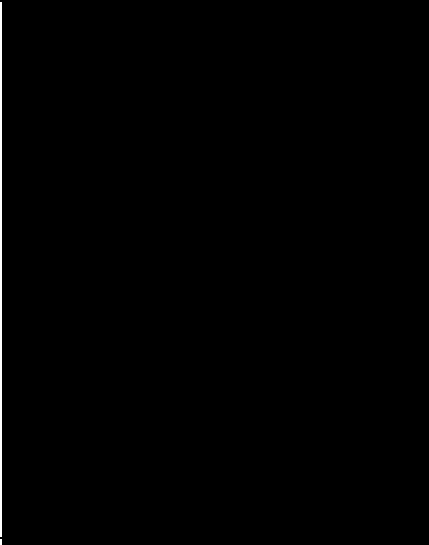


Protocol for non-interventional studies based on existing data

Document Number:	c14336616-01
BI Study Number:	1160.274
BI Investigational Product(s):	Pradaxa
Title:	The Comparative Safety and Effectiveness of dabigatran, versus rivaroxaban, and apixaban Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-A Retrospective Database Analysis
Protocol version identifier:	1.0
Date of last version of protocol:	N/A
PASS:	Yes
EU PAS register number:	<i>EUPAS16528</i>
Active substance:	<i>Dabigatran etexilate</i>
Medicinal product:	<i>Pradaxa</i>
Product reference:	<i>N/A</i>
Procedure number:	<i>N/A</i>
Joint PASS:	<i>No</i>
Research question and objectives:	To assess the safety and effectiveness of newly initiated dabigatran among patients diagnosed with NVAf in comparison to newly initiated rivaroxaban users and newly initiated apixaban users in two (2) separate study cohorts <ul style="list-style-type: none"> • dabigatran vs. rivaroxaban

	<ul style="list-style-type: none"> dabigatran vs. apixaban
Country(-ies) of study:	United States
Author(s):	
Marketing authorization holder(s):	Boehringer Ingelheim International GmbH
MAH contact person:	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein
Date:	15Dec2016
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2. LIST OF ABBREVIATIONS

ACE	angiotensin-converting-enzyme inhibitor
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin receptor blockers
BIPI	Boehringer Ingelheim Pharmaceuticals Inc
CDR	Clinical data repository
CHA ₂ DS ₂ -VASc	Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Stroke (doubled), Vascular disease, Age 65–74 years, Sex category
CHADS ₂	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism
CCI	Charlson comorbidity index
CI	Confidence Interval
COPD	Chronic objective pulmonary disease
DEERS	Defense eligibility enrollment reporting system
DoD	Department of Defense
DRG	Diagnosis-related group
█	█
EMR	electronic medical record
ER	emergency room
FDA	Federal drug administration
FFS	fee-for-service
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GIH	gastrointestinal hemorrhage
HASBLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HIPAA	health insurance portability and accountability act
HIV	Human immunodeficiency virus

HMO	health maintenance organization
█	█
ICD	International classification of diseases
ICH	intracerebral hemorrhage
IPTW	Inverse probability to weighting
IR	Incidence Rate
IRB	Institutional Review Board
█	█
KM	Kaplan-Meier
MB	Major bleed
MDR	Military health system data repository
MHS	Military health system
█	█
MTF	military treatment facilities
N	Number
NDC	National drug code
NVAF	Non-valvular Atrial Fibrillation
NOAC	Non-Vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
OV	office visit
PDTS	Pharmacy data transaction system
█	█
PPI	Proton pump inhibitor
PPO	preferred provider organization
PSM	Propensity score matching
PS	Propensity Score
PSTAT	Project Statistician
PY	Person-years at risk

RCT	Randomized controlled trial
RR	Rate Ratio
SD	Standard deviation
SAS	Statistical analysis software
TIA	transient ischemic attack
Tx	Treatment
VPN	Virtual private network



3. RESPONSIBLE PARTIES

Medical Affairs

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Associate Investigator (DoD)

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Senior [REDACTED], RWE

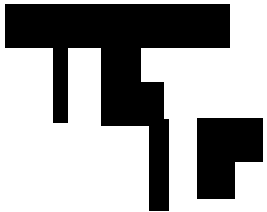
[REDACTED]
Email: [REDACTED]

[REDACTED], Biostatistics Late Stage

[REDACTED]
Email: [REDACTED]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa			
Name of active ingredient: dabigatran etexilate			
Protocol date: 15Dec2016	Study number: 1160.274	Version/Revision: 1.0	Version/Revision date: N/A
Title of study:	The Comparative Safety and Effectiveness of dabigatran, versus rivaroxaban, and apixaban Utilized in the Department of Defense (DoD) Non-Valvular Atrial Fibrillation Patient Population-A Retrospective Database Analysis		
Rationale and background:	<p>Due to the emergence of multiple pharmaceutical alternatives to warfarin, physicians in the US are faced with many anticoagulation options. To help inform their decisions physicians want to know the comparative safety and efficacy profiles of these new agents.</p> <p>Now that real world experience with dabigatran for NVAF patients has accrued, the safety and effectiveness for dabigatran, rivaroxaban, and apixaban may also be assessed and compared in this setting.</p> <p>Boehringer Ingelheim Pharmaceuticals Inc. (BIPI) has an opportunity to collaborate with DoD to conduct comparative safety and effectiveness studies of dabigatran, rivaroxaban, and apixaban using already existing real world data from DoD's claims and EMR data.</p>		
Research question and objectives:	<p>To assess the safety and effectiveness of newly initiated dabigatran among patients diagnosed with NVAF in comparison to newly initiated rivaroxaban users and newly initiated apixaban users in two (2) separate study cohorts:</p> <ul style="list-style-type: none"> • dabigatran vs. rivaroxaban • dabigatran vs. apixaban 		
Study design:	Non-interventional study based on existing data with propensity score matching (PSM)		
Population:	NVAF patients, ≥ 18 years of age, enrolled within the DoD Military Health System (MHS) who have newly initiated dabigatran, rivaroxaban or apixaban. Patients must be treatment naïve from OAC use prior to first (index) NOAC.		


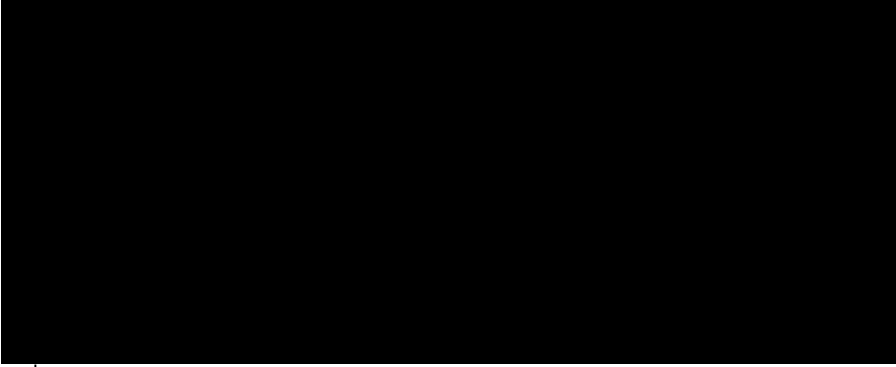
Variables:	<p>Covariates</p> <ul style="list-style-type: none"> • Gender • Age • Geographic location • Health plan type • Baseline comorbid conditions • Pre-index medication use • NOAC prescribing provider type • Baseline Charlson comorbidity index • Baseline stroke risk (CHADS₂ and CHA₂DS₂-VASc) • Baseline bleeding risk (modified HAS-BLED) • Index exposure • Time to index exposure • Duration of follow-up <p>Primary outcomes</p> <ul style="list-style-type: none"> • Stroke overall (hemorrhagic, ischemic, uncertain) • Major bleeding, overall <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Ischemic stroke • Hemorrhagic stroke • Major intracranial bleeding • Major extracranial bleeding <ul style="list-style-type: none"> ○ Major GI bleeding ○ Major other bleeding • TIA • All-cause mortality 
Data sources:	Military Health System Data Repository (MDR)
Study size:	<p>Initial study feasibility counts show newly initiated dabigatran among patients diagnosed with NVAf in comparison to newly initiated rivaroxaban users and newly initiated apixaban users in two (2) separate study cohorts:</p> <ul style="list-style-type: none"> • dabigatran (n= 16,604) vs. rivaroxaban (n=25,215); July 1, 2011 to June 30, 2016 • dabigatran (n=6,050) vs. apixaban (n=20,930); December 28, 2012 to June 30, 2016 <p>These numbers are based on initial inclusion/exclusion criteria as</p>

	<p>specified above. Additional inclusion/exclusion criteria will reduce population sizes further but feasibility estimates provide strong support for necessary sample size.</p>
Data analysis:	<p>The target population will include OAC treatment naïve NVAF patients with at least one prescription claim for dabigatran, rivaroxaban or apixaban. For each patient treated with a NOAC, the date of the first NOAC prescription (index exposure) will serve as the index date. Only those patients whose index date occurs between the respective study periods will be included. The 12-month period prior to the index date will be defined as the pre-index period. The patients will be required to have a NVAF diagnosis in the pre-index period (including index date).</p> <p>Study period NOT including pre-index period:</p> <ul style="list-style-type: none"> • Dabigatran vs. Rivaroxaban: July 1, 2011 to June 30, 2016 • Dabigatran vs. Apixaban: December 28, 2012 to June 30, 2016 <p>Study period including pre-index period:</p> <ul style="list-style-type: none"> • Dabigatran vs. Rivaroxaban: July 1, 2010 to June 30, 2016 • Dabigatran vs. Apixaban: December 28, 2011 to June 30, 2016 <p>Standard dosing for each NOAC will be used for main analyses. All doses for each NOAC will be combined for a sensitivity analysis. Standard dose for NOAC's:</p> <ul style="list-style-type: none"> • Dabigatran 150 mg, twice daily, total daily dose of 300 mg • Rivaroxaban 20 mg, once daily, total daily dose of 20 mg • Apixaban 5 mg, twice daily, total daily dose of 10 mg <p>Length of Follow-up:</p> <p>The post-index follow-up period will begin the day following the NOAC index date and end on whichever of the following occurs earliest:</p> <ul style="list-style-type: none"> • The day of discontinuation of the index NOAC exposure; • The day before a switch to an anticoagulant different from the index exposure; • The day before a change in dose for the index NOAC; • The end of continuous eligibility of a patient in the health plan (disenrollment); • The end of the study observation period; or • The date of death of the patient. • The last date of calculated days supplied if treatment gap

	<p>>30 days</p> <p>Patients need at least two days of exposure to the index NOAC to ensure they had at least one day of index NOAC exposure in the post-index follow-up period. A sensitivity analysis will also be performed using a 14 day treatment gap.</p> <p>Both claims-level data, including diagnosis codes, procedure codes, pharmacy dispensed drugs, cost information, and enrolment data, as well as EHR-level data, including relevant lab tests and results, will be extracted for all applicable patients. Patient demographics, treatment history, and comorbidities, will be derived from the electronic database. Start and stop dates of each course of treatment will be coded from the pharmacy and medical claims data using rules to be developed in the study protocol. Comorbidities of interest will be ascertained through ICD-9 and ICD-10 diagnosis codes, in combination with procedures and medications, as appropriate to the study protocol definitions.</p> <p>To account for potential selection bias, the study cohorts (dabigatran/rivaroxaban and dabigatran/apixaban) will be matched on their baseline characteristics using the propensity score matching (PSM) method. The PSM aims to balance the two treatment groups on baseline demographics, health plan type and clinical characteristics. The feasibility of PSM will be evaluated based on available sample size and descriptive results. If patient characteristics between dabigatran/rivaroxaban and dabigatran/apixaban cohorts are significantly different, i.e., less than 50% of patients in the dabigatran group can be matched to the rivaroxaban or apixaban group based on PSM, then the study design will be re-evaluated before proceeding to analysis. The Nearest Neighbor method of propensity score matching within a caliper of 0.10-0.20 (depending on resulting sample sizes) of the standard deviation of the estimated logit will be used to select the matched samples.</p> <p>The propensity score models will include baseline variables known to be confounders or factors related to the outcome only, including age, gender, health plan type, geographic region, month and year of index date, Charlson comorbidity index (CCI), stroke risk scores (i.e. CHADS₂ or CHA₂DS₂-VASc), bleeding risk scores (i.e., modified HAS-BLED), specified comorbid conditions and medication use, based on literature and clinical relevance, as well as empirical data (top diagnoses, procedures, etc.) that may account for possible unforeseen confounding.</p>
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	<p><u>Descriptive Statistics</u></p> <p>Patient characteristics, including demographics, will be reported for NVAF patients treated with dabigatran, rivaroxaban, or apixaban. Stroke risk will be quantified using the CHADS₂, CHA₂DS₂-VASc score and bleeding risk through the HAS-BLED score Other descriptive variables may include the following:</p> <p>Comorbid conditions at baseline:</p> <ul style="list-style-type: none">• Cancer• Rheumatoid arthritis• Coronary artery disease• Acute myocardial infarction• Cardiomyopathy• Ischemic stroke• Stroke (all types)• TIA• Congestive heart failure• Left ventricular heart failure• Hypertension• Peripheral artery disease• Liver disease• Renal disease• COPD/emphysema• Diabetes• Peptic ulcer (bleeding or non-bleeding)• GERD• Venous thromboembolism• Hyperlipidemia• HIV infection• Bone marrow disease (thrombocytopenia, chronic anemia, myelofibrosis)• Coagulopathy (hemophilia, Von Willebrand disease)• Chronic kidney disease <p>Medication History and Concomitant Use:</p> <ul style="list-style-type: none">• Non-Oral Anticoagulants: Number of prescription fills (normalized to a 30-day supply) will be captured during the pre-index period (See Appendix A, Table 8)<ul style="list-style-type: none">○ Argatroban (can be used in procedures in lieu of heparin)○ Unfractionated Heparin (Heparin)○ Low Molecular Weight Heparins:<ul style="list-style-type: none">▪ Enoxaparin▪ Tinzaparin
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	<ul style="list-style-type: none"> ▪ Dalteparin ▪ Fondaparinux • Other medication use: Use of other medications will be determined if patients had ever filled a medication in the following drug classes during the pre-index period (See Appendix A, Table 3, Table 8). <ul style="list-style-type: none"> ○ Beta blockers ○ Calcium channel blockers ○ Diuretics ○ Other antihypertensives (i.e., angiotensin-converting-enzyme (ACE) inhibitors, combinations) ○ Antihyperlipidemics ○ Corticosteroids ○ Antidiabetics ○ Antiarrhythmics (Amiodarone HCl, Propafenone and Flecainide, Dronedarone, Betapace (Sotalol), Tikosyn, Disopyramide (Norpace), Quinidine) ○ Ketoconazole ○ Antiplatelets (e.g., dipyridamole, aspirin, etc.) ○ NSAIDs <p><u>Outcome Analysis</u></p> <p>The follow-up period, which comprises the patient-time denominator, will start at index and will be censored at the first occurrence of either of the following:</p> <ul style="list-style-type: none"> • outcome event • switch to another anticoagulant • change in dose of index NOAC • discontinuation of therapy, as defined as a gap in therapy exceeding 30 days (a 14 day gap sensitivity analysis will also be performed) • end of DoD eligibility • end of study period <p>Primary outcomes</p> <ul style="list-style-type: none"> • Stroke overall (hemorrhagic, ischemic, uncertain) • Major bleeding, overall <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Ischemic stroke • Hemorrhagic stroke • Major intracranial bleeding • Major extracranial bleeding <ul style="list-style-type: none"> ○ Major GI bleeding ○ Major other bleeding
--	---

	<ul style="list-style-type: none">• TIA• All-cause mortality  <p>The first occurrence of each outcome will be identified, separately. For each outcome, event rates and 95% confidence intervals (CI) will be calculated using a person-time approach for each treatment and further stratified by age and gender. Time-to-event analyses (i.e. Kaplan-Meier analysis and Cox proportional hazards model analysis) will be performed for each treatment comparison. Details will be laid out in the protocol and approved by the [redacted]-[redacted]-DoD-BIPI study teams.</p> <p>Sensitivity, subgroup and/or exploratory analyses will be performed and may impact changes to the definitions to the assigned cohort, covariates, or outcome. Potential sensitivity/subgroup/exploratory analyses are below:</p> 
Milestones:	Protocol Completion Data Extraction, Preparation, and QA Data Analysis Develop Final Report

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone:	Planned date:
Protocol finalization	02 December 2016
BI Approval	05 December 2016
Start of data evaluation and specific programming rules development:	19 October 2016
Start of data analysis:	05 December 2016
Completion of ACC data analyses- Primary analyses with PSM	17 January 2016
Completion of data analyses- Secondary analyses with PSM	31 January 2017
Completion of data analyses-Sensitivity analyses (not including IPTW) with PSM	14 February 2017
Completion of data analyses-IPTW analyses	10 March 2017
Final report of study results:	March 2017

7. RATIONALE AND BACKGROUND

Non-valvular atrial fibrillation (NVAF) is an abnormal heart rhythm characterized by rapid and irregular beating. Patients may experience shortness of breath, palpitations, fainting, or chest pain. Anticoagulants have long been used to decrease the risk of stroke in NVAF patients and the efficacy of blood thinners have been well studied.

Until recently, warfarin, which was FDA-approved in 1954, was the only drug on the market used to prevent stroke in patients with NVAF. In the last few years, the FDA has approved three NOACs – dabigatran, rivaroxaban, and apixaban. All three NOACs have shown efficacy in reducing the overall risk of stroke, but, can also increase the risk for bleeding.

In several clinical trials that included more than 50,000 patients from around the world, studies concluded that all three NOACs were either equivalent to, or more effective than, warfarin in preventing strokes, with an acceptable risk of bleeding.¹⁻⁶ NOACs have some advantages, including fewer interactions with food and other drugs, rapid onset, and freedom from the need to have periodic blood test monitoring. Additionally the effects of these drugs wane within a short time frame after they are stopped, a day or so, while the effects of warfarin persist for many days after it is discontinued, potentially causing a slower resolution to bleeding events.

There is still an unmet need to truly understand utilization patterns of NOAC and non-NOAC therapies, as well as outcomes and safety associated with NOACs when compared to one another. Many traditional insurance plans do not allow for lengthy follow-up periods, as patients tend to frequently switch insurance coverage and in some cases providers. Therefore, the ability to assess longitudinal real-world data in a large patient population poses an unmet need in the medical community. The DoD patient population is well suited to help tackle these real-world issues due to its “closed loop system”. DoD beneficiaries have much longer treatment durations and follow-up periods because beneficiaries tend to have longer coverage periods when compared to traditional commercial insurance plans.

DoD, in collaboration with [REDACTED] have successfully published prior findings in a reputable medical journal comparing dabigatran and warfarin in an NVAF patient population (1). That study aimed to mitigate many of the potential biases and limitations of observational studies via vigorous methodology including inclusion of only newly treated patients, propensity score matching (PSM) to derive cohorts for comparison, and adjustments of covariates if needed based on imbalances left following PSM. Additionally, rules were pre-specified to ensure that PSM analyses of outcomes were only performed if there were enough patients per cohort to support a robust analysis.

The opportunity to expand on our initial study by including additional NOAC usage in a large patient population with a relatively long duration of continuous follow-up provides an outstanding opportunity to assess safety and outcomes in a real-world setting. Results from

our findings may better inform clinical decisions across the DoD and international medical communities.

8. RESEARCH QUESTION AND OBJECTIVES

To assess the safety and effectiveness of newly initiated dabigatran among patients diagnosed with NVAf in comparison to newly initiated rivaroxaban users and newly initiated apixaban users in two (2) separate study cohorts:

- dabigatran vs. rivaroxaban
- dabigatran vs. apixaban

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a retrospective database cohort analysis of the DoD population.

9.2 SETTING

A retrospective cohort study will be conducted using the DoD database. The target population will include OAC treatment naïve NVAf patients with at least one prescription claim for dabigatran, rivaroxaban or apixaban (new oral anticoagulant or NOAC). For each patient treated with a NOAC, the date of the first NOAC prescription (index exposure) will serve as the index date. Only those patients whose index date occurs between the respective study periods will be included. The 12-month period prior to the index date will be defined as the pre-index period. The patients will be required to have a NVAf diagnosis in the pre-index period (including index date). Inclusion and exclusion codes can be found in [Appendix B](#).

Study period NOT including pre-index period:

- Dabigatran vs. Rivaroxaban: July 1, 2011 to June 30, 2016
- Dabigatran vs. Apixaban: December 28, 2012 to June 30, 2016

Study period including pre-index period:

- Dabigatran vs. Rivaroxaban: July 1, 2010 to June 30, 2016
- Dabigatran vs. Apixaban: December 28, 2011 to June 30, 2016

NOAC approval dates used for study period determination:

- Dabigatran (Pradaxa®) – approved October 11, 2010
- Rivaroxaban (Xarelto®) – approved July 1, 2011
- Apixaban (Eliquis®) – approved December 28, 2012

Subject Inclusion Criteria:

- Age 18+ on index date
- Patients must have been prescribed either dabigatran, rivaroxaban, or apixaban identified by pharmacy claim during the study period. The first dispensing date of either study drug will be defined as the index date;
- Patients must be treatment naïve from all OAC use prior to the first NOAC prescription, during study period.
- Patients must have at least 12 months of continuous eligibility prior to the index date;
- Patients must have at least one diagnosis code of atrial fibrillation, defined as ICD-9-CM diagnosis of 427.31 or ICD-10-CM diagnosis of I48.0, I48.1, I48.2, I48.91 on the index date or during the pre-index period.

Subject Exclusion:

- Less than 12 months of continuous eligibility in the pre-index period
- Any claim for OAC drug (oral use only) in the pre-index period
- Diagnosis of hyperthyroidism during the pre-index period
- Having at least one claim for alternative indications; orthopedic procedures, VTE (includes DVT & PE) and the index NOAC prescription at the same time, or, the alternative indication for anticoagulant occurring within 3 months prior to index date in pre-period Having at least one claim with any of the following diagnoses or procedure codes in order to exclude patients with “transient” causes of Afib (3 months prior to index date in pre-period):
 - Cardiac surgery
 - Pericarditis
 - Myocarditis
- Having at least one medical claim with any of the following diagnoses or procedures codes in order to exclude patients with “valvular” Afib (pre-period):
 - Mitral stenosis
 - Mitral stenosis with insufficiency
 - Mitral valve stenosis and aortic valve stenosis
 - Mitral valve stenosis and aortic valve insufficiency
 - Diseases of other endocardial structures
 - Other and unspecified rheumatic heart diseases
 - Open heart valvuloplasty without replacement
 - Open and other replacement of unspecified heart valve
 - Open and other replacement of aortic valve

- Open and other replacement of mitral valve
- Open and other replacement of pulmonary valve
- Open and other replacement of tricuspid valve
- Heart valve replaced by transplant
- Heart valve replaced by a mechanical device/prosthesis
- Atrioventricular valve repair
- Aortic valve valvuloplasty
- Unlisted procedure, cardiac surgery
- Implantation of catheter-delivered prosthetic aortic heart valve; open thoracic approach
- Transthoracic cardiac exposure (e.g., sternotomy, thoracotomy, subxiphoid) for catheter-delivered aortic valve replacement; without cardiopulmonary bypass
- Transthoracic cardiac exposure (e.g., sternotomy, thoracotomy, subxiphoid) for catheter-delivered aortic valve replacement; with cardiopulmonary bypass
- Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or stentless valve
- Valvuloplasty, mitral valve, with cardiopulmonary bypass
- Valvuloplasty, mitral valve, with cardiopulmonary bypass; with prosthetic ring
- Valvuloplasty, mitral valve, with cardiopulmonary bypass; radical reconstruction, with or without ring
- Replacement, mitral valve, with cardiopulmonary bypass
- Implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach
- Replacement, pulmonary valve
- Valvectomy, tricuspid valve, with cardiopulmonary bypass
- Valvuloplasty, tricuspid valve; without ring insertion
- Valvuloplasty, tricuspid valve; with ring insertion
- Replacement, tricuspid valve, with cardiopulmonary bypass

Standard dosing for each NOAC will be used for main analyses. All doses for each NOAC will be combined for a sensitivity analysis. Standard dose for NOAC's include:

- Dabigatran 150 mg, twice daily for total daily dose of 300 mg
- Rivaroxaban 20 mg, once daily for total daily dose of 20 mg
- Apixaban 5 mg, twice daily for total daily dose of 10 mg

Length of Baseline

The 12-month period prior to and including the NOAC index date will be defined as the baseline period. Patients will be required to have an NVAf diagnosis during this baseline period.

The pre-index period will serve as a look-back period to measure baseline covariate data and apply other inclusion and exclusion criteria.

Length of Follow-up:

The post-index follow-up period will begin the day following the NOAC index date and end on whichever of the following occurs earliest:

- The day of discontinuation of the index NOAC exposure;
- The day before a switch to an anticoagulant different from the index exposure;
- The day before a change in dose for the index NOAC;
- The end of continuous eligibility of a patient in the health plan (disenrollment);
- The end of the study observation period; or
- The date of death of the patient.

Patients need at least two days of exposure to the index NOAC to ensure they had at least one day of index NOAC exposure in the post-index follow-up period.

For patients, index exposure will be considered discontinued if there is a treatment gap longer than the 30 day allowable gap specified from the end of the calculated days supplied.

Patients that have treatment gap longer than the specified allowable gap will be censored at that point and follow-up will be discontinued. A sensitivity analysis will also be performed using a 14 day treatment gap.

9.3 VARIABLES

9.3.1 Exposures

Exposure to NOACs for the purpose of describing the potential study population will be identified by the presence of at least one prescription for dabigatran, rivaroxaban or apixaban. Please refer to [Table 1 in Appendix A](#) for the corresponding codes to identify each therapy. As described in [Section 9.11 Study Population](#), the potential study population will be divided into the following two cohorts based on NOAC exposure:

- Dabigatran vs. Rivaroxaban: July 1, 2011 to June 30, 2016
- Dabigatran vs. Apixaban: December 28, 2012 to June 30, 2016

Standard dosing for each NOAC will be used for main analyses. All doses for each NOAC will be combined for a sensitivity analysis.

9.3.2 Outcomes

The outcomes will be assessed during the post-index period for the two cohorts. If a patient discontinued the index NOAC or switched to a different NOAC, the outcomes assessment would not continue beyond the date of discontinuation or the switch. The primary and secondary outcomes assessed will be safety and effectiveness measures as described below in the [Outcomes of Interest table](#). [REDACTED]

The safety and effectiveness analysis will be conducted for the following cohorts:

001-MCS-90-124_RD-01 (4.0)

- Oral Anticoagulant treatment naive patients: Dabigatran vs. Rivaroxaban
- Oral Anticoagulant treatment naive patients: Dabigatran vs. Apixaban

Outcomes of Interest	
Primary	Stroke (hemorrhagic, ischemic, uncertain classification) Major bleeding
Secondary	Major bleeding, by the following sites <ul style="list-style-type: none"> • Major intracranial • Major extracranial <ul style="list-style-type: none"> ○ Major gastrointestinal ○ Other Stroke by type <ul style="list-style-type: none"> • Ischemic stroke • Hemorrhagic stroke Transient ischemic attack (TIA) All-cause mortality
Further	<div style="background-color: black; width: 100px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 250px; height: 15px; margin-bottom: 5px;"></div> <div style="display: flex; align-items: center;"> <div style="background-color: black; width: 10px; height: 20px; margin-right: 5px;"></div> <div style="background-color: black; width: 200px; height: 20px; margin-left: 5px;"></div> </div>



9.3.3 Covariates

The following variables, but not limited to, will be used as covariates in the relevant analysis:

- **Gender:** Gender will be determined from eligibility file. Dichotomous variable (male=1, female=0).
- **Age:** Age in years will be determined on the index date. Continuous variable.
- **Geographic location:** Geographic locations of patient residence will be determined from eligibility file and will be grouped based on the US census classification (i.e., Northeast, Midwest, South, and West regions). South region will be the reference location.
- **Health plan type:** Health plan benefit designs such as health maintenance organization (HMO), preferred provider organization (PPO), fee-for-service (FFS), Medicare Advantage and Part D plan, etc. FFS is the reference plan type.
- **Baseline comorbid conditions:** The comorbid conditions will be captured by any inpatient claim, any two physician office visit (OV) or emergency room (ER) visits,

or a combination of both (OV+ER) with a diagnosis of the following conditions in any position during baseline (12 month pre-index period) (See [Appendix A, Table 2](#), for ICD-9-CM) and ICD-10 codes:

- Cancer
- Rheumatoid arthritis
- Coronary artery disease
- Acute myocardial infarction
- Cardiomyopathy
- Ischemic stroke
- Stroke (all types)
- TIA
- Congestive heart failure
- Left ventricular heart failure
- Hypertension
- Peripheral artery disease
- Liver disease
- Renal disease
- COPD/emphysema
- Diabetes
- Peptic ulcer (bleeding or non-bleeding)
- GERD
- Venous thromboembolism
- Hyperlipidemia
- HIV infection
- Bone marrow disease (thrombocytopenia, chronic anemia, myelofibrosis)
- Coagulopathy (hemophilia, Von Willebrand disease)
- Chronic kidney disease
- **Baseline (pre-index) medication use**
 - **Non-Oral Anticoagulants:** Number of prescription fills (normalized to a 30-day supply) will be captured during the pre-index period (See [Appendix A, Table 8](#))
 - Argatroban (can be used in procedures in lieu of heparin)
 - Unfractionated Heparin (Heparin)
 - Low Molecular Weight Heparins:
 - Enoxaparin
 - Tinzaparin
 - Dalteparin
 - Fondaparinux
 - **Other medication use:** Use of other medications will be determined if patients had ever filled a medication in the following drug classes during the pre-index period (See [Appendix A, Table 3, Table 8](#)).
 - Beta blockers
 - Calcium channel blockers
 - Diuretics
 - Other antihypertensives (i.e., angiotensin-converting-enzyme (ACE) inhibitors, combinations)

- Antihyperlipidemics
 - Corticosteroids
 - Antidiabetics
 - Antiarrhythmics (Amiodarone HCl, Propafenone and Flecainide, Dronedarone, Betapace (Sotalol), Tikosyn, Disopyramide (Norpace), Quinidine)
 - Ketoconazole
 - Antiplatelets (e.g., dypridamole, aspirin, etc.)
 - NSAIDs
- **Prescribing provider specialty of NOAC treatment on index date:** The prescribing specialties will include cardiology, pulmonary medicine, hematology, internal medicine, family/general practice, geriatrics, surgery (all types, including vascular surgery), gastroenterology, neurology, emergency medicine, other physician types, other non-physician specialty, unknown.
 - **Baseline Charlson comorbidity index (CCI) score:** Baseline CCI measures specific individual comorbidities that are associated with mortality that are observed in the pre-index period. A score will be calculated based on CCI criteria. (See [Appendix A, Table 4](#)).
 - **Baseline stroke risk:** This will be assessed during 12-month pre-index period using two alternative risk score schemes:
 - (1) the CHADS₂ stroke risk score is calculated by adding 1 point each for congestive heart failure, hypertension, diabetes, and age >75 years and 2 points for prior stroke or TIA (See [Appendix A, Table 5](#));
 - (2) the CHA₂DS₂-VASc stroke risk score - calculated by adding 1 point each for congestive heart failure/left ventricle dysfunction, hypertension, diabetes, vascular disease (prior myocardial infarction (MI), peripheral artery disease, or aortic plaque), age between 65-74, female gender, and 2 points for and age >75 years prior stroke or TIA (See [Appendix A, Table 6](#)).
 - **Baseline bleeding risk:** This will be assessed during the pre-index period using the bleeding score of modified HAS-BLED (See [Appendix A, Table 7](#)).
 - **Index exposure:** NOAC on the index date
 - **Time to index exposure:** The time period in days between the first AF diagnosis observed in the pre-index period and the index date
 - **Newly vs. Previously AF diagnosed:** patients with a claim for AF <3 months before the index date will be classified as newly diagnosed. Patients with a claim >3 months before the index date will be classified as previously diagnosed.
 - **Duration of follow-up period:** The time period in days between the index date and the end of follow-up.

9.4 DATA SOURCES

The study will use the Military Health Systems (MHS) database.

The US DoD operates the largest cradle-to-grave health care database in the US. The military database has over 30 billion archived records, including 5 billion online records spanning

over 11 years for EMRs, 20 years of ePrescribing, and decades of prescription, inpatient, and outpatient data. Its size increases by 230,000 outpatient encounters and 2,700 inpatient admissions every day. As a single-payer, fully budgeted \$55 billion health care system, there are uniform medical coverage and pharmacy benefits for the 10 million active people served. The pharmacy benefit in particular has minimal expenses for most patients, thus positioning the DOD as a dynamic platform for patient adherence. It is completely free of expense for patients utilizing military treatment facilities (MTF) and clinics. These data are commercially available only through [REDACTED].

The MHS provides 2 types of care to its beneficiaries. It provides direct care through a network of over 60 military hospitals and 411 clinics and purchased care provided by civilian providers financed through managed care contracts and fee-for-service reimbursements globally. Direct care accounts for approximately 40% of the total care provided, with the balance being purchased from civilian providers. All the administrative events generated by either a direct care or purchased care inpatient or outpatient encounter are centrally processed into the MDR. Examples of the data recorded in such encounters include patient demographic data, provider information (provider ID, specialty, facility), diagnostic codes (ICD-9 codes for outpatient; diagnosis-related group [DRG] codes for inpatient), and Current Procedural Terminology (CPT) codes for any procedures. Extensive information regarding the patient, including age, race, and gender, is also stored within the MDR via connections with the Defense Eligibility Enrollment Reporting System (DEERS). The military utilizes an electronic medication system called the Pharmacy Data Transaction System (PDTs). All the prescribing details of both direct care and purchased care outpatient medication orders, including mail order, are electronically coded, including the prescribed drug name and NDC, dose, quantity, refills, and prescribing provider. All PDTs information is fed into the MDR.

In addition to feeding data into the MDR, direct care encounters conducted at MTFs utilize the military's EMR system, called AHLTA. This robust EMR system stores the entire encounter electronically and is powered by the MEDCIN[®] Engine; AHLTA is therefore designed with extensive variables documenting the individual components of an encounter, including symptoms, vital signs, history, physical exams, laboratory and radiology results, diagnostic codes, procedure codes, pharmacy orders, and other orders such as specialty consultation. The AHLTA dataset for each encounter is stored within the Clinical Data Repository (CDR). Aspects of the CDR feed into the MDR, including vitals and lab results. Administrative information such as ICD-9 diagnoses, CPT codes, and pharmacy orders for all direct care encounters are held in common by the CDR and MDR. The CDR is a transactional database required to provide millions of interactions every day for hundreds of thousands of users.

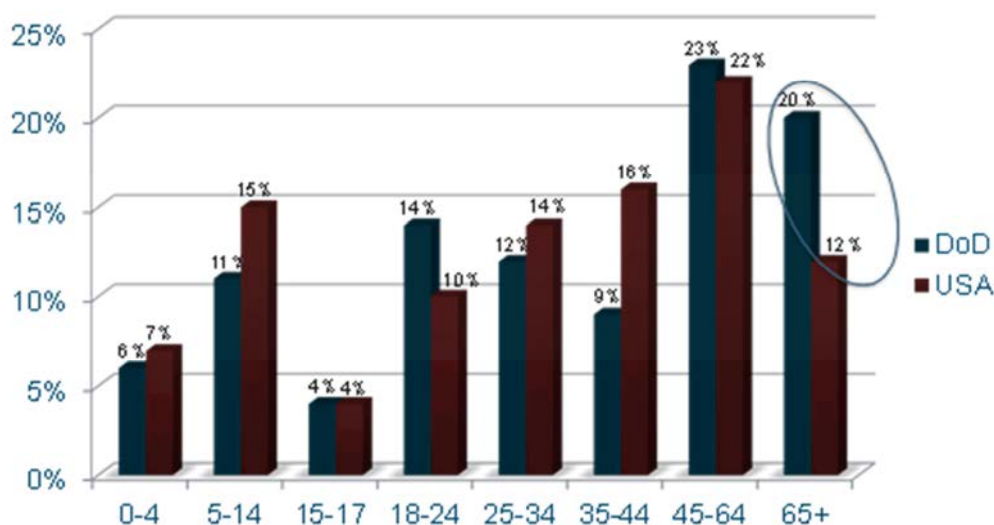


Figure 1 Age distribution among DOD active patients

9.5 STUDY SIZE

Given the non-interventional design, the study's objective is not to demonstrate superiority of dabigatran vs. rivaroxaban or apixaban but rather to provide real-world estimates of the comparative effectiveness and safety of dabigatran, rivaroxaban, and apixaban in a large US population of NVAf patients. Therefore, the planned analyses are descriptive in nature and results of the statistical tests are to be interpreted in an exploratory manner.

For each treatment comparison, the available sample size is determined by feasibility assessments of the DoD database according to the pre-specified time window and inclusion/exclusion criteria, and not by formal sample size justifications. Therefore, the purpose of the power assessments described in this section is to illustrate the precision of the effect estimates that can be achieved given the feasible sample size. The primary safety outcome of major bleeding was used for the power assessments, for which an annual event rate of 3.1% for the dabigatran patients and a mean follow-up duration of 0.82 years for both groups were assumed based on the study by Villines et al⁶. In addition, all calculations are based on a two-sided test with $\alpha=0.05$ and a 10% loss of dabigatran patients during the 1:1 propensity score matching.

For the analysis of dabigatran vs. rivaroxaban, it is estimated that a total of approximately 41,000 patients (16,000 dabigatran vs. 25,000 rivaroxaban patients) will be available for this study, based on the proposed time window of July 2011 to March 2016. Power calculations suggest that such a sample size will allow the study to detect a relative difference in the rate of major bleeding of 22% with 80% power, and 25% with 90% power, between the rivaroxaban and dabigatran groups.

For the analysis of dabigatran vs. apixaban, it is estimated that a total of approximately 27,000 patients (6,000 dabigatran and 21,000 apixaban patients) will be available for this study, based on the proposed time window of December 2012 to March 2016. Power calculations suggest that such a sample size will allow the study to detect a relative difference in the rate of major bleeding of 37% with 80% power, and 43% with 90% power, between the apixaban and dabigatran groups. The analysis may therefore have insufficient power to detect a smaller treatment difference if the expected sample size is confirmed.

The actual power of the study will be dependent on the actual event rate in each treatment group, the covariates included in the analysis models, and the actual loss of patients during matching, and may therefore differ.

9.6 DATA MANAGEMENT

Access to the DoD data will be through a VPN connection. Through this secure connection [REDACTED] and [REDACTED] will construct the study-specific analytic datasets. Data are checked for internal consistency within each patient's claims/records relevant to the study analyses and any patients with extreme or unexpected treatment patterns or diagnoses are identified. BIPI will not have direct access to the raw data. All data management and statistical analyses will be performed using SAS Version 9.4 (or later) in the secured environment

9.7 DATA ANALYSIS

All statistical analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC).

Baseline characteristics will be described for the two cohorts based on the NOAC treatment (dabigatran vs. rivaroxaban and dabigatran vs. apixaban) using standard summary statistics. Means (\pm standard deviation, SD) and median (interquartile range) will be reported for continuous variables and frequencies (%) for categorical variables. The final study sample will be newly initiating cohorts.

To account for potential selection bias, the study cohorts (dabigatran/rivaroxaban and dabigatran/apixaban) will be matched on their baseline characteristics using the propensity score matching (PSM) method. The PSM aims to balance the two treatment groups on baseline demographics, health plan type and clinical characteristics. The feasibility of PSM will be evaluated based on available sample size and descriptive results. If patient characteristics between dabigatran/rivaroxaban and dabigatran/apixaban cohorts are significantly different, i.e., less than 50% of patients in the dabigatran group can be matched to the rivaroxaban or apixaban group based on PSM, then the study design will be re-evaluated before proceeding to analysis. The Nearest Neighbor method of propensity score matching within a caliper of 0.10-0.20 (depending on resulting sample sizes) of the standard deviation of the estimated logit will be used to select the matched samples.

The propensity score will be defined as the probability of being treated with the index NOAC based on a set of baseline characteristics. If, for example, two patients, one in the dabigatran group and another in the rivaroxaban group, had the same propensity score, they would both have the same probability of being treated with dabigatran. The final list of baseline characteristics to be utilized in the PSM will be decided in conjunction with BI. The following baseline characteristics in the pre-index period will be considered: age, gender, health plan type, geographic region, month and year of index date, Charlson comorbidity index (CCI), stroke risk scores (i.e. CHADS₂ or CHA₂DS₂-VASc), bleeding risk scores (i.e., modified HAS-BLED), relevant baseline comorbid conditions and medication use as defined in Section 9.3.3. The distribution of baseline characteristics will be presented before and after the matching process. For baseline covariates that are not sufficiently balanced after PSM, the covariates will be included in an appropriate multivariate model to adjust for those differences.

9.7.1 Main analysis

Patient demographics and clinical characteristics will be reported for NVAf patients by treatment groups: dabigatran, rivaroxaban, or apixaban. Stroke risk will be quantified using the CHADS₂ score, CHA₂DS₂-VASc score and bleeding risk through the HAS-BLED score. In addition, administrative variables of eligibility time and post-index follow-up time will be described. Other descriptive variables may include, but are not limited to, the following:

Comorbid conditions at baseline (the 12 month pre-index period), based on diagnosis codes:

- Cancer
- Rheumatoid arthritis
- Coronary artery disease
- Acute myocardial infarction
- Cardiomyopathy
- Ischemic stroke
- Stroke (all types)
- TIA
- Congestive heart failure
- Left ventricular heart failure
- Hypertension
- Peripheral artery disease
- Liver disease
- Renal disease
- COPD/emphysema
- Diabetes
- Peptic ulcer (bleeding or non-bleeding)
- GERD
- Venous thromboembolism
- Hyperlipidemia
- HIV infection

- Bone marrow disease (thrombocytopenia, chronic anemia, myelofibrosis)
- Coagulopathy (hemophilia, Von Willebrand disease)
- Chronic kidney disease

Medication History and Concomitant Use at baseline (the 12 month pre-index period), based on prescription information:

- **Non-Oral Anticoagulants:** Number of prescription fills (normalized to a 30-day supply) will be captured during the pre-index period (See [Appendix A, Table 8](#))
 - Argatroban (can be used in procedures in lieu of heparin)
 - Unfractionated Heparin (Heparin)
 - Low Molecular Weight Heparins:
 - Enoxaparin
 - Tinzaparin
 - Dalteparin
 - Fondaparinux
- **Other medication use:** Use of other medications will be determined if patients had ever filled a medication in the following drug classes during the pre-index period (See [Appendix A, Table 3, Table 8](#)).
 - Beta blockers
 - Calcium channel blockers
 - Diuretics
 - Other antihypertensives (i.e., angiotensin-converting-enzyme (ACE) inhibitors, combinations)
 - Antihyperlipidemics
 - Corticosteroids
 - Antidiabetics
 - Antiarrhythmics (Amiodarone HCl, Propafenone and Flecainide, Dronedarone, Betapace (Sotalol), Tikosyn, Disopyramide (Norpace), Quinidine)
 - Ketoconazole
 - Antiplatelets (e.g., dipyridamole, aspirin, etc.)
 - NSAIDs

The follow-up period, which comprises the patient-time denominator, will start at index and will be censored at the first occurrence of either of the following:

- outcome event
- therapeutic switch
- index NOAC dose change
- discontinuation of therapy, as defined as a gap in therapy exceeding 30 days
- end of DOD eligibility
- end of study period

Patients need at least two days of exposure to the index NOAC to ensure they had at least one day of index NOAC exposure in the post-index follow-up period.

For patients, index exposure will be considered discontinued if there is a treatment gap longer than the 30 day allowable gap specified from the end of the calculated days supplied. Patients that have treatment gap longer than the specified allowable gap will be censored at that point and follow-up will be discontinued. A sensitivity analysis will be performed on patients that have treatment gaps longer than 14 days to determine if an adjustment to the gap days is necessary.

The first occurrence of each outcome will be identified, separately. For each outcome, event rates and 95% confidence intervals (CI) will be calculated using a person-time approach for each treatment and further stratified by age and gender. To compare the occurrence of each outcome between treatments, Kaplan-Meier analysis and Cox proportional hazards model analysis will be performed. Additional adjustments will be made for baseline variables that are not sufficiently balanced after PSM.

Standard dosing for each NOAC will be used for main analyses. All doses for each NOAC will be combined for a sensitivity analysis as defined below.

9.8 QUALITY CONTROL

All amendments to the study protocol will be discussed with and agreed upon by the sponsor. Actual amendments to the study protocol will be made by the vendor and sent to BIPI for review and approval. The date of the amendments will be documented on the cover page of the study protocol. Amendments to the protocol will be submitted to the Institutional Review Board (IRB) for review and approval prior to implementation in accordance with regulatory requirements.

Clinicians from two MTFs, who are well versed in the standard of care for the NVAF population in the military setting, will be available to provide oversight and feedback.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Similar to other retrospective database studies, this study is subject to limitations including coding errors of omission and commission, incomplete claims, unreliable clinical coding, and unobservable factors not equally distributed in the treatment groups that may also influence the outcomes. In addition, unrecognized confounding due to characteristics not measured or included in the PSM.

9.10 OTHER ASPECTS

Ethical Approval:

This study will be conducted using a limited administrative claims database which fully complies with HIPAA. Institutional Review Board and Independent Ethics Committee approvals will be obtained for this study.

9.11 BIAS

As for any observational study, there are many potential sources of bias, and there may be significant sources of bias that are not recognized. To minimize bias, this study will include only patients who have not previously been treated with novel oral anticoagulation, and will use propensity score IPTW. Further, effort has been made to avoid exclusions that may differentially affect the treatment groups, and be a potential bias.

10. PROTECTION OF HUMAN SUBJECTS

IRB Review and Approval

Upon contracting and once the final protocol has been agreed upon by the client, [REDACTED] will submit the protocol to an independent IRB review. All protocols including those for purely retrospective studies need to be submitted to the IRB. A request for exemption, expedited or full IRB review will be requested depending on the type of study. Only upon receipt of the IRB exemption or approval letter can the study be initiated. [REDACTED] will inform the study team once the letter is received, so the study can begin.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Safety Reporting:

This is a retrospective observational study, in which all patient data will be de-identified and analyzed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable for this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Ongoing teleconferences with the project team will be conducted to review the project status and results. Ad hoc meetings will be scheduled as needed. A face-to-face meeting to review the results of the study is complete can be scheduled at the client's request.

At the completion of all analyses, [REDACTED] will develop a full written report, which will describe the research, its results, and the implications of study findings. The report will contain an executive summary as well as detailed description of the methodology, results and conclusions. Study results will be provided in Microsoft Excel spreadsheet table shells and figures as appropriate, with results summarized in a Microsoft Word document. A draft report will be delivered to BIPI followed by a final report once feedback from BIPI is received by [REDACTED].

An abstract, poster (given abstract acceptance) and manuscript will be developed based on the study results. Abstract(s), poster(s), and/or manuscript(s) related to this study will be completed in accordance to the contractual agreement set forth between [REDACTED] [REDACTED] and BIPI. Publications resulting from this study will comply with recognized ethical standards concerning publications and authorship, including Section II – “Ethical Considerations in the Conduct and Reporting of Research” of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, established by the International Committee of Medical Journal Editors.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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[2] Patel, Manesh R. "Rivaroxaban – Once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: Rationale and design of the ROCKET study." *Am Heart Journal*. March 2010; 159 (3): 340-347.

[3] Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation" *N Engl J Med* 2011; 365:883-891.

[4] Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and *the RE-LY Steering Committee and Investigators. "Dabigatran versus Warfarin in Patients with Atrial Fibrillation." *N Engl J Med* 2009; 361:1139-1151

[5] Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators* "Apixaban versus Warfarin in Patients with Atrial Fibrillation." *N Engl J Med* 2011; 365:981-992.

[6] *Thromb Haemost*. 2015 Nov 25;114(6):1290-8. doi: 10.1160/TH15-06-0453. Epub 2015 Oct 8

13.2 UNPUBLISHED REFERENCES

Not applicable.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

APPENDIX A. VARIABLE CODING LIST**Table 1. NOACs for Exposure**

Class	Description	GPI Code
Direct thrombin inhibitors	Dabigatran	833370302001
Direct Xa inhibitor	Rivaroxaban	83370060
	Apixaban	83370010

Table 2. Baseline Comorbid Conditions

Comorbidity		
Cancer	140.xx-172.xx, 174.xx-208.xx, 230.xx-231.xx, 233.xx-234.xx	C00.xxx-D49.xxx
Rheumatoid arthritis	714.xx	M05.xxx, M06.xxx, M08.xxx, M12.0xx
Multiple sclerosis	340	G35
Coronary artery disease	411.xx, 412.xx, 413.xx, 414.xx, 429.2	I20.x, I24.x, I25.xxx
Acute myocardial infarction	410.xx	I21.xx
Cardiomyopathy	425.xx	I42.x, I43
Ischemic stroke	433.x1, 434.x1, 436.x	I63.xxx, I67.89
TIA	435.x	G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2
Heart failure	402.x1, 404.x1, 404.x3, 428.xx	I11.0, I13.0, I13.2, I50.1, I50.2x, I50.3x, I50.4x, I50.9
Atrial flutter	427.32	I48.92
Hypertension	401.x, 402.x0, 403.xx, 404.x0, 404.x2, 405.xx	I10, I11.9, I12.x, I13.1x, I15.x, I16.x
Peripheral artery disease	440.xx, 443.xx	I70.xxx, I73.xx, I77.7x, I79.1, I79.8
Liver disease	121.1, 423.2, 570-573.xx, 751.62	B661, I311. K70.0-K77, Q446
Renal disease	580.xx-588.xx,	N0x.x, N08, B52.0, E08.2x, E09.2x, N14.x, N15.x, N17.x, N18.x, N19, N25.0, N25.1, N25.9, N25.81, N25.89, N26.x,
	590.xx-593.xx	N10, N11.x, N12, N13.0, N13.0, N13.1, N13.2, N13.30, N13.39, N13.4, N13.5, N13.6, N13.70, N13.71, N13.732, N13.729, N13.721, N13.731, N13.722, N13.739, N13.8, N13.9, N15.x, N16, N20.x, N22, N28.1, N28.0, N28.81, N28.83, N28.84, N28.85, N28.86, N28.89, N28.9, N29, R80.2
COPD/emphysema	490-492.xx, 496	J40.x-J44.x

Hypothyroidism	243-244.x	E00.x, E01.8, E02, E03.0, E03.1, E03.2, E03.3, E03.4, E03.8, E03.9, E89.0
Diabetes	250.xx	E10.xxxx, E11.xxxx, E13.xxxx
Peptic ulcer/GERD	530.11, 530.81, 536.2, 536.8, 787.1, 533.xx	K21.x, K27.x, K30, R11.10, R12
Venous thromboembolism	415.11, 415.19, 451.1x, 451.2, 451.81, 451.83, 451.84, 451.9, 453.4x, 453.8x, 453.9	I2699, I80.1x-I80.9, I82.4xx, I82.6xx, I82.890, I82.90, I82.A1x, I82.B1x, I82.C1x
Hyperlipidemia	272.0 – 272.4	E78.0x-E78.5
HIV infection	V08, 042, 079.53	Z21, B20, B97.35
Bone Marrow disease		
Thrombocytopenia	287.3, 287.4, 287.5	D69.3, D69.4x, D69.5x, D69.6
Chronic anemia	285.2	D63.x
Myelofibrosis	289.83	D75.81
Coagulopathy	286.0-286.9, 287.1, 287.3-287.5	D65-D68.x, D69.1, D69.3-D69.6
Dyspepsia	536.8	K30
Left ventricular heart failure	428.1	I50.1
Bone marrow disease	289.9	D75.9
Thrombocytopenia	287.5	D69.6
Anemia	285.9	D64.9
Myelofibrosis	289.83	D75.81
Coagulopathy (other and unspec)	286.9	D68.8, D68.9
Hemophilia	286.52	D68.311
Von Willebrand Disease	286.4	D68.0
Chronic Kidney Disease (not for Renal disease)	585.1	N18.1
	585.2	N18.2
	585.3	N18.3
	585.4	N18.4
	585.5	N18.5
	585.9	N18.9

Table 3. Medications of Interest (Include antiplatelets from [Table 8](#))

Description	GPI codes starting with:	GPI 10
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Beta blockers	33	3310004510, 3310004512
Calcium channel blockers	34	3400000710, 3400000310, 3400001010, 3400001011, 3400001012, 3400001015, 3400001050, 3400001300, 3400001500, 3400001810, 3400001812, 3400001814, 3400002000, 3400002200, 3400002400, 3400003010
Antihypertensives	36	3610000510, 3610001000, 3610002010, 3610002510, 3610002710, 3610003000, 3610003310, 3610003510, 3610004010, 3610005000, 3610006000, 3615001020, 3615002010, 3615002420, 3615003000, 3615004020, 3615005520, 3615007000, 3615008000, 3617001010, 3620101010, 3620102510, 3620103000, 3620103010, 3620200510, 3620203010, 3620204010, 3620304000, 3625003000, 3630001010, 3630002010, 3630002500, 3640001010, 3640002000, 3640004010, 3640203010, 3660002010, 3699150220, 3699150223, 3699150270, 3699180215, 3699180225, 3699180235, 3699180240, 3699180255, 3699180260, 3699180265, 3699200210, 3699200213, 3699200220, 3699200230, 3699200240, 3699270250, 3699300205, 3699300210, 3699300270, 3699400210, 3699400220, 3699400225, 3699400230, 3699400245, 3699400250, 3699400260, 3699400270, 3699450320, 3699450345, 3699500220, 3699500270, 3699600215, 3699670210, 3699680320, 3699850250, 3699880260
Diuretics	37	3710001000, 3710001010, 3710002000, 3710003000, 3720001000, 3720002000, 3720002010, 3720003000, 3720008000, 3740001000, 3740003000, 3750001010, 3750002000, 3750003000, 3760001000, 3760002000, 3760002010, 3760002500, 3760004000, 3760005000, 3760005500, 3760006000, 3790003000, 3799000210, 3799000220, 3799000230, 3799200410
Antihyperlipidemics	39	3910001000, 3910001010, 3910001610, 3910002010, 3920000600, 3920002400, 3920002500, 3920002510, 3920003000, 3930003000, 3935001000, 3935002000, 3940001010, 3940003010, 3940005000, 3940005810, 3940006010, 3940006510, 3940007500, 3940990225, 3940990245, 3940990270, 3945005000, 3948005020, 3950003510, 3950004010, 3950004520, 3950005500, 3999400220, 3999400230, 3999900250
Corticosteroids	22	2210001000, 2210001020, 2210001200, 2210001510, 2210002000, 2210002010, 2210002020, 2210002500, 2210002540, 2210003000, 2210003010, 2210003020, 2210004000, 2210004010, 2210004020, 2210004500, 2210005010, 2210005020, 2210005022, 2210005030, 2210990210, 2210990215, 2210990258, 2210990260, 2210990262, 2210990263, 2210990265, 2210990285, 2210990287, 2210990290, 2210990308, 2210990310, 2210990315, 2210990320, 2210990350, 2210990360, 2210990370, 2210990373, 2210990420, 2220003010

Antidiabetics	27	2710400200, 2710400300, 2710400400, 2710400500, 2710400600, 2710400700, 2710401000, 2710402000, 2710407000, 2710408000, 2710409000, 2715005010, 2717001000, 2717001500, 2717002000, 2717005000, 2720002000, 2720002700, 2720003000, 2720004000, 2720004010, 2720005000, 2720006000, 2725005000, 2728004000, 2728006000, 2730001010, 2730001015, 2730002000, 2730003000, 2730405000, 2730990240, 2750001000, 2750005000, 2755001010, 2755005000, 2755006510, 2755007010, 2757402010, 2760705010, 2760706010, 2770002000, 2770004020, 2770005000, 2799250210, 2799250240, 2799250260, 2799250270, 2799300270, 2799400210, 2799500270, 2799600220, 2799600230, 2799600240, 2799650230, 2799700235, 2799700240, 2799780240, 2799780260, 2799800240, 2799800260, 2799900250
Antiarrhythmics:		
Amiodarone HCl	3540000	3540000500
Propafenone and Flecainide	353000	3530005000
Dronedarone	35400028	3540002810
Betapace (Sotalol)	33100045	33100045
Tikosyn	35400025	3540002500
Disopyramide (Norpac)	35100010	3510001010
Quinidine	351000301	3510003010, 3510003030
Ketoconazole	11404040	1140404000

Table 4. Charlson Comorbidity Index Calculation

Programming algorithm for the Charlson Comorbidity Index (CCI)

1. Identify all patients who ever had the following conditions during their baseline period.

Condition		
Myocardial Infarction	410.x, 412.x	I21.xx, I22.x, I25.2
Congestive Heart Failure	428.x	I50.xx
Peripheral Vascular	441.x, 443.9x,	I71.xx, I73.9, I96, Z95.828

Disease	785.4x, V43.4x	
Cerebrovascular Disease	430.x-438.x	G45.0-G45.2, G45.4-G46.8, I60.xx-I69.xxx (exclude I67.3, I67.83)
Dementia	290.x	F01.5x, F03.90
Rheumatologic Disease	710.0x, 710.1x, 710.4x, 714.0x, 714.1x, 714.2x, 725.x, 714.81	M05.xx-M06.9 (exclude M06.4), M32.xx, M33.20, M34.xx, M35.3
Peptic Ulcer Disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9x, 532.9x, 534.9x	K25.0-K28.9
Mild Liver Disease	571.2x, 571.4x, 571.5x, 571.6x	K70.2, K70.3x, K73.x, K74.xx, K75.4
Diabetes (mild to moderate)	250.0x, 250.1x, 250.2x, 250.3x, 250.7x	E10.1x, E10.5x, E10.641, E11.0x, E11.5x, E11.641, E13.0x, E13.1x, E13.5x, E13.641, E13.9
Diabetes with Complications	250.4x, 250.5x, 250.6x	E10.3xxx, E10.4x, E10.610, E11.2x, E11.3xxx, E11.4x, E11.610, E13.2x, E13.3xxx, E13.4x, E13.610
Hemiplegia or Paraplegia	342.x, 344.1x	G81.xx, G82.2x
Renal Disease	582.x, 585.x, 586.x, 588.x	N03.x, N18.x, N19, N25.xx, N27.x
Malignancy	140.x-172.x, 174.x-195.x, 201.x, 203.x, 205.x-208.x	C00.x-C43.xx, C45.x-C49.xx, C50.xxx-C76.xx, C81.xx, C88.2, C88.3, C88.8, C88.9, C90.xx, C92.xx-C95.xx, D03.xx, D45
Moderate or Severe Liver Disease	572.2x-582.8x, 456.0x, 456.1x, 456.2x	I85.xx, K72.1x, K72.9x, K75.0, K75.1, K75.2, K75.3, K75.8x, K75.9, K76.1, K76.3-K76.9, K77, K80.xx-K90.49, K90.89, K90.9, K91.2, K91.5, K92.0, K92.1, K92.2, N00.0-N03.8, N04.0-N04.9
Metastatic Solid Tumor	196.x-199.x	C77.x-C79.x, C80.x
AIDS	042.x-044.x	B20
Chronic Obstructive Pulmonary Disease and allied conditions	490.x	J40
	491.x	J41.1, J41.8, J44.x, J42
	492.x	J43.x
	493.x	J45.xxx, J44.x
	494.x	J47.x

	495.x	J67.x
	496.x	J44.9

2. If a patient had both the milder and more severe form of the condition, only count the more severe form of the condition -- Diabetes (mild to moderate) / Diabetes with complications; Mild liver disease / Moderate or severe liver disease; Malignancy / Metastatic solid tumor.
3. Weight each of the baseline conditions by the given weights and sum the number of conditions the patient has at baseline. This sum is the patient's CCI at baseline.

Table 5. CHADS₂ Stroke Risk Score

CHADS ₂ Risk Criteria		
Congestive Heart Failure	428.x	I50.xx
Hypertension	401.x–405.x, 437.2	I10-I16.x, I67.4
Diabetes	250.x	E10.xxxx, E11.xxxx, E13.xxxx
Stroke/ transient ischemic attack (TIA)	433.x1, 434.x1, 435.x, 436, 437.1x, 437.9x, 438.x	G45.0-G45.2, G45.8-G46.2, I63.xxx, I67.8xx, I67.9, I69.xxx

After assessing the risk factors and adding up the risk score, the stroke risk classifications are as below:

Score	CHADS ₂ Stroke Risk Classification
0	Low
1	Intermediate
2–6	High

Table 6. CHA₂DS₂-VAsc Stroke Risk Score

CHA ₂ DS ₂ -VAsc Criteria		
Congestive heart	428.x,	I50.xx,

failure or left ventricle dysfunction	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 425.4, 425.5, 425.7	I09.81, I11.0, I13.0, I13.2, I42.5, I42.6, I42.8, I42.9, I43
Hypertension	401.x-405.x, 437.2	I10-I16.x, I67.4
Diabetes Mellitus	250.x	E10.xxxx, E11.xxxx, E13.xxxx
Stroke/TIA	433.x1, 434.x1, 435.x, 436, 437.1x, 437.9x, 438.x	G45.0-G45.2, G45.8-G46.2, I63.xxx, I67.8xx, I67.9, I69.xxx
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	410.xx, 412.xx; 440.2x, 443.8x, 443.9x; ICD-9 proc code: 88.48; CPT code: 75710, 75716, 93922, 93923	I21.xx, I22.xx, I25.2, I70.2xx, I73.8x, I73.9, I79.1, I79.8; ICD-10 proc code: B40F0ZZ, B40F1ZZ, B40FYZZ, B40G0ZZ, B40G1ZZ, B40GYZZ, B40J0ZZ, B40J1ZZ, B40JYZZ, B41F0ZZ, B41F1ZZ, B41FYZZ, B41G0ZZ, B41G1ZZ, B41GYZZ, B41J0ZZ, B41J1ZZ, B41JYZZ

After assessing the risk factors and adding up the risk score, the stroke risk classifications are as below:

Score	CHA ₂ DS ₂ -VAsC Stroke Risk Classification
0	Low
1	Intermediate
2 or greater	High

Table 7. HAS-BLED Bleed Risk Score

HAS-BLED Criteria		
Hypertension	401.x-405.x Drugs used to treat hypertension (GPI codes 3300, 3400, 3610, 3615, 3620, 3625, 3630, 3640, 3660, 3720, 3760)	I10-I16.x
Abnormal renal and liver function	Renal: 580.xx-586.xx, V56.0, V56.8; ICD-9 procedure codes 39.95, 54.98; CPT codes 90935-90993, 99512, 99559	N00.0-N08, N17.0-N19, Z49.31, Z49.32; ICD-10 procedure code: 3E1M39Z, 5A1D00Z, 5A1D60Z

(1 point for each)	Liver: 070.x, 155.0x, 155.1x, 155.2x, 571.x, 572.x, 573.x, 576.8, 456.0x, 456.1x, 456.2x; ICD-9 procedure codes 39.1x, 42.91	B15.x-B19.xx, C22.x, I85.xx, K70.xx, K71.xx, K72.01-K76.1, K76.3-K77, K83.5; ICD10 procedure code: 0610xxx, 0611xxx, 0612xxx, 0614xxx, 0615xxx, 0616xxx, 0617xxx, 0618xxx, 0619xxx, 061Bxxx, 061Jxxx, 06L30CZ, 06L30DZ, 06L30ZZ, 06L33CZ, 06L33DZ, 06L33ZZ, 06L34CZ, 06L34DZ, 06L34ZZ
Stroke	433.xx-437.xx	G45.x, G46.x, I63.xxx-I66.9, I67.1, I67.2, I67.4-I67.82, I67.84x-I68.8
Bleeding (includes anemia and other prior hemorrhage)	285.0x, 285.1x, 285.9x, 423.0x, 430.x-432.x, 455.2x, 455.5x, 455.8x, 459.0x, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.83, 569.85, 569.86, 578.0, 578.1, 578.9, 599.7x, 719.1x, 784.7x, 786.3x; ICD-9 procedure code 44.43; CPT code 43255	D62, D64.0, D64.1, D64.2, D64.3, D64.9, I31.2, I60.xx, I61.x, I62.xx, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K55.21, K57.11, K57.13, K57.31, K57.33, K62.5, K63.1, K63.81, K64.4, K64.8, K66.1, K92.0, K92.1, K92.2, M25.0xx, R04.0, R04.2, R04.81, R04.89, R04.9, R31.0, R31.1, R31.21, R31.29, R31.9, R58; ICD-10 procedure code: 0W3P8ZZ
Labile INRs		
Elderly (Age >65 years)	-	
Drug or alcohol abuse (1 point for each)	Drug: NSAIDs (GPI codes 6410, 6610), Anti-platelets (8515), Other aspirin-containing products (3940990215, 4399100222, 4399100223, 4399100232, 4399100405, 4399400321, 4399400456, 4399590415, 4399590419, 6030990225, 6499000220, 6499000221, 6499000225, 6499000226, 6499000232, 6499000320, 6499000321, 6499000335, 6499000340, 6499000450, 6499000460, 6499100220, 6499100222, 6499100228, 6499100330, 6499100335, 6599000222, 6599100210, 6599100220, 6599100325, 6599100430, 6599100510, 6599170220, 6599400220, 7599000210, 7599000240, 7599000310, 7599000320, 8515990220, 9990000000)	

Alcohol: 291.xx, 303.xx, 305.0x, 357.5x, 425.5x, 571.1x, 571.2x, 571.3x; ICD-9 procedure codes 94.61-94.63, 94.67-94.69	F10.xxx, G62.1, I42.6, K70.xx; ICD-10 procedure code: HZ2ZZZZ, HZ30ZZZ, HZ31ZZZ, HZ32ZZZ, HZ33ZZZ, HZ34ZZZ, HZ35ZZZ, HZ36ZZZ, HZ37ZZZ, HZ38ZZZ, HZ39ZZZ, HZ3BZZZ, HZ40ZZZ, HZ41ZZZ, HZ42ZZZ, HZ43ZZZ, HZ44ZZZ, HZ45ZZZ, HZ46ZZZ, HZ47ZZZ, HZ48ZZZ, HZ49ZZZ, HZ4BZZZ, HZ50ZZZ, HZ51ZZZ, HZ52ZZZ, HZ53ZZZ, HZ54ZZZ, HZ55ZZZ, HZ56ZZZ, HZ57ZZZ, HZ58ZZZ, HZ59ZZZ, HZ5BZZZ, HZ5CZZZ, HZ5DZZZ, HZ63ZZZ, HZ83ZZZ, HZ86ZZZ, HZ88ZZZ, HZ89ZZZ, HZ93ZZZ, HZ96ZZZ, HZ98ZZZ, HZ99ZZZ
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*the maximum score will be 8 since we do not have data available for labile INRs

After assessing the risk factors and adding up the score, the bleed risk classifications are as follows:

Score	HAS-BLED Bleed Risk Classification
0-1	Low
2	Intermediate
3 or greater	High

Table 8. Atrial Fibrillation Medications

Rate control medications	GPI codes starting with:	GPI 10
Beta blockers	3300	3310004510, 3310004512
Calcium channel blockers		3400000710, 3400000310, 3400001010, 3400001011, 3400001012, 3400001015, 3400001050, 3400001300, 3400001500, 3400001810, 3400001812, 3400001814, 3400002000, 3400002200, 3400002400, 3400003010
Verapamil	34000030100	3400003010
Diltiazem	340000101	3400001010, 3400001011, 3400001012, 3400001015, 3400001050
Digoxin/digitoxin	321000	3120001000
Dronedarone	35400028100320	3540002810
Amiodarone	3540000500	3540000500
Rhythm control medications		
Disopyramide (Norpace)	35100010	3510001010
Procainamide	3510002010	3510002010

Flecainide	3530001	3530001010
Propafenone	3530005	3530005000
Betapace (Sotalol)	33100045	3310004510, 3310004512
Tikosyn (Dofetilide)	35400025	3540002500
Quinidine	351000301	3510003010, 3510003030
Mexiletine	352000251	not exist
Moricizine	35050301003	not exist
Other		
ACE Inhibitors	3610	36100005, 36100010, 36100020, 36100025, 36100027, 36100030, 36100033, 36100035, 36100040, 36100050, 36100060
Angiotensin-II Receptor Blockers (ARB)	3615	3615004020, 3615003000, 3615002010, 3615008000, 3615005520, 3615007000, 3615002420, 3615001020
Diuretics (Thiazide, loop)	3720, 3760	3710001000, 3710001010, 3710002000, 3710003000, 3720001000, 3720002000, 3720002010, 3720003000, 3720008000, 3740001000, 3740003000, 3750001010, 3750002000, 3750003000, 3760001000, 3760002000, 3760002010, 3760002500, 3760004000, 3760005000, 3760005500, 3760006000, 3790003000, 3799000210, 3799000220, 3799000230, 3799200410
Antihypertensives (excluding above group)	3620, 3625, 3630, 3640, 3660	3610000510, 3610001000, 3610002010, 3610002510, 3610002710, 3610003000, 3610003310, 3610003510, 3610004010, 3610005000, 3610006000, 3615001020, 3615002010, 3615002420, 3615003000, 3615004020, 3615005520, 3615007000, 3615008000, 3617001010, 3620101010, 3620102510, 3620103000, 3620103010, 3620200510, 3620203010, 3620204010, 3620304000, 3625003000, 3630001010, 3630002010, 3630002500, 3640001010, 3640002000, 3640004010, 3640203010, 3660002010, 3699150220, 3699150223, 3699150270, 3699180215, 3699180225, 3699180235, 3699180240, 3699180255, 3699180260, 3699180265, 3699200210, 3699200213, 3699200220, 3699200230, 3699200240, 3699270250, 3699300205, 3699300210, 3699300270, 3699400210, 3699400220, 3699400225, 3699400230, 3699400245, 3699400250, 3699400260, 3699400270, 3699450320, 3699450345, 3699500220, 3699500270, 3699600215, 3699670210, 3699680320, 3699850250, 3699880260














Fondaparinux	83103030	8310303010 (Also include HCPCS code: Injection, fondaparinux sodium, 0.5 mg - J1652)
Anticoagulants		
Dabigatran	833370302001	8333703020
Argatroban	83337015	8333701500, 8333701520
Warfarin	83200030	8320003020
Heparin	83100020	8310002020, 8310002022, 8310002025, 8310002030, (Also include HCPCS code: Injection, heparin sodium, (heparin lock flush), per 10 units - J1642 , Injection, heparin sodium, per 1000 units - J1644)
Enoxaparin	83101020	8310102010 (Also include HCPCS code: Injection, enoxaparin sodium, 10 mg - J1650)
Tinzaparin	83101080	not exist in GPI database (Include HCPCS code: Injection, tinzaparin sodium, 1000 iu - J1655)
Dalteparin	83101010	8310101010 (Also include HCPCS code: Injection, dalteparin sodium, per 2500 iu - J1645)
Rivaroxaban	83370060	8337006000
Apixaban	83370010	8337001000
Antiplatelet		
Clopidogrel	85158020	8515802010
Brilinta (ticagrelor)	85158470	8515847000
Prasugrel	85158060100330, 85158060100320	8515806010
Ticlopidine	85158080100320	8515808010
Cilostazol	85155516000320, 85155516000330	8515551600
Dipyridamole	85150030000310, 85150030000320, 85150030000330	8515003000
NSAIDs	6610	6610007000, 6610003000, 6610002000, 6610004010, 6610001010, 6610006000, 6610008000, 6610006010, 6610009010, 6610001200, 6610005000, 6610006500, 6610003500, 6610000710, 6610101000, 6610000720, 6610000800, 6610003710, 6610990220, 6610052500, 6610005200, 6610005500, 6610003010, 6610002040, 6610006050, 6610002050, 6610990328, 6610990244, 6610005260, 6610990232, 6610000700, 6610990241, 6610990340, 6610990435, 6610990337, 6610990217, 6610990338, 6610990256, 6610990440, 6610990339, 6610990315, 6610990317,

		6610990238,
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Table 9. Outcome Codes

Medical Conditions	ICD-9 Codes	Description	ICD-10 Codes
Stroke		Inclusive of ischemic stroke and hemorrhagic stroke below	
Major Bleeding		Inclusive of hemorrhagic stroke, major intracranial bleeding and major extracranial bleeding below	
Ischemic Stroke (Primary Only)	433.x1	Occlusion and stenosis of precerebral arteries with cerebral infarction	I63.xxx
	434.x1	Occlusion of cerebral arteries with cerebral infarction	
	436	Acute, but ill-defined, cerebrovascular disease	I67.89
	Exclusion	EXCLUDE above codes if hospitalization lasted <48 hours and was accompanied by carotid endarterectomy (ICD-9 procedure code 38.1)	
Hemorrhagic Stroke (Primary Only)	431	Intracerebral hemorrhage (ICH)	I61.x
	Exclusion	EXCLUDE above codes if “traumatic brain injury” ICD-9-CM code (800 to 804, 850 to 854) or “rehabilitation care” as the primary ICD-9-CM code (V57) is present.	S02.xxxA, S02.xxxB, S06.xxxA, Z51.89
Major Intracranial Bleeding (Primary or Secondary)	430	Subarachnoid hemorrhage	I60.xx
	431	Intracerebral hemorrhage	I61.x
	432.x	Other and unspecified intracranial hemorrhage	I62.xx
	852.0	Subarachnoid hemorrhage following injury without mention of open intracranial wound	S06.36xA
	852.2	Subdural hemorrhage following injury without mention of open intracranial wound	S06.4XxA
	852.4	Extradural hemorrhage following injury without mention of open intracranial wound	S06.5XxA
	853.0	Other and unspecified intracranial hemorrhage following injury without mention of open intracranial wound	S06.6XxA

	Exclusion	EXCLUDE – above codes if concomitant discharge diagnosis of major trauma was present (<i>ICD-9</i> codes 852.1, 852.3, 852.5, and 853.1)	S01.90XA, S06.36xA, S06.4XxA, S06.5XxA, S06.6XxA
Major Extracranial		Inclusive of major GI bleeding, major urogenital bleeding and major other bleeding	
Major GI Bleeding		Inclusive of major upper GI bleeding and major lower GI bleeding	
Major upper GI bleed (Primary Only)	531.0x	Acute gastric ulcer with hemorrhage with/without obstruction	K25.0
	531.2x	With hemorrhage and perforation with/without obstruction	K25.2
	531.4x	(chronic or unspecified gastric ulcer with hemorrhage with/without obstruction)	K25.4
	531.6x	(with hemorrhage and perforation with/without obstruction)	K25.6
	532.0x	(acute duodenal ulcer with hemorrhage with/without obstruction)	K26.0
	532.2x	(with hemorrhage and perforation with/without obstruction)	K26.2
	532.4x	(chronic or unspecified duodenal ulcer with hemorrhage with/without obstruction)	K26.4
	532.6x	(with hemorrhage and perforation with/without obstruction)	K26.6
	533.0x	(acute peptic ulcer of unspecified site with hemorrhage with/without obstruction)	K27.0
	533.2x	(with hemorrhage and perforation with/without obstruction)	K27.2
	533.4x	(chronic or unspecified peptic ulcer of unspecified site with hemorrhage with/without obstruction)	K27.4
	533.6x	(with hemorrhage and perforation with/without obstruction),	K27.6
	534.0x	(acute gastrojejunal ulcer with hemorrhage with/without obstruction)	K28.0
	534.2x	(with hemorrhage and perforation with/without obstruction)	K28.2
	534.4x	(chronic or unspecified gastrojejunal ulcer with hemorrhage with/without obstruction)	K28.4
534.6x	(with hemorrhage and perforation with/without obstruction)	K28.6	

	578.0	(hematemesis)	K92.0
	ICD-9 Procedure Code 44.43	(endoscopic control of gastric or duodenal bleeding)	
	CPT code 43255	(upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method)	
Major lower GI bleeding (Primary Only)	562.02	Diverticulosis of small intestine with hemorrhage	K55.21
	562.03	Diverticulitis of small intestine with hemorrhage	K57.11
	562.12	Diverticulosis of colon with hemorrhage	K57.13
	562.13	Diverticulitis of colon with hemorrhage	K57.31
	569.3x	Hemorrhage of rectum and anus	K57.32
	569.85	Angiodysplasia of intestine with hemorrhage	K62.5
	578.1x	Blood in stool	K92.1
	578.9	Hemorrhage of GI tract, unspecified	K92.2
Major urogenital bleed (Primary Only)	599.7	Hematuria	R31.0 - R31.29
	626.2x and (280.0, 285.1 or 285.9)	Excessive/frequent menstruation and secondary diagnosis indicating acute bleeding (anemia)	N92.0 and (D50.0, D62, D64.9)
Other major bleeds (Primary Only)	719.1x	Hemathrosis	D62
	423.0x	Hemopericardium	I31.2
	786.3x	Hemoptysis	M25.0xx
	784.7x	Epistaxis	R04.0
	459.0x	Hemorrhage not specified	R04.2
	285.1x	Acute posthemorrhagic anemia	R04.8x, R04.9, R58
TIA (Primary Only)	435.x	Transient cerebral ischemia as the principal (primary) discharge diagnosis	G45.0, G45.1, G45.8, G45.9, G46.0, G46.1, G46.2
			
			
			
			

			
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APPENDIX B: Inclusion and exclusion diagnosis, procedure and CPT codes**Table 1. List of codes for atrial fibrillation**

Study Inclusion DX	ICD9 Diagnosis Codes	ICD10 Diagnosis Codes
Atrial Fibrillation	427.31	I48.0, I48.1, I48.2, I48.91

Table 2. List of codes and descriptions to identify patients with exclusion diagnoses

Study Exclusion DX	ICD9 Diagnosis Codes	ICD10 Diagnosis Codes
Hyperthyroidism	242.x	E05.00, E05.01, E05.10, E05.11, E05.20, E05.21, E05.30, E05.31, E05.40, E05.41, E05.80, E05.81, E05.90, E05.91
Orthopedic Procedures (See also procedure codes)	V43.64, V43.65	Z9664x, Z9665x
DVT	451.xx, 453.xx	I80.xxx, I82.xxx
PE	415.1x	I26.01, I26.09, I26.90, I26.92, I26.99, I27.82
Perocarditis	391.x, 393, 420.x, 423.2, 036.41, 074.21, 093.81, 098.83	A39.53, B33.23, I01.0, I09.2, I30.0, I30.1, I30.8, I30.9, I31.0, I32, M32.12
Myocarditis	391.2, 422.xx, 074.23, 398.0, 429.0, 032.82, 036.43, 093.82, 130.3	A36.81, A38.1, A39.52, A52.06, A54.83, B26.82, B33.22, B58.81, D86.85, I01.2, I09.0, I40.0, I40.1, I40.8, I41, I511.4, J10.82, J11.82
Pulmonary Embolism	415.1x	I26.01, I26.09, I26.90, I26.92, I26.99, I27.82
Valvular Afib		
Mitral stenosis	394.0x	I05.0, I05.1, I05.2, I05.8, I05.9, I34.2
Mitral stenosis with insufficiency	394.2	I34.0, I34.2, I34.8, I34.9
Mitral valve stenosis and aortic valve stenosis	396.0	I06.0, I35.0, Q23.0
Mitral valve stenosis and aortic valve insufficiency	396.1	I08.0, I06.1, I25.1, Q23.1, Q23.8, Q23.9

Diseases of other endocardial structures	397.x	I07.x, I09.89, I08.1, I08.2, I08.3, I08.8, I08.9
Other and unspecified rheumatic heart diseases	398.9x	I09.9, I09.81, I09.89
Heart valve replaced by transplant	V42.2	Z95.3, Z95.4
Heart valve replaced by a mechanical device/prosthesis	V43.3	Z95.2
Atrioventricular valve repair	V43.3	Z95.2
Aortic valve valvuloplasty/diseases of aortic valve	395.x	I06.x

Table 3. List of codes and descriptions to identify patients with exclusion procedures

Subject Exclusion Criteria:	ICD9 Procedure Codes	ICD10 Procedure Codes	CPT Codes
Valvular Afib Procedure/CPT codes			
Open heart valvuloplasty without replacement	35.1x	02QF0ZZ, 02QG0ZZ, 02QH0ZZ, 02QJ0ZZ, 027F04Z, 027F0DZ, 027F0ZZ, 02NF0ZZ, 02QF0ZZ, 027G04Z, 027G0DZ, 027G0ZZ, 02NG0ZZ, 02QG0ZZ, 027H04Z, 027H0DZ, 027H0ZZ, 02NH0ZZ, 02QH0ZZ, 027J04Z, 027J0DZ, 027J0ZZ, 02NJ0ZZ, 02QJ0ZZ	

<p>Open And Other Replacement Of Heart Valve (This includes : Open and other replacement of unspecified heart valve, Open and other replacement of aortic valve, Open and other replacement of mitral valve , Open and other replacement of mitral valve , Open and other replacement of pulmonary valve, Open and other replacement of tricuspid valve.)</p>	<p>35.2x</p>	<p>02RF07Z, 02RF08Z, 02RF0JZ, 02RF0KZ, 02RF47Z, 02RF48Z, 02RF4JZ, 02RF4KZ, 02RG07Z, 02RG08Z, 02RG0JZ, 02RG0KZ, 02RG47Z, 02RG48Z, 02RG4JZ, 02RG4KZ, 02RH07Z, 02RH08Z, 02RH0JZ, 02RH0KZ, 02RH47Z, 02RH48Z, 02RH4JZ, 02RH4KZ, 02RJ07Z, 02RJ08Z, 02RJ0JZ, 02RJ0KZ, 02RJ47Z, 02RJ48Z, 02RJ4JZ, 02RJ4KZ, 02RF07Z, 02RF08Z, 02RF0KZ, 02RF47Z, 02RF48Z, 02RF4KZ, X2RF032, X2RF432, 02RF0JZ, 02RF4JZ, 02RG07Z, 02RG08Z, 02RG0KZ, 02RG37Z, 02RG38Z, 02RG3KZ, 02RG47Z, 02RG48Z, 02RG4KZ, 02RG0JZ, 02RG3JZ, 02RG4JZ, 02RH07Z, 02RH08Z, 02RH0KZ, 02RH47Z, 02RH48Z, 02RH4KZ, 02RH0JZ, 02RH4JZ, 02RJ07Z, 02RJ08Z, 02RJ0KZ, 02RJ47Z, 02RJ48Z, 02RJ4KZ, 02RJ0JZ, 02RJ4JZ</p>	
<p>Closed Heart Valvotomy</p>	<p>35.0x</p>	<p>02NF3ZZ, 02NF4ZZ, 02NG3ZZ, 02NG4ZZ, 02NH3ZZ, 02NH4ZZ, 02NJ3ZZ, 02NJ4ZZ, 02NF3ZZ, 02NF4ZZ, 02NG3ZZ, 02NG4ZZ, 02NH3ZZ, 02NH4ZZ, 02NJ3ZZ, 02NJ4ZZ, 02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, X2RF332, 02RF37H, 02RF38H, 02RF3JH, 02RF3KH, 02RH37Z, 02RH38Z, 02RH3JZ, 02RH3KZ, 02RH37H, 02RH38H, 02RH3JH, 02RH3KH, 02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, 02RG37H, 02RG37Z, 02RG38H, 02RG38Z, 02RG3JH, 02RG3JZ, 02RG3KH, 02RG3KZ,</p>	

		02RH37Z, 02RH38Z, 02RH3JZ, 02RH3KZ	
Unlisted procedure, cardiac surgery			33999
Implantation of catheter-delivered prosthetic aortic heart valve; open thoracic approach			0257T
Transthoracic cardiac exposure (e.g., sternotomy, thoracotomy, subxiphoid) for catheter-delivered aortic valve replacement; without cardiopulmonary bypass			0258T
Transthoracic cardiac exposure (e.g., sternotomy, thoracotomy, subxiphoid) for catheter-delivered aortic valve replacement; with cardiopulmonary bypass			0259T
Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or			33405

stentless valve			
Valvuloplasty, mitral valve, with cardiopulmonary bypass			33425
Valvuloplasty, mitral valve, with cardiopulmonary bypass; with prosthetic ring			33426
Valvuloplasty, mitral valve, with cardiopulmonary bypass; radical reconstruction, with or without ring			33427
Replacement, mitral valve, with cardiopulmonary bypass			33430
Implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach			0262T
Replacement, pulmonary valve			33475
Valvectomy, tricuspid valve, with cardiopulmonary bypass			33460
Valvuloplasty, tricuspid valve; without ring insertion			33463
Valvuloplasty, tricuspid valve; with ring insertion			33464
Replacement, tricuspid valve, with			33465

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cardiopulmonary bypass				
Description for CPT=33660-33665			33660 - 33665	
Description for CPT=33400-33403			33400 - 33403	
Orthopedic Procedures (Hip/Knee)				
Total/Partial Hip Replacement	81.52	0SRA009,0SRA00A,0SRA00Z,0SRA019,0SRA01A,0SRA01Z,0SRA039,0SRA03A,0SRA03Z,0SRA07Z,0SRA0J9,0SRA0JA,0SRA0JZ,0SRA0KZ,0SRE009,0SRE00A,0SRE00Z,0SRE019,0SRE01A,0SRE01Z,0SRE039,0SRE03A,0SRE03Z,0SRE07Z,0SRE0J9,0SRE0JA,0SRE0JZ,0SRE0KZ,0SRR019,0SRR01A,0SRR01Z,0SRR039,0SRR03A,0SRR03Z,0SRR07Z,0SRR0J9,0SRR0JA,0SRR0JZ,0SRR0KZ,0SRS019,0SRS01A,0SRS01Z,0SRS039,0SRS03A,0SRS03Z,0SRS07Z,0SRS0J9,0SRS0JA,0SRS0JZ		
	81.51	0SR90J9,0SR90JA,0SR90JZ,0SRB0J9,0SRB0JA,0SRB0JZ		

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	0070, 0071, 0072, 0073, 8153	0SP908Z,0SP909Z,0SP90BZ,0SP90JZ,0SPB08Z,0SPB09Z,0SPB0BZ,0SPB0JZ,0SR9019,0SR901A,0SR901Z,0SR9029,0SR902A,0SR902Z,0SR9039,0SR903A,0SR903Z,0SR9049,0SR904A,0SR904Z,0SR90J9,0SR90JA,0SR90JZ,0SRB019,0SRB01A,0SRB01Z,0SRB029,0SRB02A,0SRB02Z,0SRB039,0SRB03A,0SRB03Z,0SRB049,0SRB04A,0SRB04Z,0SRB0J9,0SRB0JA,0SRB0JZ,0SP908Z,0SP909Z,0SP90BZ,0SPA0JZ,0SPB08Z,0SPB09Z,0SPB0BZ,0SPE0JZ,0SRA009,0SRA00A,0SRA00Z,0SRA019,0SRA01A,0SRA01Z,0SRA039,0SRA03A,0SRA03Z,0SRA0J9,0SRA0JA,0SRA0JZ,0SRE009,0SRE00A,0SRE00Z,0SRE019,0SRE01A,0SRE01Z,0SRE039,0SRE03A,0SRE03Z,0SRE0J9,0SRE0JA,0SRE0JZ,0SP908Z,0SP909Z,0SP90BZ,0SPB08Z,0SPB09Z,0SPB0BZ,0SPR0JZ,0SPS0JZ,0SRR019,0SRR01A,0SRR01Z,0SRR039,0SRR03A,0SRR03Z,0SRR0J9,0SRR0JA,0SRR0JZ,0SRS019,0SRS01A,0SRS01Z,0SRS039,0SRS03A,0SRS03Z,0SRS0J9,0SRS0JA,0SRS0JZ,0SP908Z,0SP909Z,0SP90BZ,0SP90JZ,0SPB08Z,0SPB09Z,0SPB0BZ,0SPB0JZ,0SU909Z,0SUA09Z,0SUB09Z,0SUE09Z,0SUR09Z,0SUS09Z,0SW90JZ,0SW93JZ,0SW94JZ,0SWA0JZ,0SWA3JZ,0SWA4JZ,0SWB0JZ,0SWB3JZ,0SWB4JZ,0SWE0JZ,0SWE3JZ,0SWE4JZ,0SWR0JZ,0SWR3JZ,0SWR4JZ,0SWS0JZ,0SWS3JZ,0SWS4JZ	
			27125 , 27130 , 27132

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			, 27134 , 27137 , 27138
Total/Partial Knee Replacement	81.54	0SRC07Z,0SRC0JZ,0SRC0KZ, 0SRC0LZ,0SRD07Z,0SRD0JZ, 0SRD0KZ,0SRD0LZ,0SRT07Z, 0SRT0JZ,0SRT0KZ,0SRU07Z, 0SRU0JZ,0SRU0KZ,0SRV07Z, 0SRV0JZ,0SRV0KZ,0SRW07Z ,0SRW0JZ,0SRW0KZ	
	0080, 0081, 0082, 0083, 0084, 8155	0SPC08Z,0SPC09Z,0SPC0JZ,0 SPC48Z,0SPC4JZ,0SPD08Z,0S PD09Z,0SPD0JZ,0SPD48Z,0SP D4JZ,0SRC0J9,0SRC0JA,0SRC 0JZ,0SRD0J9,0SRD0JA,0SRD0 JZ,0SPC08Z,0SPC09Z,0SPC48 Z,0SPC4JZ,0SPD08Z,0SPD09Z ,0SPD48Z,0SPD4JZ,0SPT0JZ,0 SPU0JZ,0SRV0J9,0SRV0JA,0S RV0JZ,0SRW0J9,0SRW0JA,0S RW0JZ,0SPC08Z,0SPC09Z,0S PC48Z,0SPC4JZ,0SPD08Z,0SP D09Z,0SPD48Z,0SPD4JZ,0SPV 0JZ,0SPW0JZ,0SRT0J9,0SRT0 JA,0SRT0JZ,0SRU0J9,0SRU0J A,0SRU0JZ,0QPD0JZ,0QPD3J Z,0QPD4JZ,0QPF0JZ,0QPF3JZ ,0QPF4JZ,0QRD0JZ,0QRD3JZ, 0QRD4JZ,0QRF0JZ,0QRF3JZ, 0QRF4JZ,0QUD0JZ,0QUD3JZ, 0QUD4JZ,0QUF0JZ,0QUF3JZ, 0QUF4JZ,0SUC09C,0SUD09C, 0SPC09Z,0SPD09Z,0SUV09Z,0 SUW09Z,0SWC0JC,0SWC0JZ, 0SWC3JC,0SWC3JZ,0SWC4JC ,0SWC4JZ,0SWD0JC,0SWD0J Z,0SWD3JC,0SWD3JZ,0SWD4 JC,0SWD4JZ,0SWT0JZ,0SWT 3JZ,0SWT4JZ,0SWU0JZ,0SW U3JZ,0SWU4JZ,0SWV0JZ,0S WV3JZ,0SWV4JZ,0SWW0JZ,0 SWW3JZ,0SWW4JZ	

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			27447 , 27486 , 27487 , 27437 , 27438 , 27440 , 27441 , 27442 , 27443 , 27445 , 27446
Cardiac Surgery	00.5x, 35.xx, 36.xx, 37.xx	0210083,0210088,0210089,021008C,021008F,021008W,0210093,0210098,0210099,021009C,021009F,021009W,02100A3,02100A8,02100A9,02100AC,02100AF,02100AW,02100J3,02100J8,02100J9,02100JC,02100JF,02100JW,02100K3,02100K8,02100K9,02100KC,02100KF,02100KW,02100Z3,02100Z8,02100Z9,02100ZC,02100ZF,0210344,02103D4,0210444,0210483,0210488,0210489,021048C,021048F,021048W,0210493,0210498,0210499,021049C,021049F,021049W,	
		02104A3,02104A8,02104A9,02104AC,02104AF,02104AW,02104D4,02104J3,02104J8,02104J9,02104JC,02104JF,02104JW,02104K3,02104K8,02104K9,02104KC,02104KF,02104KW,02104Z3,02104Z8,02104Z9,02104ZC,02104ZF,0211083,0211088,0211089,021108C,021108F,021108W,0211093,0211098,0211099,021109C,021109F,021109W,021	

		10A3,02110A8,02110A9,02110AC,02110AF,02110AW,02110J3,02110J8,02110J9,02110JC,02110JF,02110JW,02110K3,02110K8,02110K9,02110KC,02110KF,02110KW,02110Z3,02110Z8,02110Z9,02110ZC,02110ZF,0211344,	
		02113D4,0211444,0211483,0211488,0211489,021148C,021148F,021148W,0211493,0211498,0211499,021149C,021149F,021149W,02114A3,02114A8,02114A9,02114AC,02114AF,02114AW,02114D4,02114J3,02114J8,02114J9,02114JC,02114JF,02114JW,02114K3,02114K8,02114K9,02114KC,02114KF,02114KW,02114Z3,02114Z8,02114Z9,02114ZC,02114ZF,0212083,0212088,0212089,021208C,021208F,021208W,0212093,0212098,0212099,021209C,021209F,021209W,02120A3,02120A8,02120A9,02120AC,02120AF,02120AW,02120J3,02120J8,02120J9,02120JC,	
		02120JF,02120JW,02120K3,02120K8,02120K9,02120KC,02120KF,02120KW,02120Z3,02120Z8,02120Z9,02120ZC,02120ZF,0212344,02123D4,0212444,0212483,0212488,0212489,021248C,021248F,021248W,0212493,0212498,0212499,021249C,021249F,021249W,02124A3,02124A8,02124A9,02124AC,02124AF,02124AW,02124D4,02124J3,02124J8,02124J9,02124JC,02124JF,02124JW,02124K3,02124K8,02124K9,02124KC,02124KF,02124KW,02124Z3,02124Z8,02124Z9,02124ZC,02124ZF,0213083,0213088,0213089,021308C,021308F,021308W,0213093,0213	

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		098,0213099,021309C,021309F,021309W,02130A3,02130A8,02130A9,02130AC,02130AF,02130AW,	
		02130J3,02130J8,02130J9,02130JC,02130JF,02130JW,02130K3,02130K8,02130K9,02130KC,02130KF,02130KW,02130Z3,02130Z8,02130Z9,02130ZC,02130ZF,0213344,02133D4,0213444, 0213483,0213488,0213489,021348C,021348F,021348W,0213493,0213498,0213499,021349C,021349F,021349W,02134A3,02134A8,02134A9,02134AC,02134AF,02134AW,02134D4,02134J3,02134J8,02134J9,02134JC,02134JF,02134JW,02134K3,02134K8,02134K9,02134KC,02134KF,02134KW,02134Z3,02134Z8,02134Z9,02134ZC,02134ZF,021608P,021608Q,021608R,021609P,	
		021609Q,021609R,02160AP,02160AQ,02160AR,02160JP,02160JQ,02160JR,02160KP,02160KQ,02160KR,02160Z7,02160ZP,02160ZQ,02160ZR,021648P,021648Q,021648R,021649P,021649Q,021649R,02164AP,02164AQ,02164AR,02164JP,02164JQ,02164JR,02164KP,02164KQ,02164KR,02164Z7,02164ZP,02164ZQ,02164ZR,021708P,021708Q,021708R,021708S,021708T,021708U,021709P,021709Q,021709R,021709S,021709T,021709U,02170AP,02170AQ,02170AR	

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		,02170AS,02170AT,02170AU,02170JP,02170JQ,02170JR,02170JS,02170JT,02170JU,02170KP,02170KQ,02170KR,02170KS,02170KT,02170KU,02170ZP,02170ZQ,02170ZR,02170ZS,02170ZT,02170ZU,	
		021748P,021748Q,021748R,021748S,021748T,021748U,021749P,021749Q,021749R,021749S,021749T,021749U,02174AP,02174AQ,02174AR,02174AS,02174AT,02174AU,02174JP,02174JQ,02174JR,02174JS,02174JT,02174JU,02174KP,02174KQ,02174KR,02174KS,02174KT,02174KU,02174ZP,02174ZQ,02174ZR,02174ZS,02174ZT,02174ZU,021K08P,021K08Q,021K08R,021K09P,021K09Q,021K09R,021K0AP,021K0AQ,021K0AR,021K0JP,021K0JQ,021K0JR,021K0KP,021K0KQ,021K0KR,021K0Z5,021K0Z8,021K0Z9,021K0ZC,021K0ZF,021K0ZP,021K0ZQ,021K0ZR,021K0ZW,	
		021K48P,021K48Q,021K48R,021K49P,021K49Q,021K49R,021K4AP,021K4AQ,021K4AR,021K4JP,021K4JQ,021K4JR,021K4KP,021K4KQ,021K4KR,021K4Z5,021K4Z8,021K4Z9,021K4ZC,021K4ZF,021K4ZP,021K4ZQ,021K4ZR,021K4ZW,021L08P,021L08Q,021L08R,021L09P,021L09Q,021L09R,021L0AP,021L0AQ,021L0AR,021L0JP,021L0JQ,021L0JR,021L0KP,021L0KQ,021L0KR,021L0Z5,021L0Z8,021L0Z9,021L0ZC,021L0ZF,021L0ZP,021L0ZQ,021L0ZR,021L0ZW,021L48P,021L48Q,021L48R,021L49P,021L49Q,021	

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		L49R,021L4AP,021L4AQ,021L4AR,021L4JP,021L4JQ,021L4JR,	
		021L4KP,021L4KQ,021L4KR,021L4Z5,021L4Z8,021L4Z9,021L4ZC,021L4ZF,021L4ZP,021L4ZQ,021L4ZR,021L4ZW,021V08S,021V08T,021V08U,021V09S,021V09T,021V09U,021V0AS,021V0AT,021V0AU,021V0JS,021V0JT,021V0JU,021V0KS,021V0KT,021V0KU,021V0ZS,021V0ZT,021V0ZU,021V48S,021V48T,021V48U,021V49S,021V49T,021V49U,021V4AS,021V4AT,021V4AU,021V4JS,021V4JT,021V4JU,021V4KS,021V4KT,021V4KU,021V4ZS,021V4ZT,021V4ZU,024F07J,024F08J,024F0JJ,024F0KJ,024G072,024G082,024G0J2,024G0K2,024J072,024J082,024J0J2,024J0K2,02540ZZ,02543ZZ,02544ZZ,02550ZZ,02553ZZ,02554ZZ,	
		02560ZZ,02563ZZ,02564ZZ,02570ZK,02570ZZ,02573ZK,02573ZZ,02574ZK,02574ZZ,02580ZZ,02583ZZ,02584ZZ,02590ZZ,02593ZZ,02594ZZ,025D0ZZ,025D3ZZ,025D4ZZ,025F0ZZ,025F3ZZ,025F4ZZ,025G0ZZ,025G3ZZ,025G4ZZ,025H0ZZ,025H3ZZ,025H4ZZ,025J0ZZ,025J3ZZ,025J4ZZ,025K0ZZ,025K3ZZ,025K4ZZ,025L0ZZ,025L3ZZ,025L4ZZ,025M0ZZ,025M3ZZ,025M4ZZ,025N0ZZ,025N3ZZ,025N4ZZ,0270046,027004Z,0270056,027005Z,0270066,027006Z,0270076,027007Z,02700D6,027	

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ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

N/A

ANNEX 3. ADDITIONAL INFORMATION

N/A

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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