| | |
|---|---|
| **Document Number:** | |
| **BI Study Number:** | 1160-0304 |
| **BI Investigational Product(s)** | Dabigatran (Pradaxa®) |
| **Title:** | Relationship of Advanced Holding Education and ADherence on antithrombotic in younger NVAF patients |
| **Brief lay title:** | ReAHEAD |
| **SAP version identifier:** | Version 1.0 |
| **Date of last version of SAP:** | NA |
| **NIS Statistician**<br>[SAP author] | [redacted]<br>Tel: [redacted] ext. [redacted]<br>Fax: [redacted]<br>Email: [redacted] |
| **NIS** [redacted]<br>[SAP reviewer] | [redacted]<br>Tel: [redacted]<br>Mobile: [redacted]<br>Fax: [redacted]<br>Email: [redacted] |
| **NIS Data** [redacted]<br>[SAP reviewer] | [redacted]<br>Tel: [redacted] ext. [redacted]<br>Fax: [redacted]<br>Email: [redacted] |
| | |

# TABLE OF CONTENTS

# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AF | Atrial fibrillation |
| ALP | ALkaline Phosphatase |
| ALT | ALanine aminoTransferase |
| AST | ASpartate aminoTransferase |
| BI | Boehringer Ingelheim |
| Ccr | Creatinine clearance rate |
| CrCl | Creatinine Clearance |
| CI | Confidence Interval |
| CRF | Case report form |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| DMP | Data Management Plan |
| DVP | Data Validation Plan |
| GCP | Good Clinical Practice |
| GEP | Good Epidemiological Practice |
| GPP | Good Pharmacoepidemiology Practice |
| eGFR | estimated Glomerular Filtration Rate |
| ICH | International Conference on Harmonisation |
| IQR | Interquartile range |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| MMAS-8 | Morisky 8-Item Medication Adherence Questionnaire |
| NIS | Non-interventional study |
| NOAC | New Oral AntiCoagulants |
| NSAID | NonSteroidal Anti-Inflammatory Drug |
| NVAF | Non-valvular atrial fibrillation |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis Software |
| SD | Standard Deviation |

# 2. RESPONSIBLE PARTIES

| Title | Name |
|---|---|
| [redacted] | |
| Medical Advisor | [redacted] |
| Medical Affairs Operation Specialist | |
| [redacted] | |
| [redacted] | [redacted] |
| Project [redacted] | |
| Medical Affairs | |
| Regulatory Affairs/Assistant [redacted] | |
| Data [redacted]/Biostatistician [redacted] | |
| Clinical Research [redacted] | |

# 3. PURPOSE AND SCOPE

This document is based on the final protocol (Version 1.0/21-Oct-2020) of BI Study Number 1160-0304 that have been approved by Institutional Review Board (IRB). This document is intended to provide comprehensive details on all statistical programming specifications and statistical methodology for analysis of BI Study Number 1160-0304. This document also provided anticipated data transformations, manipulations, coding, and other details of the analysis not provided in the study protocol. A detailed description of the planned table and figures presented in the clinical study report (CSR) is provided in the mock-up tables documents. This SAP only covers the planned analysis of all safety and efficacy data collected on paper (source documents) and captured in case report forms (CRFs).

This document is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, “Guidance for Industry: Statistical Principles for Clinical Trials” and the ICH E3 guideline entitled, “Guidance for Industry: Structure and Content of Clinical Study Reports”.

# 4. AMENDMENTS AND UPDATES

(None)

# 5. RESEARCH QUESTION AND OBJECTIVE

The primary objective of this study is to explore whether the advanced educational intervention would improve the adherence to dabigatran, in a 12-month follow-up period for newly diagnosed atrial fibrillation (AF) adult patients under 75 years old.

The secondary objectives are to describe comorbidities and [redacted] VASc score at baseline and at the end of the study; and to describe stroke, thromboembolic events, and bleeding events in dabigatran patients in a 12-month follow-up period for AF adult patients under 75 years old.

# 6. RESEARCH METHODS

## 6.1 STUDY DESIGN

This is a multi-center, 1:1 randomized study to evaluate the effects of educational intervention on adherence to dabigatran, for up to 12 months. The study will be carried out at around 20 hospitals (20 ± 3), where AF patients are mainly treated in Taiwan. A total of 1,200 patients are planned to be enrolled to target 1,000 patients included in the analysis.

Patients newly diagnosed with AF within 1 month, under 75 years old, and newly prescribed with dabigatran on physician's decision per local labelling will be enrolled and equally randomized to receive standard of care (routine clinical practice) or standard of care (routine clinical practice) with advanced educational intervention. To create the randomization numbers, we will use block randomization by Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Cary, NC, USA).

The study duration consists of a 1-year enrolment period and a 12-month follow-up period consisting of visits at 3, 6, 9, and 12 months for each individual patient. Being an NIS, the time points of follow-up visits are set in accordance with the routine outpatient follow-ups of AF management in Taiwan. Patients will be continuously followed until death, lost to follow-up, or end of data collection at 12 months, whichever comes first.

The educational materials from "Shared decision making of treatment of NOAC in AF patients" (NTA: 180647) and "Atrial Fibrillation Patient Care in Hospitals" (NTA: 190707) will be used as the educational materials for the experimental group. The education materials will be delivered after randomization (baseline); and at 3, 6, and 9 months thereafter. The adherence to dabigatran will be measured by MMAS-8 score at 3, 6, 9, and 12 months.

The comorbidities, [redacted]VASc score, and HAS-BLED score will be recorded at baseline; and at 3, 6, 9, and 12 months. Stroke, thromboembolic events, and bleeding-related events will also be captured during 12 months of follow-up.

The whole NIS will be implemented by a Contract Research Organization (CRO) under Local Boehringer Ingelheim's governance.

## 6.2 SETTING

The study is planned to be carried out at around 20 hospitals (20 ± 3), where AF patients are mainly treated in Taiwan. A total of 1,200 patients will be enrolled to have 1,000 patients included in the analysis.

### 6.2.1 Study sites

Selected sites include around 20 hospitals (20 ± 3) (mostly are major medical centers) in Taiwan, from Northern to Southern area, with physicians, facilities, and adequate clinical data that reflect the locally clinical practice. The site selection criteria will help to ensure that the patients recruited into this study will be the representative of the AF population treated with dabigatran and the healthcare settings in Taiwan.

### 6.2.2 STUDY POPULATION

Potential patients will be screened in accordance with the following study criteria. Only patients who meet all study criteria will be enrolled and randomized into study groups.

A subject screening log should be kept at the site, recording basic information (e.g., initials, gender, date of birth, and reasons for not enrolling the patient) on all patients who are invited to participate in the study, with the information on the eligibility (or reasons for non-eligibility) and date of signed informed consent. In addition, a log of all patients included into the study (i.e., having given informed consent) will be maintained in the study file at the study site.

**Inclusion criteria**

Patients can be included if ALL the following criteria are met:

(1) Provide written informed consent prior to participation

(2) Female or male patients aged ≥ 20 years and < 75 years, newly diagnosed with non-valvular atrial fibrillation (NVAF) within 1 month and has newly prescribed with dabigatran on physician' s decision before study enrolment.

**Exclusion criteria**

Patients should not be included if ANY ONE of the following criteria is met:

(1) Contraindication to the use of dabigatran (i.e., active pathological bleeding, history of a serious hypersensitivity reaction to dabigatran [e.g., anaphylactic reaction or anaphylactic shock], severely impaired renal function [Ccr < 30 mL/min], hemorrhagic manifestations, bleeding diathesis, mechanical prosthetic heart valve, congenital or acquired coagulation disorders, organic lesions with bleeding tendency, or concomitantly use systemic ketoconazole, cyclosporine, and itraconazole)

(2) Participate in other interventional trials currently or in the past 30 days.

**Withdrawal criteria**

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her well-being. If a patient ends the study earlier, the physician must record the discontinuation/withdrawal reason on the CRF. A patient may discontinue the study participation due to any one of the following reasons:

(1) Withdrawal of consent

(2) Lost to follow-up

(3) Administrative problems

(4) Death

### 6.2.3 STUDY VISITS

The collection of patient data will be managed in line with routine clinical practice in an outpatient manner, which will have follow-ups at approximately every 3 months in Taiwan. Information on variables of interest will be collected at inclusion (baseline visit) and captured during the follow-up period at 3, 6, 9, and 12 months (time window: ± 6 weeks) until completion of the study.

Data will be collected and recorded on the CRF according to Table 1 which lists all of the data of interests with an "X" to show the time points when they are collected. Data will be collected after the patient has consented to participate in the study. Once the patient has signed the informed consent form, the patient is considered to be enrolled in the study and patient details should be recorded on the enrolment log.

Table 1 Data collection schedule

| **Event** | **Screening/Baseline** | **Follow-up** | | | |
|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** |
| **Month** | **0** | **3** | **6** | **9** | **12** |
| **Week** | **0** | **12** | **24** | **36** | **48** |
| Allowed window | -- | ± 6 weeks | | | |
| Informed consent | X | | | | |
| Inclusion/exclusion | X | | | | |
| Randomization | X | | | | |
| Demographics[1] | X | W/A | W/A | W/A | W/A |
| AF-related medical histories[2] | X | | | | |
| Comorbidities | X[3] | X[4] | X[4] | X[4] | X[4] |
| Serum creatinine (for CrCl) and eGFR[5] | X | X | X | X | X |
| [redacted]VASc score | X | X | X | X | X |
| HAS-BLED score | X | X | X | X | X |
| Lab data for HAS-BLED[6] | X | X | X | X | X |
| Concomitant therapies for HAS-BLED[7] | X | X | X | X | X |
| Education (experimental group) | X | X | X | X | |
| Dabigatran treatment | X | X | X | X | X |
| Concomitant therapies for AF or stroke[8] | X | X | X | X | X |
| MMAS-8 score | | X | X | X | X |
| Stroke and thromboembolic events[9] | → | | | | |
| Bleeding-related events[10] | → | | | | |
| Safety reporting[11] | → | | | | |

1. Demographics include date of birth, gender, race, education level, height, weight, and alcoholic status (defined as ≥ 8 units [1 unit = approximately 355-mL beer, 150-mL wine, 20-mL Kaoliang] of consumption per week). Follow-up visits will only collect weight (W) and alcoholic status (A).
2. Include date of AF diagnosis and type of AF (paroxysmal, persistent or permanent).

3. At baseline, comorbidities will be recorded as follows according to the medical records:
   - Currently ongoing diseases: Hypertension, diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
   - Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque) ischemic heart disease, stroke, transient ischemic attack, and thromboembolism
4. At follow-up visits, only the current and newly onset of comorbidities since the last visit should be recorded. Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia
5. CrCl will be calculated using Cockcroft-Gault formula.
   - For baseline, the most updated results prior to the enrolment will be collected.
   - For follow-up visits, data within the allowed window and closest to the visit will be collected.
6. Lab data include liver function tests (bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]) and coagulation tests (international normalized ratio [INR] and prothrombin time [PT]. For baseline, the most updated results prior to the enrolment will be collected.
   - For follow-up visits, data within the allowed window and closest to the visit will be collected.
7. Concomitant therapies are chronic dialysis or renal transplant due to abnormal renal function & medication usage predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs [NSAIDs]).
   - For baseline, chronic dialysis or renal transplant prior to baseline will be collected, while medication usage predisposing to bleeding within 1 month prior to baseline will be collected.
   - For follow-up visits, concomitant therapies used during the interval of visits will be collected.
8. Concomitant therapies for AF or stroke prevention within 1 month prior to the enrolment will be collected at baseline.

   Changes in concomitant therapies will be collected at follow-up visits.

9. Events include but not limited to stroke, myocardial infarction, peripheral arterial occlusion, pulmonary embolism, venous thrombosis, transient ischemic attack, and thromboembolism.
10. Events include but not limited to intracranial, gastrointestinal, intraspinal, intraocular, pericardial, intra-articular, intramuscular, perioperative, retroperitoneal, and genitourinary bleeding.
11. Dabigatran relevant adverse drug reaction (ADR, serious and non-serious), fatal adverse events (AEs), and pregnancies.

6.2.3.1 Screening/Baseline (Visit 1)

The following procedures will be performed at the baseline visit. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Collect signed informed consent form. A copy of the signed consent should be given to the patient.
- Assess the eligibility according to the inclusion/exclusion criteria and record the date of inclusion
- Randomize the eligible patients into one of the study groups (standard of care OR standard of care with advanced educational intervention)
- Collect demographic data (date of birth, gender, race, education level, height, weight, and alcoholic status [defined as ≥ 8 units of consumption per week])
- Record AF-related medical histories
- Record the following comorbidities:
  - Currently ongoing diseases: Hypertension, diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
  - Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, stroke, transient ischemic attack, and thromboembolism
- Collect the latest results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR prior to the baseline
- To acquire HAS-BLED score:
  - Record the latest results of bilirubin, AST, ALT, ALP, INR, and PT prior to the baseline
  - Record if the subject is receiving chronic dialysis or had undergone renal transplant due to abnormal renal function prior to the baseline; and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) within 1 month prior to the baseline

- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the concomitant therapies for AF or stroke prevention within 1 month prior to the baseline (generic name or name of the therapy)
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

Information to be collected from screen failure individuals

The screening log entry with demographic information and the primary reason for not continuing or ineligibility must be completed for all screened patients that do not qualify for study entry. No CRF other than the screening log will be collected from these patients. The subject number of ineligible patients should be kept. The following enrolments will be numbered in sequence.

#### 6.2.3.2 Month 3 ± 6 weeks (Visit 2)

The following procedures will be performed at 3 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since the baseline (during baseline to Month 3). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 3 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 3 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during baseline to 3 months

- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention after baseline (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

#### 6.2.3.3 Month 6 ± 6 weeks (Visit 3)

The following procedures will be performed at 6 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since Visit 2 (during Month 3 to Month 6). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 6 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 6 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 3 to 6 months
- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any

- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

#### 6.2.3.4 Month 9 ± 6 weeks (Visit 4)

The following procedures will be performed at 9 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since Visit 3 (during Month 6 to Month 9). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 9 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR, and PT if available in medical record. Only the values within the allowed window and closest to 9 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 6 to 9 months
- The educator delivers advanced education to subjects in the experimental group.
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

6.2.3.5 Month 12 ± 6 weeks (Visit 5)

The following procedures will be performed at 12 months after the baseline. Data will be collected from the medical charts and recorded on the CRF when they are available.

- Record the weight and alcoholic status (defined as ≥ 8 units of consumption per week)
- Record the active or newly onset of comorbidities since the visit 4 (during Month 9 to Month 12). Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 μmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Collect the results of serum creatinine (will be used to calculate CrCl by Cockcroft-Gault formula) and eGFR if available in medical record. Only the values within the allowed window and closest to 12 months will be collected.
- To acquire HAS-BLED score:
  - Record the results of bilirubin, AST, ALT, ALP, INR and PT if available in medical record. Only the values within the allowed window and closest to 12 months will be collected.
  - Record if the subject is receiving chronic dialysis or have undergone renal transplant due to abnormal renal function, and medication usage predisposing to bleeding (antiplatelet agents or NSAIDs) during 9 to 12 months
- Record the use of dabigatran (dose, date of administration)
- Record the change of concomitant therapies for AF or stroke prevention since the last visit (generic name or name of the therapy)
- Complete the measurement of MMAS-8 score
- Record the occurrence of stroke and thromboembolic events, if any
- Record the occurrence of bleeding-related events, if any
- Do safety reporting if any dabigatran relevant ADR, fatal AEs, and pregnancies occurs

### 6.2.4 Study discontinuation

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

(1) Failure to meet expected enrolment goals overall or at a particular study site

(2) Emergence of any efficacy/safety information that could significantly affect the continuation of the study, or any other administrative reasons.

(3) Violation of Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), or Good Pharmacoepidemiology Practice (GPP) (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).

# 7. VARIABLES

### 7.1.1 Exposures

Being an NIS, the prescription of dabigatran will be in accordance with the Summary of Product characteristics and physician's discretion. Treatment record of dabigatran will be collected and recorded on CRF across the 12 months of study period. Data to be collected include start/end date of administration, dose, and the reason for dose adjustment or interruption.

Mean daily dose of dabigatran will be summarize by study group. If dabigatran treatment recorded in CRF had discontinued (that's the end date of administration had been recorded), the dabigatran treatment duration will be the time range of start/end date of administration. However, if dabigatran treatment recorded in CRF is ongoing, the dabigatran treatment duration will be the time range of start date of administration to the date of last dabigatran treated.

### 7.1.2 Outcomes

#### 7.1.2.1 Primary outcomes

The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 12 months in patients with and without advanced educational intervention

- The MMAS-8 is an 8-item structured, self-report measure that assesses medication adherence. It has been proved to be a valuable resource to address adherence concerns, such as forgetting to take medications or discontinuing medications without guidance. If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with non-adherence.
- The validated Chinese MMAS-8 will be used to evaluate the adherence to dabigatran at baseline and every follow-up visit. Patients are considered to have low adherence with scores less than 6, medium adherence with scores of 6 to 7, and high adherence with a score of 8.

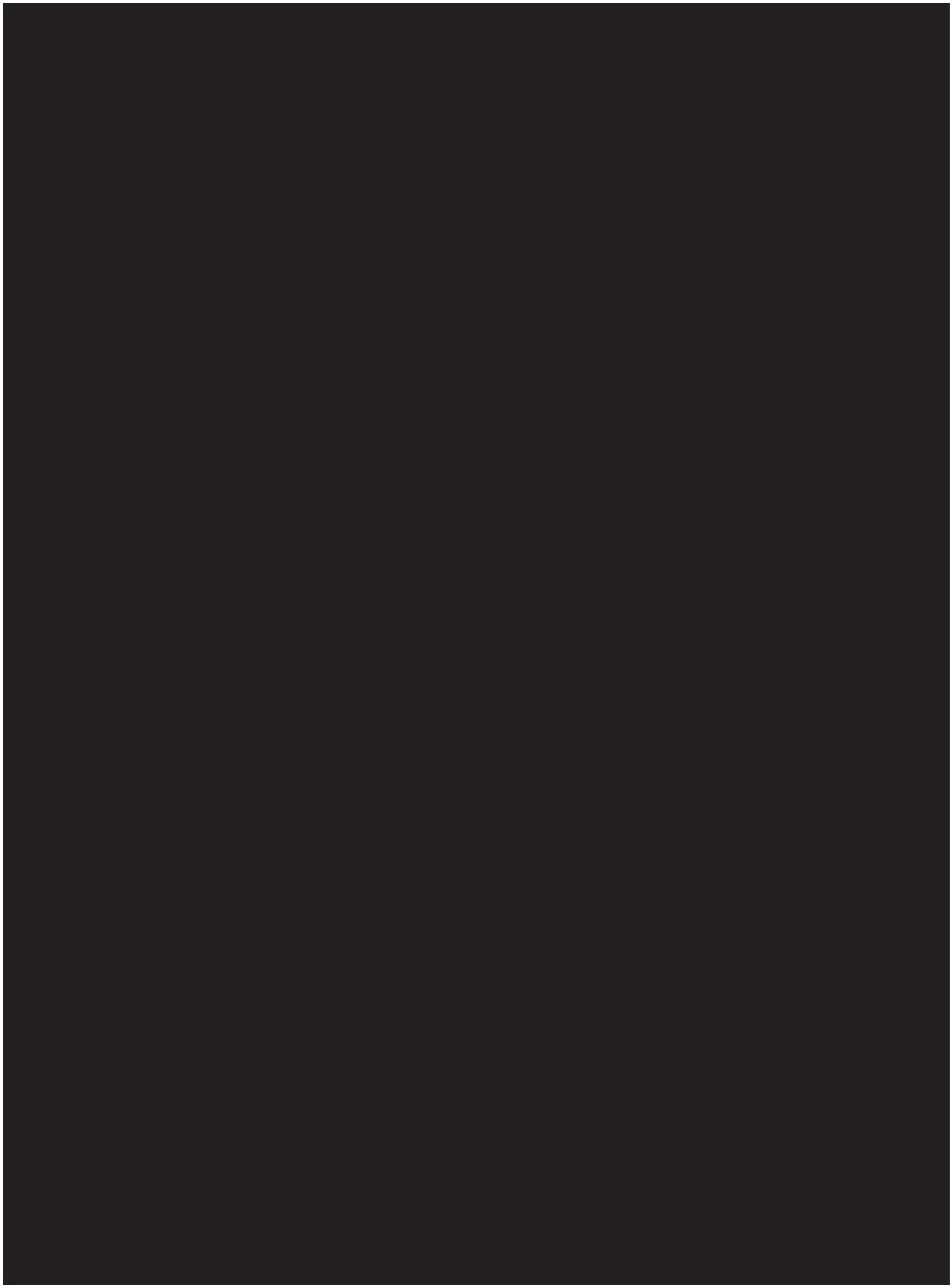
#### 7.1.2.2 Secondary outcomes

(1) The proportion of patients with high adherence to dabigatran treatment which is defined as achieving the MMAS-8 score of 8 points at 3, 6, and 9 months in patients with and without advanced educational intervention

(2) The proportion of patients with medium (MMAS-8 score: 6 – 7 points) and low (MMAS-8 score < 6 points) adherence to dabigatran treatment at 3, 6, 9, and 12 months in patients with and without advanced educational intervention

(3) The mean MMAS-8 score at 3, 6, 9, and 12 months in patients with and without advanced educational intervention

(4) The discontinuation rate of dabigatran and reasons for discontinuation (switch or stop treating dabigatran) in patients with and without advanced educational intervention



### 7.1.3 Covariates

Patients recruited will be evaluated for covariates at the visit of baseline. Potential confounders include demographics (age, gender, race, and educational level), [redacted] VASc score, HAS-BLED score, comorbidities, concomitant therapies, dose of dabigatran, and renal function.

Statistical methods will be performed to test the difference of covariates between the study group at the visit of baseline (please referred to section 10. data analysis). If any significant difference occurred, linear regression will be conducted to model the relationship between dependent variable and all explanatory variables.

As for linear regression model, the primary endpoint (MMAS-8 score at 12 months) will be considered as dependent variable, and all covariates listed above including study group variable will be considered as explanatory variable.

#### 7.1.3.1 Baseline characteristics

- Demographics (date of birth, gender, race, educational level, height, weight, and alcoholic status [defined as ≥ 8 units of consumption per week])
- AF-related medical histories (date of AF diagnosis and type of AF [paroxysmal, persistent or permanent])
- Kidney function (CrCl and eGFR)

Value of serum creatinine within the allowed window (i.e., the latest data before baseline & data within ± 6 weeks for follow-up visits) will be collected from medical chart to calculate the CrCl value by Cockcroft-Gault formula as below.

When serum creatinine is measured in mg/dL, the value is multiplied by a constant of 0.85 if the patient is female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

(1) When serum creatinine is measured in μmol/L, constant is 1.23 for male and 1.04 for female.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

- [redacted] VASc score (Section 7.1.3.4)
- HAS-BLED score (Section 7.1.3.5)
- Comorbidities (Section 7.1.3.2)
- Concomitant therapies for AF or stroke prevention: Generic name or name of the therapy

#### 7.1.3.2 Comorbidities

Comorbidities include hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque), ischemic heart disease, left ventricular dysfunction, stroke, transient ischemic attack, thromboembolism,

abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.

At baseline, comorbidities will be recorded as follows according to the medical records:

- Currently ongoing diseases: Hypertension; diabetes, congestive heart failure, left ventricular dysfunction, abnormal kidney function (chronic dialysis, renal transplantation, serum creatinine ≥ 200 µmol/L, or eGFR < 60 mL/min/1.73 $m^2$), abnormal liver function (chronic hepatic disease [e.g., cirrhosis] or biochemical evidence of significant hepatic derangement [e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal]), major bleeding, and predisposition to bleeding/anemia.
- Prior events: Vascular disease (myocardial infarction, peripheral artery disease, and complex aortic plaque) ischemic heart disease, stroke, transient ischemic attack, thromboembolism

At follow-up visits, only the current and newly onset of comorbidities since the last visit (regardless of its condition, resolved or unresolved) should be recorded on the CRF.

#### 7.1.3.3 Concomitant therapy

The study will collect two types of concomitant therapies, including (1) therapies related to the calculation of HAS-BLED score and (2) therapies for AF or stroke prevention. These therapies will be collected according to the plan as below:

(1) Therapies related to HAS-BLED score include chronic dialysis or renal transplant due to abnormal renal function & medication usage predisposing to bleeding (antiplatelet agents or NSAIDs).

- Baseline: Chronic dialysis or renal transplant prior to baseline will be collected, while medication usage predisposing to bleeding within 1 month prior to baseline will be collected.
- Follow-up visits at every 3 months: Used during the interval of visits will be collected

(2) Therapies for AF or stroke prevention:

- Baseline: Used within 1 month prior to the enrolment will be collected at baseline.
- Follow-up visits at every 3 months: Changes in concomitant therapies will be collected.

#### 7.1.3.4 [redacted] VASc score

The [redacted] VASc score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF. The [redacted]-VASc score is composed of eight items with a maximum score of 9. Among all the items, two of them have extra weight of 2 points, including “age 75 and above” and “stroke, transient ischemic attack, and thromboembolism”;

while the other six items are counted as 1 point of each. A higher score corresponds to a greater risk of stroke. The [redacted] VASc score is calculated according to Table 2.

If any of the clinical characteristic shown in Table 2 is missing or not known, the $CHA_2DS_2$-VASc score will be considered as a missing value during data analysis.

Table 2 Acronym [redacted] VASc and the score

| Letter | Clinical Characteristic | Score |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| V | Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque) | 1 |
| A | Age 65 – 74 years | 1 |
| Sc | Sex category (i.e., female sex) | 1 |

7.1.3.5 HAS-BLED score

HAS-BLED[18] is a scoring system developed to assess 1-year risk of major bleeding in patients with AF. The HAS-BLED score is composed of seven items with a maximum score of 9. Among all the items, 2 of them will be scored with 1 or 2 points depending on the number of corresponding description, including “abnormal renal and liver function” and “drugs or alcohol”, while the other five items are counted as 1 point of each. A higher score corresponds to a greater risk of bleeding, and a score of ≥ 3 points indicates "high risk". The HAS-BLED score will be calculated according to Table 3.

If labile INRs in current study is not known, we will consider it as no labile INRs in calculating HAS-BLED score under the premise of no statistical significant difference in the distribution of labile INRs between two study group.

Besides labile INRs, if any of the clinical characteristic shown in Table 3 is missing or not known, the HAS-BLED score will be considered as a missing value during data analysis.

Table 3 Clinical characteristics composing the HAS-BLED score

| Letter | Clinical Characteristic | Score |
|---|---|---|
| H | Hypertension[1] | 1 |
| A | Abnormal renal function[2] and abnormal liver function[3] (1 point each) | 1 or 2 |
| S | Stroke[4] | 1 |
| B | Bleeding[5] | 1 |

| | | |
|---|---|---|
| L | Labile INRs[6] | 1 |
| E | Elderly, age > 65 years | 1 |
| D | Drugs or alcohol (1 point each)[7] | 1 or 2 |

1. Hypertension should be uncontrolled, with systolic blood pressure > 160 mmHg.
2. Abnormal kidney function is classified as a presence of chronic dialysis, renal transplantation, or serum creatinine ≥ 200 μmol/L.
3. Abnormal liver function is defined as the chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2 × upper limit of normal, in association with AST/ALT/ALP > 3 × upper limit normal, and so forth.)
4. Previous history, particularly lacunar.
5. Bleeding history, such as prior major bleeding or predisposition to bleeding (e.g., anemia).
6. Labile INR (e.g., therapeutic time in range < 60%).
7. Drugs are medication usage predisposing to bleeding (e.g. antiplatelet agents or NSAIDs). Ethanol abuse is classified as ≥ 8 units of alcoholic consumption per week.

# 8. DATA SOURCES

As this is a NIS, no diagnostic or monitoring procedures additional to the standard of care and routine practice (except for the additional education delivered to the experimental group) will be applied to the patients. All the assessment will be performed by the investigator if they are deemed necessary for the medical treatment procedure.

This study will collect the data from medical charts and MMAS-8 questionnaires. Investigators or delegated site staffs will record the data on the CRF. Data source includes questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, etc.

# 9. DATA MANAGEMENT AND SOFTWARE/TOOLS

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

Designated CRO will serve as the statistical and data coordinating center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

The data from enrolling patients in this study will be recorded on a CRF or other applicable forms. The designated CRO will capture, check, store, and analyze the data. The designated CRO will follow Boehringer Ingelheim standard operating procedures (SOPs) and their own internal SOPs.

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning, and validation. Validation process will be performed as outlined in a data validation plan (DVP). Queries will be reviewed and sent to the study investigators for clarification. Designated site staffs for investigation are required to reply the queries and make any necessary changes to the data. The queries will be resolved and data will be updates under the agreement of investigator. Once all queries have been resolved, the database will be locked. The locked data will be exported to generate the subject listings, tabulations, and statistical analyses.

Data will be transferred to Boehringer Ingelheim after the closure of the study.

## 9.1 Software/Tools

The data collected will be entered into the study database against the paper CRF. The data will be further exported to Statistical Analysis System® (SAS) for Windows (Version 9.4 or higher, SAS Institute, Cary, North Carolina, USA) to generate the subject listings, tabulations, and statistical analysis.

## 9.2 Handling of Missing Values

No imputation method will be performed to estimate the missing values for all the study variables.

## 9.3 Handling of Inconsistencies in Data and Outliers

Data validation plan will be developed to define validation rules for all the collected data in this study. Data manager will perform the validation process based on validation plan to clarify the inconsistencies if any. The extremely high and/or low value of laboratory data need to be marked as abnormal in CRF. Statistician will perform ST review prior to data lock to identify if any possible wrong values. Query will be generated for the questionable data and site staff need to clarify the data to make sure it is consistent with the source document. No other statistical methods will be performed to modify or exclude the inconsistencies and outliers.

# 10. DATA ANALYSIS

The main and further analysis population will consist of all eligible patients (i.e., all patients who have signed the informed consent and have fulfilled all eligibility criteria).

Continuous variables will be reported as number, mean, standard deviation (SD), minimum, maximum, and 95% confidence interval (CI). Categorical variables will be summarized as number and frequency or percentage with observed (non-missing) data. Missing numbers of both continuous and categorical variables will also be summarized.

As for comparisons of continuous data between baseline and follow-up visit, paired-t test will be performed at the significant level of 0.05. Shapiro–Wilk test will be performed to test the normality of data. When normality assumption is violated, Wilcoxon signed-rank test will be performed instead. On the other hand, McNemar's test will be performed to for comparisons of categorical data between baseline and follow-up visit at the significant level of 0.05.

For the endpoints pre-identified to compare between patients with and without advanced educational intervention, the analyses will be done by independent t-test for continuous data at the significant level of 0.05. Shapiro–Wilk test will be performed to test the normality of data. When normality assumption is violated, Wilcoxon rank-sum test will be performed instead. On the other hand, Chi-square or Fisher's exact test will be performed to for comparisons of categorical data at the significant level of 0.05.

## 10.1 Main analysis

The primary outcome is to describe the proportion of patients with high adherence to dabigatran treatment which is defined as achieving MMAS-8 score of 8 points at 12 months for each group.

- The proportion of patients with high (MMAS-8 score: 8 points) adherence to dabigatran treatment at x months ($P_{H,x}$) is defined as following formula:

$$P_{H,x} = \frac{\text{Number of subjects with 8 points of MMAS} - \text{8 score at x months}}{\text{Number of subjects at x months}}$$

Subjects without MMAS-8 value recorded at 12 months will be excluded from the analysis of primary endpoint. The Chi-square test or Fisher's exact test will be used to test the equality between two study groups.

The secondary analyses are described below:

(1) The proportion of patients with high (MMAS-8 score: 8 points) adherence to dabigatran treatment at each visit (3, 6, and 9 months),

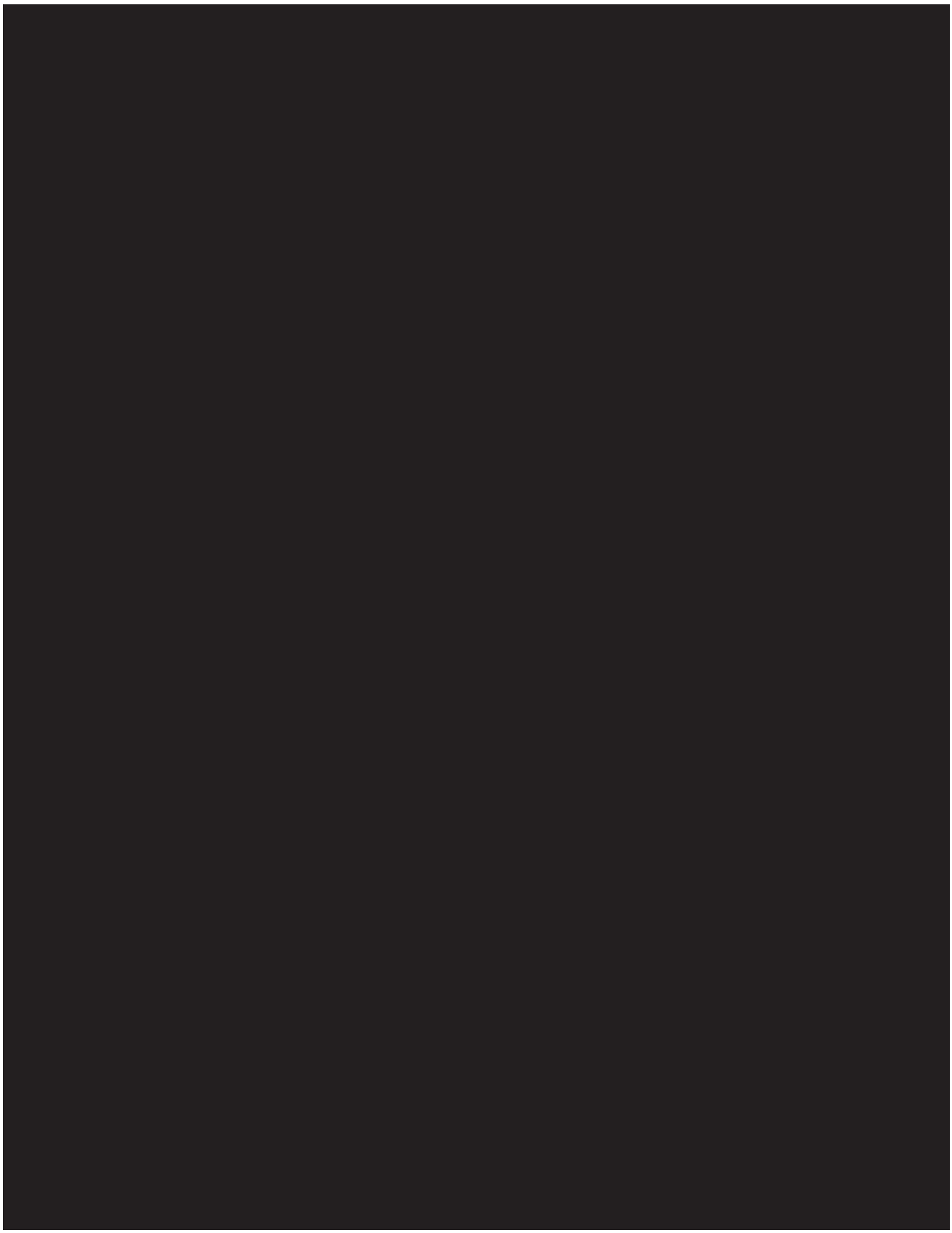
(2) The proportion of patients with medium (MMAS-8 score: 6 – 7 points) and low (MMAS-8 score < 6 points) adherence to dabigatran treatment at each visit (3, 6, 9 and 12 months),

(3) The mean MMAS-8 score at each visit (3, 6, 9 and 12 months) and

(4) The discontinuation rate of dabigatran and reasons for discontinuation (switch or stop treating dabigatran).

Similar as primary endpoint, Chi-square test or Fisher's exact test will be used to test the equality of MMAS-8 score, discontinuation rate and reasons for discontinuation between two

study groups. Lastly, the mean MMAS-8 score between two study groups will be test by Independent t test or Wilcoxon rank-sum test.



[redacted]

# 11. QUALITY CONTROL

The quality control details for study data is referred to study protocol section 9.8.

As for statistical results, responsible biostatistician in current study should stick to all the statistical programming specifications and statistical methodology described in the current document.

Last but not least, designated CRO will assigned an independent biostatistician as double programmer for current study. All statistical results generated by responsible biostatistician need to be the same as those generated by double programmer to ensure the reliability and correction of statistical results.

# 12. REFERENCES

## 12.1 PUBLISHED REFERENCES

None.

## 12.2 UNPUBLISHED REFERENCES

None.

# ANNEX 1. ADDITIONAL INFORMATION

None.

# ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SAP must be sent for review to the following individuals **prior to approval**.

[redacted]

[redacted]

**Study Title:** Relationship of Advanced Holding Education and ADherence on antithrombotic in younger NVAF patients

**Study Number:** 1160-0304

**Protocol Version:** Version 1.0

**I herewith certify that I agree to the content of the study SAP and to all documents referenced in the study SAP.**

| | | |
|---|---|---|
| Position: NIS [redacted] | Name/Date: [redacted] /16 Mar 2023 | Signature: _____ |
| Position: BI Trial Statistician (TSTAT) | Name/Date: [redacted] / 16 Mar 2023 | Signature: _____ |
| Position: BI Trial Statistical Programmer (TPROG) | Name/Date: [redacted] / 16 Mar 2023 | Signature: _____ |
| Position: _____ | Name/Date: _____ | Signature: _____ |