MINI-SENTINEL MEDICAL PRODUCT ASSESSMENT

A PROTOCOL FOR ASSESSMENT OF DABIGATRAN

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History of Modifications

Version	Date	Modification	By
V2	03/18/2014	• Expanded target patient subgroups • Updated relevant ICD-9-CM codes for key outcomes • Expanded list of potential confounders • Expanded description of analysis plan • Provided minor edits and clarifications in response to public comments	Mini-Sentinel Dabigatran Assessment Workgroup
V3	02/06/2015	• Clarification of analytic plan details and addition of subgroup analyses	Mini-Sentinel Dabigatran Assessment Workgroup

**This protocol is modified periodically to document
all major changes made during protocol implementation.**

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I. BACKGROUND

Atrial fibrillation independently increases the risk of ischemic stroke by 4-to-5-fold and is the most common significant cardiac rhythm disorder in adults, affecting 2.5-6 million adults nationally.[1,2] Currently, the estimated lifetime risk for persons aged 40 years is 20%.[3] The prevalence of atrial fibrillation increases strikingly with age, increasing to 10% of those aged ≥80 years old.[1] With the aging of the "baby boom" generation and rising prevalence of risk factors such as hypertension, diabetes and heart failure in the U.S., the prevalence of atrial fibrillation will continue to increase rapidly, with an estimated 6-12 million by 2050.[1,2] In all, atrial fibrillation is a substantial and growing public health concern. Given that randomized controlled trials have not shown any significant differences in stroke rates using aggressive rhythm control,[4] the cornerstone of stroke prevention in remains the judicious and evidence-based use of anticoagulants.

For years, the only proven oral anticoagulants available for stroke prevention in atrial fibrillation were oral vitamin K antagonists (e.g., warfarin). Warfarin has been demonstrated to reduce the risk of ischemic stroke by about 68% compared with a control strategy but is associated with an increased absolute risk of intracranial hemorrhage and other major bleeding.[5] However, warfarin has a narrow therapeutic window, with optimal efficacy and safety at an anticoagulation intensity reflected by an international normalized ratio (INR) 2.0-3.0 and thus requires regular monitoring.[6] For INR <2.0, stroke risk increases sharply; for INR >3.5, risk of intracranial bleeding rises markedly.[7] Warfarin appears to be very effective outside of clinical trial protocols and settings if adequate quality of anticoagulation is achieved.[8]

Dabigatran, an oral direct thrombin inhibitor, was approved in 2010 by the FDA to reduce the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[9] Dabigatran at a dose of 150 mg twice daily was shown to be superior to warfarin for reducing the combined rate of all stroke and systemic embolism among these patients in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.[10,11] The rates of all major bleeding in the trial were similar for dabigatran vs. warfarin (3.3 vs. 3.6 per 100 patient-years, respectively), but the rate of intracranial bleeding was lower for dabigatran (0.3 vs. 0.8 per 100 patient-years) while the rate of major gastrointestinal bleeding was higher (1.6 vs. 1.1 per 100 patient year). Dabigatran is given as a fixed-dose, twice daily regimen and requires no therapeutic monitoring, but does require dose adjustments for severe kidney dysfunction and cannot be used in patients with mechanical prosthetic heart valves and does not currently have any specific antidote.[9]

Questions remain, however, about the outcomes associated with dabigatran outside of the clinical trial setting and in typical clinical practice populations. To address this, this protocol aims **to assess systematically the rates of bleeding and thromboembolic outcomes associated with the use of dabigatran and warfarin for patients with atrial fibrillation** using data from the FDA Mini-Sentinel Distributed Database (MSDD).

II. GOAL OF THE PROTOCOL

Our overall goal is to compare safety outcomes in adults with atrial fibrillation who are new users of dabigatran or warfarin therapy.

III. PROTOCOL DETAILS

A. ASSESSMENT DESIGN

This one-time assessment will employ a "new user" parallel cohort design.[12]

B. COHORT IDENTIFICATION

1. Target Population

We will focus on the identification of **adult (age ≥21 years) patients with diagnosed nonvalvular atrial fibrillation and who are new users of dabigatran or warfarin**.

2. Sample Inclusion and Exclusion Criteria

The target sample inclusion and exclusion criteria are summarized in **Table 1** below. Please see **Appendix A** and *Section D* for additional details, definitions and rationale.

Table 1. Inclusion and exclusion criteria for comparison of adults with atrial fibrillation who are new users of dabigatran or warfarin in the MSDD.

Inclusion Criteria	Exclusion Criteria
• First dispensing of dabigatran or warfarin therapy from November 1, 2010 to the most recent data available in the MSDD from participating Data Partners[*] • Age 21 years or older at the first dispensing of dabigatran or warfarin therapy • One or more diagnoses of atrial fibrillation or atrial flutter based on ICD-9-CM codes (ICD-9-CM 427.31, 427.32) from any practice setting (inpatient or outpatient) any time before the first identified prescription for dabigatran or warfarin therapy during the study period[*]	• Less than 180 days of continuous enrollment with prescription and medical coverage immediately preceding the date of the index dispensing (i.e., index date) • Any prior dispensing for warfarin, dabigatran, rivaroxaban or apixaban during the 180 days before index date[**] • Known mechanical heart valve or diagnosed mitral stenosis at index date based on corresponding administrative diagnosis and/or procedure codes • Chronic hemodialysis or peritoneal dialysis at index date based on corresponding administrative diagnosis and/or procedure codes • History of kidney transplant at index date based on corresponding administrative diagnosis and/or procedure codes • At a skilled nursing facility or nursing home at index date

[*]A single standard "look back" period for determining diagnoses of atrial fibrillation (and other patient characteristics) will be employed that is longer than 180 days and will be determined after an initial evaluation of data from participating Data Partners.

[**]We recognize that a significant fraction of patients who initiate dabigatran are switching from previously using warfarin therapy. While the safety outcomes of patients who switch from warfarin to dabigatran are of interest, assessing the outcomes for patients who switch anticoagulant strategies is complicated by many factors. Toward that end, the focus of this protocol will specifically be on **new users of both warfarin and dabigatran** during the study period. Please see *Section D* for additional details and discussion.

3. Target Patient Subgroups

There are selected patient subgroups for which the outcomes associated with new dabigatran or warfarin use are of particular interest. These include the following:

- Age:
    - < 65 years
    - ≥ 65 years
        - 65-74 years
        - 75-84 years
        - ≥ 85 years
- Gender
- Age and gender:
    - Females age 65-74 years
    - Females age 75-84 years
    - Females age ≥ 85 years
    - Males age 65-74 years
    - Males age 75-84 years
    - Males age ≥ 85 years

Given that the FDA-approved labeling for dabigatran includes dose adjustment for impaired kidney function,[9] if adequate data are available after the feasibility assessment is completed, we will examine the availability of measures or proxies of reduced kidney function in participating Data Partners (e.g., outpatient estimated glomerular filtration rate [eGFR] and/or relevant International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes for chronic kidney disease [e.g., codes 585.3, 585.4, 585.5]) and will conduct exploratory analyses in the subgroup of patients who appear to have varying degrees of kidney function.

C. CHOICE OF COMPARATORS

Based on results from the RE-LY study using adjusted-dose warfarin as the comparator therapy,[10] dabigatran represented the first new oral anticoagulant approved by the FDA for the use in adults with atrial fibrillation for stroke prevention. The approval in October 2010 was for two different doses of dabigatran (150 mg and 75 mg) given twice daily. Since its approval, the use of dabigatran has increased over time in the U.S. and that is also reflected within the MSDD involving the participating Data Partners. Questions remain, however, about the outcomes associated with dabigatran outside of the clinical trial setting and in typical clinical practice populations.

Warfarin therapy at a therapeutic anticoagulation intensity (reflected by INR 2.0 to 3.0) has been the primary recommended therapy during the past 20 years for patients with nonvalvular atrial fibrillation considered at moderate to high risk for ischemic stroke.[13] Data from certain real-world populations have also demonstrated the effectiveness and safety of adjusted-dose warfarin for nonvalvular atrial fibrillation and that it is possible to achieve a high level of quality in delivering warfarin therapy comparable to or even better than observed in recent RCTs. [8] Aspirin is a substantially less effective stroke preventive agent in the setting of atrial fibrillation,[14] is over-the-counter and cannot be ascertained completely in claims and administrative data such as the MSDD. Furthermore, aspirin in combination with clopidogrel is also less effective and associated with a higher rate of bleeding compared with

warfarin therapy in patients with atrial fibrillation.[15] Toward that end, the primary comparison will be examining **bleeding and thromboembolic outcomes between new use of dabigatran or warfarin in patients with nonvalvular atrial fibrillation in the MSDD.**

However, as the effectiveness and safety of warfarin is dependent on the level of anticoagulation intensity (i.e., INR level)[16,17], we will explore the feasibility of obtaining information on outpatient INR test results (and not just administrative claims for testing) in new warfarin users within the MSDD. If there is adequate longitudinal information on outpatient INR test results, then we will consider secondary analyses comparing bleeding and thromboembolic outcomes in new dabigatran users vs. different levels of INR among new warfarin users in the MSDD.

D.   IDENTIFICATION OF THE OUTCOMES OF INTEREST

1.   Primary Outcomes

The primary outcomes will be the occurrence of <u>ischemic stroke</u>, <u>intracranial hemorrhage</u>, <u>all strokes</u> (ischemic stroke + intracranial hemorrhage) as well as episodes of <u>major bleeding</u>. This approach will provide the relevant information on outcomes that matter most to providers and patients with regards to the safety of each therapeutic approach.

Previously described algorithms[8,18] will be used to identify potential ischemic stroke, intracranial hemorrhage and other hemorrhage events. Based on previous work by ATRIA-CVRN Study investigators, the estimated positive predictive values of the following codes and definitions are 82.6% for ischemic stroke, 75.5% for intracranial hemorrhage and 91.8% for major extracranial hemorrhage (A. Go, personal communication):

- **Ischemic stroke** will be identified using hospital claims for <u>primary</u> discharge diagnoses indicating potential stroke events (ICD-9-CM codes 433.x1, 434.x1, 436.xx)
- **Intracranial hemorrhage** will be using hospital claims for relevant <u>primary and secondary</u> discharge diagnoses (ICD-9-CM codes 430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0) We will also conduct a sensitivity analysis that excludes intracranial hemorrhage associated with major trauma (i.e., codes 852.0x, 852.2x, 852.4x, 853.0).
- **Major extracranial hemorrhage** will be identified by using hospital claims for <u>primary</u> discharge diagnoses of extracranial hemorrhage (ICD-9-CM codes 423.0, 455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6, 534.0-534.6, 535.01-535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9, 599.7, 719.11, 784.7, 784.8, and 786.3).
  - **Gastrointestinal (GI) bleeding** will be defined using the major extracranial hemorrhage diagnosis codes indicative of bleeding in the GI tract (ICD-9-CM codes 455.2, 455.5, 455.8, 456.0, 456.20, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6, 534.0-534.6, 535.01-535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, and 578.9).
  - **Non-GI major bleeding** will be defined using the major extracranial hemorrhage diagnosis codes that are not indicative of GI bleeding (ICD-9-CM codes 423.0x, 459.0x, 599.7x, 719.11, 784.7x, 784.8x, and 786.3x).

2. Secondary Outcome

Based on findings from the RE-LY trial[10] and data available in the MSDD, a secondary outcome of clinical and public health interest to compare between new dabigatran and warfarin users will be hospitalized acute myocardial infarction (MI). We will use the approach used in previous Mini-Sentinel protocols which relies on primary hospital discharge diagnoses for myocardial infarction (ICD-9-CM codes 410.x0 or 410.x1) or deaths occurring within one day of an emergency department visit for acute ischemic heart disease (ICD-9-CM code: 410.x0, 410.x1, 411.1, 411.8, 413.x)[19].

E. ANALYSIS PLAN

1. Overview of Study Design

We will employ a "new user" cohort design[12] in comparing outcomes related to new dabigatran vs. warfarin therapy between November 2010 through the most recently available data from participating Data Partners at the time of protocol implementation. New use will be defined using ≥180-day washout period (i.e., patients must be naïve to warfarin, dabigatran, rivaroxaban, and apixaban for at least 180 days before their index dabigatran or warfarin dispensing). The index date will be defined as the dispensing date for the first eligible dabigatran or warfarin dispensing during the study period. The same ≥180-day baseline period, plus the index date, will be used for covariate assessment.

2. Characterizing Longitudinal Exposure to Dabigatran and Warfarin Therapy

Dabigatran exposure. We will rely on pharmacy dispensing data from the MSDD to characterize the initiation and longitudinal exposure to dabigatran (a twice daily drug) in an "as treated" (or "on treatment") approach as the primary goal of the study is to understand outcomes associated with active exposure to dabigatran (vs. warfarin). Follow-up will begin the day after the index date. Dabigatran initiators will contribute person-time for as long as they continue to fill prescriptions for dabigatran. In the primary analyses, we will allow a **"grace period" of 7 days between serial dispensed prescriptions** based on the days supply algorithms to be considered continuously exposed. A sensitivity analysis will use a 14-day grace period.

Warfarin exposure. In primary analyses, we will define continuous warfarin exposure using the same definition used for characterizing continuous dabigatran exposure described above based only on serial dispensing information (using the 7-day grace period as the main approach and also examining use of a 14-day grace period).

We will address early refills of a medication using an approach that attempts to balance accounting for possible stockpiling versus other situations in which the patient has actually used up the earlier prescription. Toward that end, we will use **a 7-day limit for early refill for both dabigatran and warfarin** such that for any refill that occurs within 7 days before the predicted end of a first prescription, the additional days will be added to the end of the second prescription for consecutive prescriptions.

Given the age and comorbidity of the population, it is anticipated that a significant number of patients will be hospitalized each year of the study period, which will lead to periods of person-time in which they will likely not be using their outpatient medications and have a certain amount of drug stockpiling. We recognize that not accounting for this may lead to some drug exposure misclassification and is as a limitation, but we will not attempt to account for

it in defining exposed person-time for either dabigatran or warfarin.

3. Follow-Up and Censoring Events

In primary analyses, follow-up will begin on the day after the index date and patients will be followed for as long as they continue to receive dispensings for their index medication (as described above in *Section C.5.b*). Patients will be censored when they discontinue treatment or are otherwise censored at:

- Death
- Disenrollment from the respective Data Partner
- Initiation of the other comparator treatment (i.e., warfarin or dabigatran) or other anticoagulant (i.e., rivaroxaban, apixaban)
- Admission to a nursing home or skilled nursing facility

Patients will be eligible to enter the analysis only once and will therefore contribute only a single continuous treatment episode. If patients experience multiple events during eligible follow-up time, we will include each of the events, but we will not consider recurrent events of the same type. For example, if a patient experiences an ischemic stroke and then goes on to experience an MI, both events would be counted and analyzed separately. However, if a patient has two ischemic stroke events, only the first would be counted in the analysis of anticoagulant type and risk of ischemic stroke.

4. Approach to Confounding Adjustment

Confounding is a key threat to the validity of observational drug safety assessments. Prior studies have found that patients initiating dabigatran can differ in important ways from those initiating warfarin.[20,21] This assessment will include adjustment for a large number of confounders from several broad categories, including: (1) risk factors for bleeding; (2) risk factors for stroke/thromboembolism in atrial fibrillation as well as MI; (3) indirect measures of frailty; and (4) medications used for cardiovascular conditions and others associated with the risk of stroke and major bleeding – including cardiovascular agents and medications that increase bleeding risk (clopidogrel, prasugrel, ticagrelor, non-steroidal anti-inflammatory drugs [NSAIDs], etc.). These potential confounders are listed in **Table 2** below.

a. Potential confounders

Table 2. Potential confounders measured in the 180 days prior to and including the index date

	Broad categories of confounders	Specifics
1	Risk factors for bleeding	- Hospitalized intracranial bleed - Hospitalized gastrointestinal bleed - Other gastrointestinal ulcer disorder - Other hospitalized bleed - Coagulation defects
2	Risk factors for MI and stroke/thromboembolism in atrial	- Age - Gender

	Broad categories of confounders	Specifics
	fibrillation	- Atrial fibrillation - Atrial flutter - Ischemic stroke - Transient ischemic attack - Other ischemic cerebrovascular events - Nonspecific cerebrovascular symptoms - Other arterial embolism - Prior VTE/phlebitis - VTE risk NOS indicators - Prior central venous thrombosis - Major trauma potential causing prolonged immobilization - Major surgery - Chronic heart failure - Hypertension - Hyperlipidemia - Diabetes mellitus - Level of kidney function (eGFR)* - Advanced diagnosed kidney dysfunction - Advanced liver disease - Metastatic cancer - Alcoholism - Smoking* - MI - Acute coronary syndrome (ACS) - Percutaneous coronary intervention (PCI) - Coronary artery bypass surgery (CABG) - Peripheral arterial disease - Anemia
3	Measures of overall health status, including of frailty	# of distinct dispensed medications # of prior hospitalizations # of prior physician visits - Combined comorbidity score[22] - Use of home oxygen - Wheelchair use* - Walker use* - Cane use* - Commode chair use*

	Broad categories of confounders	Specifics
		• Osteoporotic fracture • Falls
4	Medications – including cardiovascular agents, medications that may increase bleeding risk, and medications listed on label	• Antiplatelet agents (clopidogrel, prasugrel, ticagrelor, ticlopidine) • Prescription non-steroidal anti-inflammatory drugs (NSAIDs) • Statins • Non-statin lipid-lowering agents • ACE inhibitors • Angiotensin receptor blocker (ARBs) • Aldosterone receptor antagonists • Beta blockers • Calcium channel blockers • Selective serotonin receptor inhibitors (SSRIs) • Prescription H2 blocker or proton pump inhibitors (PPIs) • Prescription aspirin • Diabetes drugs • Anti-arrhythmic drugs • Diuretics • Other antihypertensives • Antianginal vasodilators • Estrogens • Progestins • Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors • Heparin and low-molecular weight heparins

*We will assess the feasibility of including these variables based on the availability and adequacy of the data element found in the MSDD. The data source for these elements will be from relevant diagnosis (ICD-9-CM), procedure (ICD-9-CM and Current Procedural Terminology [CPT]) and Healthcare Common Procedure Coding System (HCPCS) codes, or pharmacy dispensing databases.

b. Confounding adjustment strategy

New dabigatran and warfarin initiators will be 1:1 propensity score (PS) matched for the primary analyses. PS matching offers several important advantages in this assessment. First, as some of the outcomes of interest are uncommon (e.g., intracranial hemorrhage), PSs will permit adjustment of more potential confounders than would be possible with traditional multivariable outcome regression models.[23] PS matching also enables assessment of multiple outcomes in the same matched cohorts and facilitates assessments of covariate balance by examining distributions of covariates between treatment groups. Finally, PSs permit multivariable confounding adjustment while preserving the proprietary and confidential nature of the individual-level data in a distributed data setting. PSs summarize all of the measured potential confounders into a single de-identified score.[24]

Separate PS models will be developed in each Data Partner given that practice patterns based on patient characteristics may vary across Data Partners. PSs will be estimated using a logistic regression model to predict initiation of dabigatran among all eligible dabigatran and warfarin initiators in each participating Data Partner.[25] All potential confounders listed in **Table 2** will be included in each PS model within each Data Partner. The Data Partner-specific PSs will be used to match patients within each Data Partner using a nearest-neighbor matching algorithm.[26] Fixed ratio matching (e.g., 1:1) permits collapsing matched pairs across Data Partners, while maintaining baseline covariate balance between dabigatran and warfarin initiators. This will also allow for Kaplan-Meier plots of each outcome of interest to be created in the matched population.

We will evaluate PS distributions between treatment groups in each Data Partner. Visual inspection of PS distributions provides insight into the extent to which patients in the two treatment groups overlap on PS values. Overlapping PS distributions are required for valid effect estimation. Completely non-overlapping distributions can indicate errors in the PS model building and estimation. We will assess baseline characteristics and balance in baseline confounders both before and after matching in each Data Partner using absolute and standardized differences in means and proportions. We will also compute the Mahalanobis distance, which describes overall balance across all baseline confounders while accounting for correlation among the variables.[27] Evaluation of covariate balance enables assessment of the extent of confounding in the marginal population and degree to which confounding by measured variables is mitigated in the matched population.

In subgroup analyses, we will re-match dabigatran and warfarin initiators within each subgroup of interest in each Data Partner. This will ensure covariate balance between dabigatran and warfarin initiators in each subgroup. A prior simulation study has shown that valid estimates can be obtained without having to re-estimate the PS in each subgroup, which would otherwise be limited in those subgroups with few patients.[28]

5. Effect Estimation

Effect estimation will be conducted using time-to-event models to account for variable follow-up times among patients. Cox proportional hazards regression models stratified by Data Partner to estimate adjusted hazard ratios (HRs) and associated 95% confidence intervals (CIs) for each outcome. Separate Cox regression models will also be estimated for each Data Partner to allow assessment of potential effect modification across participating Data Partners. We will evaluate the proportional hazards assumption by visually inspecting the Kaplan-Meier plot among the pooled matched cohort and also within each Data Partner. We will also formally test for interactions between treatment and time. Models will be further stratified by matching set for variable ratio matched analyses.

We will also estimate rate differences and 95% CIs using inverse-variance weighted summary rate difference analyses for person-time data stratified by Data Partner in the pooled matched cohort.[29] Furthermore, we will estimate rate differences and 95% CIs within each Data Partner. Analyses of variable ratio matched data will also be stratified by matching set.

6. Sensitivity Analyses

a. Alternate outcome definitions

Consistent with current recommendations by the Mini-Sentinel Data Core, primary analyses will rely on outcome definitions based predominantly on "primary discharge diagnosis" codes and, in sensitivity analyses, we will expand these definitions to include all "non-secondary discharge diagnoses" (i.e., inpatient codes not designated as secondary, which includes those designated as primary and those with a missing designation).

Our primary intracranial hemorrhage outcome definition will include codes for both traumatic and non-traumatic intracranial bleeding events (ICD-9-CM codes 430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0). In a sensitivity analysis, we will exclude those codes associated with trauma i.e., codes 852.0x, 852.2x, 852.4x, 853.0).

b. Characterizing longitudinal exposure of dabigatran and warfarin therapy

As the "grace period" for the primary analysis between serial drug dispensings is 7 days to be considered a continuous drug exposure episode , we will conduct a sensitivity analysis in which we extend this "grace period" to 14 days in between serial prescriptions.

In sensitivity analyses, given that the daily dosage of warfarin is frequently adjusted over time for individual patients, we will employ computerized algorithms developed by Drs. Go and Singer from prior studies that classify longitudinal warfarin exposure using a combination of dispensed prescriptions for warfarin and intervening INR test claims (regardless of the INR value),[8,18,30,31] if the data from the MSDD can support this approach. Using this algorithm, patients will be considered continuously exposed to warfarin if they have (1) a gap of fewer than 60 days between serial dispensed prescriptions; or (2) a gap of fewer than 42 days between INR tests in the case where there is a gap of 60 days or longer between serial dispensed prescriptions.

c. Characterizing longitudinal quality of anticoagulation in new warfarin users

The effectiveness and safety of warfarin therapy is dependent on the intensity of anticoagulation (as reflected by the INR level and the amount of time a patient spends in the target INR range of 2.0-3.0). However, it is known that currently not all of the Data Partners have laboratory results data to include in the MSDD. We will explore the feasibility of obtaining information on outpatient INR test results in new warfarin users within the MSDD for participating Data Partners and constructing longitudinal periods on warfarin therapy at different INR levels using a modified linear interpolation approach based on INR tests separated by no more than 8 weeks.[32] If there is adequate longitudinal information on outpatient INR test results, then we will consider conducting a sensitivity analysis in which the warfarin comparator will include only the subset of patients that have longitudinal INR measures during periods of apparent warfarin exposure over time to examine whether outcomes between dabigatran and warfarin therapy varies by the quality of anticoagulation. We will classify warfarin initiators into those with high (≥60%) proportion of time in therapeutic range and those with low (<60%) proportion of time in therapeutic range. Using the original PS in each Data Partner, initiators of dabigatran will be re-matched to and compared to each of these groups. Because we anticipate that INR test results will not be available for a large portion of patients in the MSDD, this analysis will be considered exploratory.

d. Increasing the number of warfarin initiators as a comparator group

Preliminary data from the MSDD suggest there are many more patients exposed to warfarin than dabigatran during the first part of the assessment period, which is expected in the setting for the release of a new drug into clinical practice. While the statistical power of the effect estimation derives primarily from the number of exposed (i.e., dabigatran-exposed) cases in an analysis, increasing the number of warfarin-exposed patients may increase the precision of effect estimation, particularly for the outcomes with the fewest numbers of total events. As such, we will conduct a sensitivity analysis in which we match warfarin to dabigatran patients in a n:1 ratio. That is, we will match as many warfarin initiators as possible to each dabigatran initiator within the pre-defined caliper using a nearest-neighbor matching algorithm.[26] All analyses described in previous sections will then be repeated with the n:1 matched cohort with these sensitivity analyses also being conditional on the matched sets within each Data Partner.

e. Addressing time-varying confounding

Time-varying confounding has been raised as a potential concern to the validity of the study results comparing outcomes between anticoagulant strategies. Time-varying confounding occurs when a risk factor for the outcome of interest affects exposure status during follow-up and is itself affected by prior exposure status. [33] For example, use of anticoagulants may influence a patient's risk of MI. MI is often treated with antiplatelet agents, which in turn could affect both subsequent use of the anticoagulants and the risk of outcomes in this assessment comparing dabigatran to warfarin. While the RE-LY trial did not consider time-varying confounding, we will conduct a marginal structural model analysis to evaluate the robustness of the primary analysis results to potential time-varying confounding. As with PSs, which will be used to address baseline confounding, marginal structural models require that all relevant time-varying confounders be measured.[33,34] Among the PS-matched primary analysis cohort (to ensure that any potential difference in results are not due to differences in analysis populations), we will measure potential time-varying confounders (i.e., the same variables in **Table 2** of potential confounders) in each 30-day period following the index date with appropriate time-ordering of variables and outcomes within each 30-day period per patient. The variables will be used to estimate the probability that patients discontinue their index anticoagulant, the probability of experiencing another outcome of interest (e.g., the probability of experiencing MI in the analysis of stroke), and the probability of a right-censoring event (e.g., death or end of health plan membership). These probabilities will then be used to generate relevant inverse probability weights to be incorporated into the marginal structural models.

f. Patients with reduced kidney function

As dabigatran is renally excreted, we will explore the possibility of conducting subgroup analyses within strata of patients with varying degrees of kidney function, using standard cut points for eGFR (i.e., ≥90.ml/min/1.73m^2, 60 to <90, 45 to <60, 30 to <45, 15 to <30, and <15). We will evaluate which Data Partners have available outpatient serum creatinine data available in the MSDD and we will re-run the primary analysis in eligible Data Partners restricting only to those patients with a creatinine value available in the pre-index baseline period. Because we anticipate that lab data will not be available for a large portion of patients in the MSDD from participating Data Partners, this analysis will be considered exploratory.

g. Dabigatran dose

For patients with eGFR of greater than 30 ml/min, the recommended daily dose of dabigatran is 150mg twice daily. For patients with eGFR between 15 and 30 ml/min, the recommended daily dose of dabigatran is 75mg twice daily. In addition to the exploratory analyses stratified by eGFR described above, we will stratify our main results according to the initial dabigatran dose.

F. PRELIMINARY DATA AND POWER CALCULATIONS

Based on the identification approach outlined above in *Section C.5.c* for outcomes of interest, preliminary data from the MSDD showed the following potential event rates (expressed as number of events per 100 person-years exposed to warfarin) among new warfarin initiators (as defined using a 180-day washout period) with a diagnosis of atrial fibrillation:

Ischemic stroke:	1.7 events per 100 person-years
Intracranial hemorrhage:	0.7 events per 100 person-years
Extracranial bleeding:	4.4 events per 100 person-years
Myocardial infarction:	1.3 events per 100 person-years

Preliminary data on uptake of dabigatran in the MSDD are available through December 31, 2011. Between October 19, 2010 and December 31, 2011, there were approximately 10,400 initiators of dabigatran and 44,000 initiators of warfarin who were naïve to both drugs and had a recorded diagnosis of atrial fibrillation. Because it is difficult to project the trajectory of subsequent dabigatran uptake, we calculated estimated power under two scenarios: (1) conservatively assuming a 2.5-fold increase in the numbers of initiators of each drug (n = 26,000 dabigatran initiators and n = 110,000 warfarin initiators) during the assessment period; and (2) assuming a 2.5-fold increase in the total number of initiators (n = 136,000) with quadrupling of dabigatran use (n = 41,600 dabigatran initiators and 94,400 warfarin initiators) during the assessment period.

Assuming a mean follow-up of 180 days and a two-sided $\alpha = 0.05$, we will have greater than 78% power to detect a 50% change in relative risk (either increase or decrease) in each of the outcomes of interest and greater than 94% power to detect a 50% change for all but one outcome. **Table 3** displays estimated power to detect 10%, 25%, and 50% changes (both increases and decreases) in each outcome under each dabigatran trajectory model.

Table 3. Power calculations to detect 10%, 25% and 50% changes for each of four outcomes under two dabigatran and warfarin exposure scenarios.

Exposure Scenario	Outcome	Direction of change	Magnitude of change		
			10%	25%	50%
(1) n = 26,000 dabigatran initiators and n = 26,000 matched warfarin initiators	Ischemic stroke	Increase	17%	71%	100%
		Decrease	19%	81%	100%
	Intracranial hemorrhage	Increase	7%	29%	78%
		Decrease	8%	35%	94%
	Extracranial bleeding	Increase	37%	98%	100%
		Decrease	41%	100%	100%
	Myocardial infarction	Increase	14%	60%	99%
		Decrease	15%	71%	100%
(2) n = 41,600 dabigatran initiators and n = 41,600 matched warfarin initiators	Ischemic stroke	Increase	26%	89%	100%
		Decrease	28%	95%	100%
	Intracranial hemorrhage	Increase	10%	44%	94%
		Decrease	11%	53%	99%
	Extracranial bleeding	Increase	55%	100%	100%
		Decrease	55%	100%	100%
	Myocardial infarction	Increase	21%	80%	100%
		Decrease	22%	89%	100%

IV. ADDITIONAL RATIONALE FOR PROPOSED MEASUREMENT APPROACHES AND ANALYTIC STRATEGIES AND ALTERNATIVES CONSIDERED

A. STUDY DESIGN

There are several advantages to the active comparator "new user" design, including capturing early events after starting a therapy, establishing clear temporality among baseline covariates, exposures, and outcomes, and helping to balance unmeasured patient factors by restricting the cohort to patients with atrial fibrillation who are receiving some type of pharmacological therapy for stroke prevention. As dabigatran was approved by the FDA in October 2010, exposure to this agent within the anticipated assessment timeframe will represent recent new use. We anticipate identifying a large set of patients with atrial fibrillation receiving warfarin during the same time period as new dabigatran users. The simultaneous identification of comparator patients should mitigate bias associated with any secular trends in risk factors for stroke and major bleeding that could occur if historical controls were used. Furthermore, alternative comparator approaches such as self-controlled methods are less useful given that (1) anticoagulants are prescribed as lifelong therapy rather than intermittent or pro re nata, (2) concern about the potential risks associated with dabigatran is not focused on any particular window of perceived risk, and (3) atrial fibrillation affects the risk of several of the outcomes of interest. [35-37]

B. SWITCHING FROM WARFARIN THERAPY TO DABIGATRAN

As noted in *Sections C.2.a*. and *C.2.b*, the primary analysis will focus on patients who are considered anticoagulant naïve (based on no evidence of receipt of dabigatran or warfarin for at least 180 days before index date). However, in current clinical practice in the U.S., we recognize that a significant fraction of patients who initiate dabigatran are switching from previously using warfarin therapy. While the safety outcomes of patients who switch from warfarin to dabigatran are of great interest, assessing the outcomes for patients who switch anticoagulant strategies is complicated by many factors. In particular, identifying a valid comparison group may be especially difficult. Patients who switch from warfarin to dabigatran are likely different from patients who remain on warfarin, and the specific reasons for switching likely are not well measured in the MSDD. Moreover, determining the start of follow-up for patients who switch might be straightforward, but there is no obvious time point at which the start of follow-up for patients who remain on warfarin, and the validity of such a switcher comparison will likely depend heavily on the appropriate selection of the start of follow-up. Toward that end, the focus of this protocol will specifically be on **new users of both warfarin and dabigatran** during the study period. However, we intend to document the frequency of switching from one therapy to the other during the follow-up period.

C. CHARACTERIZING LONGITUDINAL DABIGATRAN AND WARFARIN THERAPY

Characterizing longitudinal exposure using prescription dispensing records is relatively straightforward for most drugs, such as dabigatran, that are usually used in a daily, fixed-dose regimen. As such, the standard method of linking together information from serial prescription dispensings will be used for dabigatran, where patients are considered continuously exposed until they reach a gap of <u>more than 7 days</u> following the date of the most recent prescription plus the days supply without a subsequent dispensing record (see *Section C.5.b*)—this will be the primary approach used for characterizing exposure to dabigatran and warfarin. As described in *Section C.5.f.ii*, this gap will be extended to 14 days in sensitivity analyses. However, warfarin requires routine therapeutic monitoring in clinical practice which often results in relatively frequent dose changes in response to INR values during follow-up to try to achieve the target INR range of 2.0-3.0.[6] As such, the "days supply" field, which pharmacists enter based on prescribing instructions on the original prescription, may not accurately reflect the duration of actual use for a particular dispensing when dose adjustment occurs. Thus, relying on the standard approach for estimating the duration of use of a dispensing can lead to significant misclassification of warfarin exposure. In particular, it would often lead to censoring of patients who have dose reductions but who remain continuously exposed to warfarin. Drs. Go and Singer and colleagues have developed an algorithm that incorporates claims for INR tests (without having to know the results of the tests) to account for dose adjustments.[8,18,38] This approach extends patients' assumed warfarin use beyond the recorded days supply of prescriptions as long as patients receive regular outpatient INR tests in between serial warfarin prescriptions. One potential limitation of this approach is that it could lead to differential misclassification of exposure when doses are not actually being reduced in response to an INR value. In addition, as noted previously, there is concern about the systematic availability of INR test claims in the MSDD from participating Data Partners and we will need to evaluate the feasibility of characterizing warfarin therapy using the combination of warfarin dispensings and outpatient INR tests. Toward that end, as described in *Section C.5.b*, we will conduct sensitivity analyses in which we use the same standard approach to characterizing exposure to both dabigatran and warfarin based only on the days supply and grace period between serial dispensings, without considering INR testing for warfarin patients.

D. CONSIDERATION OF OTHER COMPARATORS

The protocol will not attempt to study other comparators, such as aspirin alone (as this exposure cannot be measured accurately because it is widely used as an over-the-counter medication) or the combination of clopidogrel plus aspirin (as it has no demonstrated benefit in stroke prevention so this comparison does not have implications for regulatory action). We will also not conduct analyses for other alternative anticoagulants (i.e., rivaroxaban or apixaban) as their use is expected to be too uncommon for an adequately powered analysis during the assessment period.

E. ASCERTAINMENT OF SAFETY OUTCOMES

The approach outlined in *Section C.4* relies on identification of relevant ICD-9-CM diagnostic codes in the primary (or principal) discharge position for a hospitalization for ischemic stroke, major extracranial hemorrhage and MI. Based on previous studies,[8] we will search for relevant ICD-9-CM diagnostic codes in any position for intracranial hemorrhage. We recognize that even using this approach that tends to emphasizes specificity over sensitivity, the positive predictive value (PPV) for the outcome of intracranial events (ischemic stroke or intracranial hemorrhage) may not be optimal in each Data Partner depending on their coding patterns during the assessment period. Thus, we will also conduct sensitivity analyses in which we include all "non-secondary" inpatient codes.

The Mini-Sentinel Workgroup and the FDA recognized the strong scientific rationale for validating the utility of the proposed algorithms for identifying outcome events within each Data Partner and evaluating for variation between Data Partners and over time. However, for several reasons, the FDA determined that the project will not validate the outcome events identified through the electronic data. These include the estimated costs associated with an adequately-sized chart review validation effort to generate precise estimates of PPV; variation within Data Partners that may not be accurately characterized given that each Data Partner is not a uniform entity; and the anticipated change from ICD-9 to ICD-10 coding methods that may limit generalizability of the validation study findings in the future.

In addition, we note that there was a notably higher rate of dyspepsia reported as a serious adverse event in participants who received dabigatran in the RE-LY trial,[10] but the challenge of capturing gastrointestinal distress accurately using administrative databases like the MSDD is substantial and this outcome will not be included in the protocol.

F. ANALYTIC APPROACH

As noted in *Section B*, the initial implementation will be a one-time assessment of outcomes related to new dabigatran vs. warfarin therapy in adults with atrial fibrillation. This decision (vs. a sequential monitoring approach) was based on the estimated sample sizes for new dabigatran and new warfarin users, as well as the projected event rate during the follow-up period.

Even in the comparison of new users, differences are expected between the baseline characteristics of those taking dabigatran and of those initiating warfarin therapy. Many design and statistical approaches exist to attempt to balance differences between treatment groups, including matching/restriction, stratification, multivariable regression modeling, propensity scores, disease risk scores, and instrumental variable analysis. Each approach has advantages and disadvantages. The distributed data setting, in which identifiable patient-level data will remain behind each Data

Partner's firewall, combined with the intent to evaluate multiple outcomes, some of which are uncommon, make PS matching a particularly appealing primary strategy.[24] PSs enable the adjustment of many potential confounders, even in the setting of few outcome events. Matching on the PS permits the evaluation of multiple outcomes without the need to fit multiple models and while ensuring that the population to which inferences apply remains constant across analyses of each outcome. PS matching also enables evaluation of balance on measured covariates using standard descriptive statistics. Furthermore, PSs allow for the sharing of de-identified individual level data, which strikes a balance between maintaining data privacy and maintaining flexibility in analyses. Finally, the PS matching approach permits straightforward estimate of both rate difference and ratio effect measures.

The primary analysis – based on a PS-matched new user cohort design – implies that the assessment of factors that may influence choice of therapy are assessed once just before the treatment decision is made. As in a randomized trial, this assumes the absence of time-varying confounding. However, if there is time-dependent confounding that affects the likelihood of continuing a therapy such as dabigatran or warfarin, then more advanced adjustment methods would be needed to obtain a less biased estimate of the associations with adverse events. Time-varying confounders are factors that are affected by exposure status during follow-up and affect subsequent exposure and the outcome of interest. The list of potential confounders (**Table 2**) that could potentially affect the likelihood of continuing therapy is the same as those included in the baseline PS, as these are the risk factors for the outcomes of interest. In addition, having an outcome of interest (e.g., bleeding) during follow-up may affect subsequent treatment and risk for a different outcome of interest (e.g., stroke). The primary analysis will assume the absence of time-varying confounding because most of the potential confounders are chronic in nature and therefore are less like to be caused or be affected by warfarin or dabigatran and because the duration of follow-up in this study will be relatively modest.

To assess potential time-dependent confounding, an analysis of new onset confounders (e.g., medical conditions and medications) will be undertaken for new users in the primary analysis cohort. We will compare the presence of each confounder in **Table 1** among dabigatran and warfarin initiators in each 30-day interval following the index date. If evidence suggests the possibility of time-dependent confounding, as indicated by differences in presence of confounders between treatment groups during follow-up, then a sensitivity analysis will be conducted using a history-adjusted marginal structural modes with inverse probability of treatment and censoring.[22] The feasibility and utility of these methods, as well as additional approaches for selection of model weights (e.g., Super Learner) to further improve control of time-dependent confounding, will be evaluated with consideration of available data.[24]

Finally, we considered a case-centered logistic regression approach to data analysis and pooling, which is a data/computational strategy for fitting a stratified Cox regression model.[39] This approach has been used in other Mini-Sentinel assessments and limits individual-level data sharing.[40] In the case-centered approach, Data Partners transmit only risk-set level information. This approach limits patient-level information sharing, but does not entirely avoid it since Data Partners still transmit the exposure status for each patient who experiences an outcome (along with the log-odds of exposure among the group of patients in each case's risk set). While the PS matching and pooling process requires transmission of more patient-level information, the approach has been reviewed by a health care law expert and deemed compliant with current HIPAA rules. Whereas the case-centered approach requires modeling the outcome at each Data Partner and transmitting separate datasets for each outcome model, the PS approach requires only a single model for exposure, and therefore transmittal of only a single dataset. Further, the PS matching approach permits straightforward estimation of both rate ratios and differences, which is important to the assessment of safety outcomes for new dabigatran vs. new warfarin users with atrial fibrillation.

V. LIMITATIONS

We recognize that accurate characterization of longitudinal exposure to dabigatran and warfarin therapy is a critical element of the protocol, and we will leverage various pharmacoepidemiological methods and sensitivity analyses for examining how different definitions and assumptions based on data from serial dispensed prescriptions and, in the case of warfarin, ambulatory INR test claims, impact on the results, if there are available and adequate data in the MSDD from participating Data Partners. However, as we will not have data on actual patient adherence, misclassification of exposure to the drugs of interest may still occur based on our algorithms.

In addition, preliminary data suggest that ambulatory INR test results will be incomplete for many of the Data Partners which will limit power for assessing outcomes among new dabigatran users compared with warfarin therapy at different levels of anticoagulation quality (i.e., percent of person-time at different INR levels). In addition, as the amount of missing INR test results is likely non-random, we cannot rule out potential selection bias. Therefore, as described previously, we will evaluate whether there are adequate data available from participating Data Partners to conduct exploratory analyses assessing safety outcomes associated with new dabigatran use compared with high- or low-quality anticoagulation with warfarin therapy.

As described in *Section D.2*, the current protocol will not address outcomes associated with new dabigatran use among patients who were previous warfarin users. Even though preliminary data suggest that approximately 50% of new dabigatran users are "switchers" from warfarin therapy, methodological concerns and resource constraints preclude our addressing outcomes in this subgroup of patients compared with warfarin-naïve dabigatran users, new warfarin users or ongoing prevalent warfarin users.

Residual confounding is a concern in any observational study of outcomes associated with exposure to various treatments. In particular, several important risk factors for the outcomes of interest may not be well captured in the MSDD. These include the presence and severity of obesity, level of blood pressure, targeted laboratory test results, smoking status, and diet and physical activity. The active comparator design, in which outcome event rates are compared among new dabigatran versus warfarin users, mitigates confounding to the extent that the outcome-related risk factors may similarly determine whether patients are treated with dabigatran or warfarin. We will also use PS methods to adjust for a large number of potential measured baseline confounders. However, outcome risk factors that are not measured or not accurately measured may cause residual confounding which should be considered when interpreting the results of this assessment. Furthermore, PS methods do not address the problem of time-dependent confounding.

Informative censoring occurs when patients in each treatment group differentially discontinue treatment or are otherwise censored (e.g., due to death) in the analysis due to factors that are related to the outcomes of interest. Differential censoring could occur, for example, if patients in one treatment group are more likely to discontinue that treatment because of minor bleeding that does not ultimately lead to major bleeding events.

The marginal structural model sensitivity analysis is designed to partially address time-dependent confounding and informative censoring.[33,41,42] As with PS methods, marginal structural models can only address confounding by measured variables. However, unlike the PS approach which addresses only confounding at baseline, marginal structural models can appropriately account for time- dependent confounders that are affected by prior treatment

history. Thus, to the extent that the primary results are impacted by time-dependent confounding, the marginal structural model approach should help to mitigate this problem. Further, the marginal structural model can address informative censoring by measured variables. By constructing inverse probability weights based on the likelihood of being censored, the marginal structural model can provide results that reflect what would have occurred in the cohort had no patients been right-censored, provided that the reasons for censoring are measured in the available data.

While the power calculations indicate that we will have sufficient power to detect even modest changes in the rates of outcomes of interest in the pooled data, we expect that some of the Data Partners will contain only small numbers of selected outcomes (e.g., intracranial hemorrhage). Since we will be using PSs to model the exposure, this should minimize the problem of model fitting. However, it is possible that certain Data Partners may have limited dabigatran use, and the small numbers of outcomes will limit inferences from Data Partner-specific sensitivity analyses.

Finally, despite the large and diverse source populations from the participating Data Partners, the findings from this assessment may not be fully generalizable to all patient subgroups and health care settings in the U.S.

VI. REFERENCES

1.   Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
2.   Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-25.
3.   Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-6.
4.   Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
5.   Hart R, Benavente O, McBride R, Pearce L. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. Ann Intern Med 1999;131:492-501.
6.   You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S-75S.
7.   Hylek E, Skates S, Sheehan M, Singer D. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335:540-6.
8.   Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685-92.
9.   Pradaxa (dabigatran etexilate mesylate) capsules. 2013. (Accessed August 7, 2013, 2013, at http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250657.htm.)
10.   Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
11.   Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. N Engl J Med 2010;363:1875-6.
12.   Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20.
13.   Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:546S-92S.
14.   Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis Ann Intern Med 1999;131:537-8.
15.   Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.
16.   Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-26.
17.   Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation N Engl J Med 1996;335:540-6.
18.   Singer DE, Chang Y, Borowsky LH, et al. A New Risk Scheme to Predict Ischemic Stroke and Other Thromboembolism in Atrial Fibrillation: The ATRIA Study Stroke Risk Score. J Am Heart Assoc 2013;2:e000250.
19.   Mini-Sentinel Meidcal Product Assessment: A Protocol for Active Surveillance of Acute Myocardial Infarction in Association with use of Anti-Diabetic Agents. (Accessed at http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_AMI-and-Anti-Diabetic-Agents_Protocol.pdf.)
20.   Atay JK, Fanikos J, Barnes GD, et al. Effect of Dabigatran on Referrals to and Switching from Warfarin in Two Academic Anticoagulation Management Services. The American journal of cardiology 2013.

21. Sorensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open 2013;3.

22. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol 2011;64:749-59.

23. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. American journal of epidemiology 2003;158:280-7.

24. Rassen JA, Moran J, Toh D, et al. Evaluating strategies for data sharing and analyses in distributed data settings. Boston, MA; 2012.

25. Gagne JJ, Glynn RJ, Rassen JA, et al. Active Safety Monitoring of Newly Marketed Medications in a Distributed Data Network: Application of a Semi-Automated Monitoring System. Clin Pharmacol Ther 2012.

26. Pharmacoepidemiology Toolbox. 2012. (Accessed at http://www.hdpharmacoepi.org.)

27. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.

28. Rassen JA, Glynn RJ, Rothman KJ, Setoguchi S, Schneeweiss S. Applying propensity scores estimated in a full cohort to adjust for confounding in subgroup analyses. Pharmacoepidemiology and drug safety 2012;21:697-709.

29. Rothman KJ. Modern Epidemiology. Boston/Toronto: Little, Brown and Company; 1986.

30. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. Journal of the American College of Cardiology 2011;58:395-401.

31. Singer DE, Chang Y, Fang MC, et al. Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation?: the ATRIA study. Circulation Cardiovascular quality and outcomes 2009;2:297-304.

32. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.

33. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60.

34. Neugebauer R, Fireman B, Roy JA, O'Connor PJ, Selby JV. Dynamic marginal structural modeling to evaluate the comparative effectiveness of more or less aggressive treatment intensification strategies in adults with type 2 diabetes. Pharmacoepidemiol Drug Saf 2012;21 Suppl 2:99-113.

35. Gagne JJ, Fireman B, Ryan P, et al. Taxonomy for monitoring methods within a medical product safety surveillance system: Report of the Mini-Sentinel Taxonomy Project Work Group. Boston; 2010.

36. Gagne JJ, Fireman B, Ryan PB, et al. Design considerations in an active medical product safety monitoring system. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:32-40.

37. Gagne JJ, Nelson JC, Fireman B, et al. Taxonomy for monitoring methods within a medical product safety surveillance system: year two report of the Mini-Sentinel Taxonomy Project Workgroup. Boston; 2012.

38. Hylek EM, Go AS, Chang Y, et al. Impact of intensity of oral anticoagulation on stroke severity and stroke mortality in patients with non-valvular atrial fibrillation. New England Journal of Medicine 2003;349:1019-26.

39. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. American journal of epidemiology 2009;170:650-6.

40. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012;172:1582-9.

41. Rotnitzky A, Lei Q, Sued M, Robins JM. Improved double-robust estimation in missing data and causal inference models. Biometrika 2012;99:439-56.

42. Hernan MA, Robins JM. Estimating causal effects from epidemiological data. Journal of epidemiology and community health 2006;60:578-86.

VII.   APPENDIX A. COHORT INCLUSION AND EXCLUSION CRITERIA

The primary comparator arms will be adults with atrial fibrillation who are new users of dabigatran or warfarin therapy. Various inclusion and exclusion criteria were also considered and the following decisions were made:

1. Definition of atrial fibrillation

As noted previously, atrial fibrillation will be defined based on the presence of one or more ICD-9-CM diagnostic codes (427.31 or 427.32) from any clinical setting and in any diagnosis position on or before the index date (defined as the dispensing date for the first eligible warfarin or dabigatran dispensing during the assessment period). Given the requirement that patients will be receiving either new dabigatran or warfarin therapy, even one instance of diagnosed atrial fibrillation should be sufficient and consistent with nearly comprehensive capture of patients with atrial fibrillation who are being treated with dabigatran or warfarin therapy in participating Data Partners.

2. Inclusion of both presumed nonvalvular and valvular atrial fibrillation

Our primary analyses will focus on nonvalvular atrial fibrillation because this is the indication for which dabigatran is currently FDA-approved.[9] Patients with known mechanical heart valves and mitral stenosis (based on relevant ICD-9-CM and CPT codes will be excluded but we will not attempt to identify and exclude people with other types of cardiac valvular disease.

3. Inclusion of patients with atrial flutter (in the absence of additional codes indicating atrial fibrillation)

Patients who have only atrial flutter diagnostic codes will be included because a large fraction of these patients have both atrial fibrillation along with atrial flutter, and per national clinical practice guidelines,[6] they should be treated similarly to patients with atrial fibrillation with regards to stroke prevention.

4. Additional inclusion/exclusion considerations and decisions

The goal of this assessment is to examine the most generalizable sample of patients with nonvalvular atrial fibrillation being treated with dabigatran or warfarin therapy for the purpose of stroke prevention. Toward that end, the following additional issues were considered and decisions made about inclusion and exclusion criteria.

Include (based on information on or before the index date):

- There will be no upper age limit. The lower age limit will be 21 years old. This is consistent with the target population age range.
- Patients with perioperative atrial fibrillation who are treated with dabigatran or warfarin therapy.
- Patients undergoing percutaneous coronary interventions with or without insertion of an intra-coronary stent.
- Patients with other documented coronary heart disease (prior myocardial infarction or coronary revascularization).
- Patients undergoing internal or external cardioversion or catheter ablation.
- Patients with significant renal impairment (i.e., estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) not receiving renal replacement therapy (i.e., dialysis or kidney transplant).

- Patients with diagnosed advanced liver disease (based on ICD-9-CM diagnostic codes). It is acknowledged that this is an important, albeit infrequent, consideration in selection of antithrombotic therapy and could impact outcomes, and it will be addressed analytically.
- Patients with known metastatic cancer (identified from ICD-9-CM diagnostic codes). It is acknowledged, however, that this is an important consideration in selection of antithrombotic therapy and could impact outcomes, and it will be addressed analytically.

Exclude (based on information on or before the index date):

- Less than six (6) months of continuous health plan membership (including both medical and pharmacy/drug benefit) before assessment entry. This approach balances the goals of having adequate data on comorbidities, indication for use or non-use, prior drug exposure and prior events against the potential loss of otherwise eligible patients.
- Patients who are identified to come from a skilled nursing facility or nursing home at baseline will be excluded from the analyses due to the concern of incomplete data.
- Patients receiving chronic hemodialysis or peritoneal dialysis based on corresponding ICD-9-CM or CPT procedure codes.
- Patients who have received a kidney transplant based on corresponding ICD-9-CM or CPT procedure codes.