myocardial infarction yes/no
3. History of heart failure yes/no
4. History of diabetes mellitus yes/no
5. History of dyslipidemia
6. History of arterial hypertension yes/no
7. History of peripheral artery disease
8. History of kidney impairment
9. History of valvular disease
10. History of liver disease
11. History of dementia
12. History of trauma
13. History of fracture
14. Nursing home resident
15. History of bleeding
16. Charlson co-morbidity index [3]
17. Concomitant medication yes/no for the following:
    a. aspirin
    b. clopidogrel
    c. angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACE)
    d. beta-blocker
    e. amiodarone
    f. calcium-channel blocker (CCB)
    g. diuretics
    h. statins
    i. proton-pump inhibitor
    j. H_2 receptor antagonist

The disease, Charlson co-morbidity index and concomitant medication are defined as Table 1-Table 4. Nursing home resident is defined as MDV codes 113011710, 113016010, 114020910.

Table 1 Definition of clinical history

Disease	Definition	
	ICD10code	prescription
Stroke or transient ischemic attack	I60-I64, G45	-
Myocardial infarction	I21-I23	-
Heart failure	I110, I130, I132, I420, I50	Prescribed furosemide (defined by generic name)
Diabetes mellitus	E100, E101, E109, E110, E111, E119, E14	Prescribed drugs used in diabetes (defined by Anatomical Therapeutic Chemical (ATC) code as A10)
Dyslipidemia	E78	-
Arterial hypertension	I10-I15	Prescribed 2 or more types of anti-hypertensive (defined in Table 2)
Peripheral artery disease	I702-I709, I71, I739	-
Kidney impairment	N28	-
Valvular disease	I059, I089, I358, I38, I48	-
Liver disease	K70-K77	-
Dementia	F00-F03, G30	-
Trauma	S00-S09, I620, M125, M164, M165, M172, M173, M191, M483, M872, S065, S066, S081, S089, S130, S18, S230, S480, S481, S532, S533, S580, S581, S589, S633, S634, S680, S681, S684, S688, S689, S780, S789, S889, S980, S981, S982, T050, T053, T058, T059, T116, T136, T147, T794, T795, T796, T797, S271, S272, S330, S334, S382, S480, S481, S532, S580, S581, S589, S633, S634, S680, S681	
Fracture	M484, M80, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142	
Bleeding (gastro-intestinal, etc.)	K25-K29, K922, R04, R31, R58, K250, K260, K270, K280, K290, S063, S064, S065, S066	-

Table 2 Definition of anti-hypertensive

Class/type	ATC code
CCB	C08A0
ARB	C09C0
ACE	C09A0
Diuretics	C03A1, C03A2, C03A3, C03A7, C03A9
Thiazide diuretic	C03A3 (Thiazide, plane), C02D0 (Rauvolfia alkaloids)
Beta blocker	C07A0
Alpha-adrenoreceptor antagonists	C02A2
Potassium-sparing agents	C03A1
Others	C02A1 (Antihypertensives), C02A3 (Antihypertensives for pulmonary arterial hypertension), C09X0 (Other agents acting on the renin-angiotensin system)
Combination agents	C09D1 (ARB and diuretics), C09D3 (ARB and CCB)

Table 3 Definition of disease/conditions and weighted index for Charlson co-morbidity score

Score	Desease/conditions	Definition (ICD-10 code)
1	Myocardial infarct	See Table 1
1	Congestive heart failure	I110, I130, I132, I500
1	Peripheral vascular disease	I70-I74, I77
1	Cerebrovascular disease	I60-69
1	Dementia	See Table 1
1	Chronic pulmonary disease	J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983
1	Connective tissue disease	M05, M06, M08, M09, M30-M36, D86
1	Ulcer disease	K221, K25-K28
1	Mild liver disease	B18, K700-K703, K709, K71, K73, K74, K760
1	Diabetes mellitus	See Table 1
2	Hemiplegia	G81, G82
2	Moderate/severe renal disease	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
2	Diabetes mellitus with chronic complications	E102-E018, E112-E118
2	Any tumor	C00-C75
2	Leukemia	C90-C96
2	Lymphoma	C81-C85, C88, C90, C96

Table 3 (cont'd)

Score	Desease/conditions	Definition (ICD-10 code)
3	Moderate/severe liver disease	B150, B160, B162, B190, K704, K72, K766, I85
6	Metastatic solid tumor	C76-C80
6	AIDS	B21-B24

Table 4 Definition of concomitant medication

Drug	Definition	
	ATC code	Generic name
Aspirin	-	Aspirin, aspirin dihydroxyaluminum aminoacetate magnesium carbonate
Clopidogrel	-	Clopidogrel sulfate
ARB or ACE	C09A0, C09C0, C09D1	-
Beta blocker	C07A0	-
Amiodarone	-	Amiodarone hydrochloride
CCB	C08A0	-
Diuretics	C03A1, C03A2, C03A3, C03A7, C03A9	-
Statins	C10A1	-
Proton pump inhibitor	A02B2	-
H_2 receptor antagonist	A02B1	-

9.4 DATA SOURCES

MDV commercial claims database will be used.
Observation period for the primary objective is planned from March 2011 to June 2016 considering the launch date of dabigatran. The observation period for the secondary objective is from March 2008 to June 2016.

9.5 STUDY SIZE

This study plans no formal hypothesis testing.
The previous study 1160.279 has identified the patients with confirmed 6 months of baseline period and no OAC treatment (defining "treatment naïve" new starter population). The total of these patients was 62,888. The breakdown by OAC initiated was 7,441 for dabigatran, 23,412 for warfarin, 16,026 for apixaban, 12,779 for rivaroxaban and 3,230 for edoxaban. The average on-treatment follow-up period for pooled OAC in patients with at least one year of baseline period prior to index date excluding the time after switching from one OAC to another was approximately 0.3 year. The average on-treatment follow-up period for pooled

OAC including the time afer switching with 6 months of baseline period is unknown, but should be longer than 0.3 year.

9.6 DATA MANAGEMENT

Data are provided as electrical data formatted csv by MDV and stored and managed in Milliman Inc.
SAS and Microsoft Excel are used for statistics.

9.7 DATA ANALYSIS

9.7.1 Main analysis

For the primary outcome
Incidence rate of emergency surgery and major bleeding due to fracture/trauma will be described with each number of patients with event, patient-year and 95% confidence interval overall and stratified by age (age <64, 65-74 and >75). Baseline characteristics of patients overall and stratified by age will be provided in a tabulated format.

For the secondary outcome
2. Incidence rates of cardiac tamponade and peri-cardiocentesis, along with number of events, patient year of follow-up not including time after switch, and 95% confidence interval.

9.8 QUALITY CONTROL

Milliman will conduct a quality check as below:
Calculation check: both of program codes for calculation and the data codes used the calculation will be checked by different person from that who calculated.
Pre-release peer review: comprehensive check on methodology, calculation process, and consistency of results will be performed by a qualified peer-reviewer.
Post-release peer review: comprehensive check on the project will be conducted by qualified peer-reviewer belonging to another office.

9.9 LIMITATIONS OF THE RESEARCH METHODS

- The sensitivity and specificity of the definitions used in this study, particularly the use of urgent fee, trauma, fracture MDV codes, is unknown. Additionally, there have been no published studies validating the codes to identify emergency surgery, trauma, fracture, cardiac tamponade or pericardiocentesis.
- The findings from this study may not be generalizable to other Japanese population outside of DPC hospitals
- All information of each patient is from consent giving DPC hospitals. If patients have visits to other medical institutions, these data are not included in the MDV data.

9.10 OTHER ASPECTS

None

9.11 SUBJECTS

The source population is Japanese patients who have claims data in MDV commercial database. In order to have claims in the database, the patients must have received some medical intervention, out or in-patient hospital visit, or pharmacy prescription from the DPC hospitals in Japan. DPC hospitals are large hospitals, often associated with medical schools or government funding, providing both acute and chronic medical care in Japan. Compared to non-DPC hospitals, they tend to provide more specialized, intensive medical care in addition to outpatient primary care tending to chronic disease requiring non-urgent care. MDV database has contractual agreement to receive claims data from approximately 12% of all DPC hospitals in Japan, and the selection is based on the willingness on the side of DPC hospitals to receive either financial compensation or data services from MDV.
The inclusion and exclusion criteria are intended to select those Japanese atrial fibrillation patients who have non-valvular etiology and have newly initiated oral anti-coagulants for stroke prevention. The exclusion criteria also include patients on dialysis or kidney transplant and having records of deep vein thrombosis or pulmonary embolism to exclude those patients who are presumed to have high risk of bleeding and those receiving OAC for indications other than atrial fibrillation.
The data cut-off of 14 Mar 2011 to 30 June 2016 is to select those claims that have occurred after the launch of dabigatran and to the most recent available data cut from MDV at the time of protocol writing.

The availability of co-variates for matching was evaluated in the feasibility analysis of CTMS 1160.279. External validity was assessed by comparing the incidence of claims defined incidence of stroke, intracraniala haemorrhage and systemic embolism in MDV database against previously reported prospective atrial fibrillation registry conducted in Japan by Koretsune et al [4]

9.11.1 Cases

Not Applicable

9.11.2 Controls

Not Applicable

9.12 BIAS

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1. Selection bias: the database is derived from claims arising from DPC hospitals which tend to treat patients with acute and severe disease, and thus may not reflect the general NVAF population of Japan.
2. Misclassification bias: outcomes of emergency surgery and bleeding due to fracture/trauma are not validated.

10. PROTECTION OF HUMAN SUBJECTS

As this is a study based on databases using anonymous and personally unidentifiable data; therefore protection of human subjects is not applicable for this study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

No safety reporting is needed as this is a retrospective study using anonymized, existing database.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A manuscript describing this work will be submitted for publication in a peer-reviewed journal (Japanese medical journal).

13. REFERENCES

13.1 PUBLISHED REFERENCES

[1] Büchele G, Rapp K, König HH, Jaensch A, Rothenbacher D, Becker C, Benzinger P. The Risk of Hospital Admission Due to Traumatic Brain Injury Is Increased in Older Persons With Severe Functional Limitations. J Am Med Dir Assoc. 2016;17(7):609-12.
[2] Curtis EM, van der Velde R, Moon RJ, van den Bergh JP, Geusens P, de Vries F, van Staa TP, Cooper C, Harvey NC. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016 Jun;87:19-26.
[3] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
[4] Koretsune Y, Yamashita T, Yasaka M, Oda E, Matsubayashi D, Ota K, Kobayashi M, Matsushita Y, Kaburagi J, Ibusuki K, Takita A, Iwashita M, Yamaguchi T. Usefulness of a healthcare database for epidemiological research in atrial fibrillation. J Cardiol. 2016: S0914-5087(16)30289-1.

13.2 UNPUBLISHED REFERENCES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
	None		

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

None

APPROVAL / SIGNATURE PAGE

Document Number: c18071759 **Technical Version Number:1.0**

Document Name: non-intervention-study-protocol-1321-0022

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor		20 Jul 2017 04:09 CEST
Approval- Medical Affairs		20 Jul 2017 07:01 CEST
Approval- Medicine		20 Jul 2017 13:30 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed