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PROTOCOL SUMMARY

Title:	Impact of Anticoagulation Therapy on the **C**ognitive Decline and Dementia in Patients with Non-Valvular **A**trial **F**ibrillation (CAF Trial)
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Purpose:	The purpose of this study is to demonstrate that long-term anticoagulation therapy with dabigatran (150 mg BID or 75 mg BID, dose based upon renal clearance) will reduce incident dementia and worsening cognitive decline compared to dose-adjusted warfarin.
Design:	Prospective, Non-blinded, 1:1 Randomized Controlled Trial
Enrollment:	120 subjects
Brief Description:	Patients will be screened at Intermountain Facilities and at Intermountain-affiliated anticoagulation clinics. Patients with non-valvular atrial fibrillation will be considered for study. After written informed consent is obtained, subjects who meet eligibility criteria will be randomized 1:1 to 2 treatment arms: Group 1: Dabigatran etexilate (150 mg BID if CrCL > 30 mL/min, or 75 mg BID if CrCL > 15 to 30 mL/min or per USPI; and Group 2: Warfarin (Dose-adjusted (INR 2.0 – 3.0). Assessment of kidney function every 6 months will be done for Group 1. Standard warfarin follow-up and education, based upon system criteria, will be done for Group 2. All subjects will be followed for 24 months, and will be assessed at 1-week, then 3-, 6-, 12-, 18- and 24-months post-anticoagulation visits as well as other visits deem necessary for clinical care. All subjects will undergo protocol-specified laboratory tests and will complete 6 standard, validated questionnaires at each follow-up visit following the week 1 visit, except at the 3-month visit when only

	one questionnaire will be administered. To determine brain volume and characteristic changes representative of micro-bleeding, 10 subjects in each treatment group who are willing and able to undergo the procedure will participate in a MRI sub-study. The cranial MRI will be done at baseline and at 24-months post-anticoagulation on this sub-group.
Subject Population:	Inclusion Criteria: 1. Male or female ≥65 years of age. 2. Non-valvular atrial fibrillation documented by electrocardiogram, ambulatory event monitor, telemetry, or medical records within 12 months of enrollment. 3. Moderate risk of thromboembolism based upon a CHADS score or CHADS2 Vasc score of ≥2. 4. Ability to complete a mini-mental status evaluation. 5. Ability to independently comprehend and complete a quality of life and dementia questionnaires. 6. Ability to provide informed consent for study participation. 7. Willing and able to comply with the prescribed follow-up tests and schedule of evaluations. Exclusion Criteria: 1. Inability to take an anticoagulant due to known or perceived bleeding risk. 2. Known coagulopathy that may impact the choice, duration, efficacy and safety of anticoagulation therapy. 3. Atrial Fibrillation in the setting of valvular heart disease. Valvular heart disease defined as any surgical valve, mitral stenosis, or moderate-severe valvular heart disease. 4. Severe renal dysfunction, defined as a creatinine clearance rate <15 mL/min (documented within the last 3 months). 5. Have a history of any form of dementia. 6. Have a life expectancy less than 24 months. 7. Are unable to comply with the follow-up schedule. 8. Are currently participating in a clinical investigation that includes an active pharmacologic treatment arm. 9. An upper age limit not to be used if participation inclusion criteria are met. 10. Participation in any other clinical trials involving investigational or marketed products within 30 days prior to entry in the study. 11. Other conditions that in the opinion of the Principal Investigator(s) may increase risk to the subject and/or compromise the quality of the clinical trial. 12. Concurrent pharmacologic treatment that is required to treat a condition long-term in which concurrent use of dabigatran etexilate is contraindicated. 13. Treatment with any anticoagulant drug for stroke prevention for more than 90 days. - Aspirin and P2Y12 inhibitors (e.g. clopidogrel (Plavix), or prasugrel (Effient)) are not considered anticoagulant drugs. - If the subject has received any anticoagulant drug for stroke prevention for less than 90 days, the Principal Investigator(s) or a Co-Investigator will decide whether or not the subject is eligible for this study **14.** The Principal Investigator(s) determine(s) that the subject is not eligible for participation in this research study.
Primary Endpoints:	1. Incident dementia between the treatment arms. 2. Moderate decline in cognitive function: This endpoint will be determined by measuring

	the change from baseline to study conclusion on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70, and higher scores indicating greater impairment) and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100, and higher scores indicating less impairment). An increase in ADAS-cog11 of >30% is considered significant for moderate cognitive decline. In subjects that score <50% on the DAD, there is a direct correlation with global deterioration scales and scores. Subjects with a 30% decrease in DAD score or those with a score <50% will be considered to have moderate cognitive decline.
Secondary Endpoints:	1. Stroke or Transient ischemic attack (TIA), intracranial bleed. 2. Changes from baseline scores on the mini-mental status evaluation and the Hachinski Ischemic Scale. 3. Whole brain volume by MRI at 24 months.
Analysis Population(s):	Subjects will be classified into 2 analysis groups: 1) Dabigatran etexilate treatment group; and 2) Warfarin treatment group. The sample size of 120 subjects for this study alone may be potentially too small for statistically meaningful data analysis, but at minimum is expected to provide insight into trends and to assess the feasibility of recruitment, study subject retention, budget adherence and likelihood of obtaining the desired outcomes, safety, and identification of adverse effects.
Funding Source	Boehringer Ingelheim Pharmaceuticals Inc.

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DEFINITIONS

AF	Atrial Fibrillation; The most common irregularly irregular cardiac rhythm, resulting from chaotic multiple electric impulses in the atria.
AVERROES	Apixaban Versus Acetylsalicylic Acid to prevent Stroke in Atrial Fibrillation patients who have failed or are unsuitable for VKA treatment; A randomized controlled trial which randomized patients to apixaban vs. aspirin, and confirmed that when comparing bleeding risks apixaban was similar to aspirin.
Cerebrovascular Accident (CVA), Cerebral ischemia	Blood clot or a plaque lodged in an artery precluding adequate blood flow, causing lack of oxygen and nutrients to a part of the brain.
CHADS/CHADS2	Stroke risks schemas used to predict stroke risks in a clinical setting. Refers to **C**ongestive heart failure, **H**ypertension history, **A**ge ≥ 75 years, **D**iabetes mellitus history, **S**troke or TIA symptoms previously.
Cognition	Awareness, processes for acquiring and understanding knowledge.
CPAS	Clinical Pharmacist Anticoagulation Service; Dedicated anticoagulation management service that uses a standardized algorithmic approach to make warfarin dose adjustments.
Dementia	Impaired memory and intellectual capacity interfering with at least one quality of life domain.
DOAC	Direct Oral Anticoagulation; New oral anticoagulants used for the prevention of thromboembolism that do not require blood test monitoring.
Epiphenomenon	A secondary symptom occurring simultaneously with the target disease, that is not directly related to it.
Gene polymorphism	Natural variations in a gene which have no adverse effects on the individual and is frequently encountered
Hemorrhages	Any spontaneous and excessive bleeding.
INR	International Normalized Ratio; A standardized test that is used to monitor individuals taking blood-thinning medications.
Microbleed	Very small chronic brain hemorrhages or bleeds.
Microemboli	An embolus (plug or clot) of microscopic size.
Microvascular dysfunction	Disease that affects small arteries.
NVAF	Non-Valvular Atrial Fibrillation; defined as patients with mitral stenosis, moderate-severe valvular heart disease, or surgical heart valves
RE-LY	A study of 18,113 patients, comparing 2 doses of dabigatran etexilate with warfarin; this is the largest randomized controlled trial of antithrombotic therapy for stroke prevention performed to date.

Systemic inflammation	When an inflammation (the body's attempt to protect itself) moves beyond the local tissues into the lining of the blood vessels and organs
TIA	Transient Ischemic Attack; Transient episode of a plaque or blood clot in the artery of the brain causing transient neurological deficits, but lacking infarction.
TTR	Time in Therapeutic Range; The period patients remain within INR levels (2-3) when taking warfarin.
Valvular Heart Disease	Valvular heart disease defined as any surgical valve, mitral stenosis, or moderate-severe valvular heart disease
VKA treatment	Vitamin K antagonists used to thin blood in order to prevent blood clots

1.0 INTRODUCTION

1.1 Background and Rationale

Atrial Fibrillation (AF) is an emerging disease epidemic and is currently affecting approximately 2.3 million people in the United States. This rhythm disorder is predicted to extend its reach to 5.6 million people in the United States by the year 2050 due to the "Baby Boom" (people born between 1946 and 1964) population reaching 85 years and older (1).

Factors that often drive progression of AF are age- and coexistent cardiovascular disease state related. All forms of AF, including paroxysmal AF, can negatively alter left atrial size, substrate, and function. These changes often characterized by dilatation, and contractile dysfunction, which develop very early after arrhythmia diagnosis, and can significantly impact response to therapeutic interventions (2). These maladaptive changes over time often increase arrhythmia burden, severity and may be responsible for the morbidity and mortality associated with the disease state. They also can specifically impact contractile function of the atrium of left atrial appendage and as a consequence increase risk of macro- and micro-cerebral ischemic events.

Dementia is a condition describing a constellation of symptoms that cause alterations in memory, social functions and cognitive abilities. Alzheimer's disease is the most common form of dementia in the United States, accounting for 60 to 80% of dementia occurrences, while 10 to 20% are attributable to vascular dementia (3). Alzheimer's disease afflicts 5.4 million in the United States, with the vast majority of these people being 65 years and older (4). Similar to AF, the dementia burden is increasing as the "Baby Boom" generation reaches ages 65 and older. The numbers of people affected by Alzheimer's dementia are projected to triple by the year 2050 in the United States (4).

Despite general declines in stroke and cardiovascular mortality and morbidity, the prevalence of dementia has remained relatively stable. The decline in stroke and cardiovascular mortality has been attributed to early recognition, smoking reduction, and early and/or more aggressive treatment of diabetes, hypertension, and dyslipidemia (5). The lack of simultaneous impact on dementia, despite lower rates of stroke and vascular disease that were felt to increase risk of dementia, suggests that we need to think broadly about risk factors and expand research into novel strategies for disease prevention and treatment.

<u>Atrial Fibrillation and dementia</u>

There is significant evidence that confirms the association between AF and dementia, including idiopathic or Alzheimer's dementia. Our group has explored the relationship between AF and dementia in a study of 37,025 patients from the Intermountain Heart Collaborative Study (3). We included patients with no history of dementia and at least 5 years of follow-up data. Given the large nature of this study, we used ICD-9 codes to define dementia. To minimize risk of misclassification, we used ICD-9 codes that were entered by neurology only. Our results showed that AF contributed to the development of all types of dementia (Figure 1, Appendix A1).

The prevalence of both diseases advances with increasing age, and predisposes patients to a rise in the incidence of mortality. Interestingly, in our study the younger group studied (patients <70 years) had the highest relative risk of developing Alzheimer's dementia (odd ratio 2.30, p=.001). This highest relative risk of dementia in the younger AF patients suggests that the association is more than an epiphenomena stemming from disease states that share advancing age as a common risk (Figure 2, Appendix A1).

Each disease state shares many common risk factors with the other, many of which are potentially modifiable if disease-based preventative life style changes are started early in life (Figure 1, appendix A1). Although a

common thought is that AF resulted in cognition impairment due to stroke, all forms of dementia, including idiopathic variants, are increased in AF patients (Table 1).

The association between AF and dementia is complex. Both disease states share many common risk factors (Figure 3, Appendix A1), and understanding these risk factors may provide clues into the key mechanisms of both disease states. More importantly, many of the shared risk factors are modifiable, and if early preventative life style changes are adopted, the disease states may be avoided altogether. However, given the complexity and variability of both disease states, it is likely that multiple potential mechanisms underlie the association between AF and dementia.

Understanding mechanisms of disease association and then discovering avenues to reduce risk is paramount. In patients with AF, there is also a significant association between dementia onset and total mortality (3). In our prior study, we found that in patients with AF that develop dementia of any subtype mortality is significantly increased (HR: 1.46-2.14). Similar to the general association data, the greatest risk of death in those patients with AF and dementia was found in the youngest cohort studied (<70 years, HR across multiple subtypes: 1.55-2.07).

Potential mechanisms underlying dementia in AF patients

There are multiple potential mechanisms that may explain the associations found between AF and the various dementias. Similar to the shared risk factors between AF and dementia, the associations are like complex, interactive, and vary in stages of the disease (Figure 4, Appendix A1).

Injury Repetitive from Microemboli and/or Microbleeds

One of the most feared complications of AF is disabling stroke. The majority of strokes in patients with AF are macroembolic originating from the left atrial appendage. The presence of multiple strokes in itself can cause dementia. Patients with AF tend to have larger strokes at older ages and as a consequence are at particular risk for cognitive decline that is associated with significant functional deficit and dependency (6).

Although this mechanism helps shed light into the association of AF and multiinfarct dementia, it does not explain the consistent association with idiopathic dementia in which prior stroke(s) are excluded. However, it is possible the dementia association with AF is a spectrum related to repetitive cerebral injuries that stem from macro events (multi-infarct dementia) to micro events (idiopathic dementia with chronic volume loss). An autopsy study of 84 patients with Alzheimer's dementia provided evidence in support of this mechanism. The authors found that cerebral microvascular injury was a common root mechanism that stemmed from cerebral atherosclerosis, silent previously undetected lacunar infarcts, and microemboli (7). Small repetitive vascular injuries are felt to be a common cause of white matter lesions. Cerebral white matter lesions in patients with AF are associated with cognitive impairment (8).

As the brain ages many of its small vessels become diseased and consequently become predisposed to cerebral microbleeds, especially in the presence of anticoagulation. Microbleeds have also been correlated with hippocampal atrophy and as such may result in volume loss from repetitive injury (9). Mechanistically it is plausible the microbleeds may increase risk of dementia in anticoagulated AF patients, particularly in cognitive domains involving memory. The hippocampus is the most vulnerable area of the brain to develop microbleeds and damage to this area is also not uncommon in patients with Alzheimer's disease, hypertension, and AF (10) (Figure 5, Appendix A1).

Do Stroke Management Strategies Influence Dementia Risk?

If dementia is a manifestation of one end of the spectrum of cerebral injuries in atrial fibrillation patients, then it is plausible the stroke prevention strategies will influence risk. We sought to understand the role of

anticoagulation on long-term risk of dementia in AF patients with no history of dementia. If the above mechanisms increase risk of dementia in AF patients, then patients with lower percent times in therapeutic range (TTR, defined as an INR: 2-3) should display an increased risk of cognitive decline. We studied 2693 patients that were started on warfarin anticoagulation by the Intermountain Healthcare Clinical Pharmacist Anticoagulation Service (CPAS) for atrial fibrillation. The average percent TTR was 62.7±22.9%. Long-term dementia outcomes were compared by quartiles of percent TTR. After multivariate adjustment for all baseline demographic risk factors for stroke or bleed, decreasing categories of percent TTR were associated with increased dementia risk (vs.>75%): <25%: HR=4.58, p<0.0001, 26-50%: HR=4.14, p<0.0001, 51-75%: HR=2.52, p=0.001) (11). Additional insight was obtained in looking at those patients that were consistently over versus under anticoagulated. In both groups, there was a similar increased risk of dementia in support of both microbleeds as well as microemboli as mechanisms (Figure 6, Appendix A1).

One of the most intriguing aspects of the trial that examined dementia risk by time percent with a therapeutic INR (International Normalized Ratio) was the significant correlation with age. Similar to our initiation findings that showed an association between AF and dementia, the highest relative risk of developing dementia from low percent TTR was seen in the younger patients compared to the older patients (Figure 7, Appendix A1).

Finally, amongst AF patient populations approximately 20-30% also use an antiplatelet agent, most commonly aspirin, due to the coexistence of coronary artery disease. These agents can influence both efficacy and safety of anticoagulants.

In regard to the microbleed hypothesis of dementia in AF patients, we explored the impact of aspirin therapy in the setting of over anticoagulation. In a cohort of patients that were all using antiplatelet drugs, predominantly aspirin, patients that were exposed to over anticoagulation (INR ≥ 3) >30% of the time were 2.5 times more likely to develop dementia compared to those with over anticoagulation times <10% (HR 2.59, p<0.001) (Figure 8, Appendix A1). Over anticoagulation time was the strongest predictor of dementia risk amongst all baseline variables collected.

Role of novel anticoagulants

Two prominent possibilities arise from review of the warfarin and dementia data. First, if anticoagulation is precisely used and monitored then dementia risk in AF patients be reduced. Second, if dementia is a part of the spectrum of cerebral injuries from clots and bleeds, then anticoagulation approaches that lower risk of both bleeding and clotting better than warfarin may further lower dementia risk.

There are many potential advantages of novel anticoagulant therapies compared to warfarin including fewer drug-drug, drug-food, and drug-supplement interactions, higher compliance rates, better dosing schemes, and rapid onset/offset of action. Recent randomized prospective trials involving dabigatran etexilate, rivaroxaban, apixaban, and edoxaban have shown that these agents compare favorably with warfarin for risk of stroke and intracranial bleeding.

Dabigatran etexilate, an oral direct thrombin inhibitor, was studied versus standard dosed warfarin in patients with non-valvular atrial fibrillation to determine if patients experience less cerebral ischemic events (stroke: ischemic and hemorrhagic) and systemic thomboembolism. A total of 18,113 patients with non-valvuar atrial fibrillation and one or more additional risk factors of stroke were randomized to receive fixed doses of dabigatran etexilate (110 mg or 150 mg) twice daily or open-label warfarin. Over a median follow-up of 2 years, the primary endpoint of stroke or systemic embolism was reduced in the dabigatran etexilate -treated groups (3.4% per year with warfarin compared with 3% per year with 110 mg of dabigatran etexilate and 2.2% per year with150 mg of dabigatran etexilate). Major bleeding rates were lower in the dabigatran etexilate treated groups, in particular those attributed to intracranial bleed. The rate of hemorrhagic stroke was reduced significantly with dabigatran etexilate compared to warfarin (hazard ratio 0.26 (95% CI: 0.14-0.49).

These favorable outcomes correlated with a mortality reduction in patients treated with dabigatran etexilate (12). Data continues to emerge regarding the role of dabigatran etexilate as it relates to macro cerebral ischemic events that may translate into micro events and impact cognition (13). . For example, in a subanalysis of the RE-LY trial, concurrent single and dual antiplatelet therapy impacted risk of major bleeding, but events were lower than warfarin with both fixed doses of dabigatran etexilate (13). As we have demonstrated nearly one third of atrial fibrillation patients are on at least one antiplatelet agent and as such are vulnerable to brain injury when exposed to supratherapeutic warfarin levels.

In regards to additional safety outcomes, the AVERROES (Apixaban Versus Acetylsalicylic Acid to prevent Stroke in Atrial Fibrillation patients who have failed or are unsuitable for VKA treatment) trial expanded the current understanding significantly as the comparative arm was aspirin (14). This study compared apixaban, 5 mg twice daily (reduced to 2.5 mg twice daily >80 years, weighed <60 kg and had a serum creatinine of >1.5 mg/dl), with aspirin, 81- 324 mg daily, in patients that were not candidates or did not tolerate warfarin for prevention of stroke. Apixaban significantly reduced the risk of stroke and systemic embolism (1.6% using apixaban vs. 3.7% using aspirin; $p < 0.001$). More important, the use of apixaban was not found to be associated with increased incidence of bleeding (1.4% in apixaban group vs. 1.2 % in aspirin group, $p = 0.57$).[44] In a recent indirect comparative analysis of available novel anticoagulants, dabigatran etexilate 150 mg bid was associated with lower total stroke (HR 0.73; 95% CI 0.55-0.96) and hemorrhagic stroke (HR 0.48; 95% CI 0.23-0.99) risks (15). As such, we would anticipate similar cranial injury risk rates both on a macro and micro level with dabigatran etexilate as was observed in the AVERROES trial.

Application of Direct Anticoagulant Data to Cognition

If the micro cerebral ischemic and hemorrhagic events track the macro cerebral ischemic and hemorrhagic events then dabigatran etexilate will significantly reduce the risk of cognitive decline and dementia in patients with non-valvular atrial fibrillation (NVAF). Furthermore, since the highest risk of dementia with anticoagulation variance with warfarin therapy is seen in the youngest cohorts of AF patients studied, we anticipate the populations that typically select direct anticoagulant therapies with covered benefit plans, will be the most likely to benefit from changing to this anticoagulant long-term.

The **C**ognitive Decline and Dementia in **A**trial **F**ibrillation Patients (CAF) Trial is proposed to determine if AF patients randomized to dabigatran etexilate will have long-term higher cognition scores and lower rates of dementia compared to dose-adjusted warfarin (INR: 2.0-3.0).
Preliminary Evidence

We sought to determine if there was an early signal of cognitive benefit in the community since direct oral anticoagulants (DOAC) have been introduced. In a propensity-matched study of 5,254 (2,627 per group) patients, long-term outcomes were examined in patients using a direct oral anticoagulant versus warfarin. The distribution for specific direct oral anticoagulants were: apixaban= 590 (22.5%), dabigatran etexilate =583 (22.2%), and rivaroxaban=1,454 (55.3%). Average age was 72.4±10.9 and 59.0% were male. The majority of patients were receiving long-term anticoagulation for AF management (warfarin: 96.5% vs. DOAC: 92.7%, p<0.0001). History of a prior stroke/TIA were similar between the groups (warfarin: 10.7% vs. DOAC: 10.8%, p=0.89). The composite outcome of dementia, stroke, and TIA occurred in 4.7% of warfarin patients and 1.8% of DOAC patients (p<0.0001). Dementia incidence alone was lower in the DOAC group compared to the warfarin group (0.3% vs. 1.6%, p<0.0001). After adjustment, patients taking DOACs had a 51% decreased risk of dementia incidence or having a follow-up stroke or TIA compared to patients taking warfarin (HR=0.49 (0.35, 0.69), p<0.0001). Despite the longest follow-up time with dabigatran etexilate in the community, long-term use was associated with the lowest dementia incidence (Figure 9, Appendix A1).

1.2 Previous Work

The proposed Principal Investigator, Co-Principal Investigator and Co-Investigators for this study have extensive previous work with atrial fibrillation and its various treatment options (CVs available on request).

2.0 STUDY OBJECTIVES

The primary functional objective of this study is to evaluate if long-term anticoagulation therapy with dabigatran etexilate (150 mg BID or 75 mg BID, dose based upon renal clearance, or per USPI) will reduce incident dementia and worsening cognitive decline compared to dose-adjusted warfarin.

The primary anatomic objective of this study is to demonstrate that long-term anticoagulation therapy with dabigatran etexilate will reduce micro- and macro-cerebral ischemic events (both bleeds and clots) as compared to dose-adjusted warfarin.

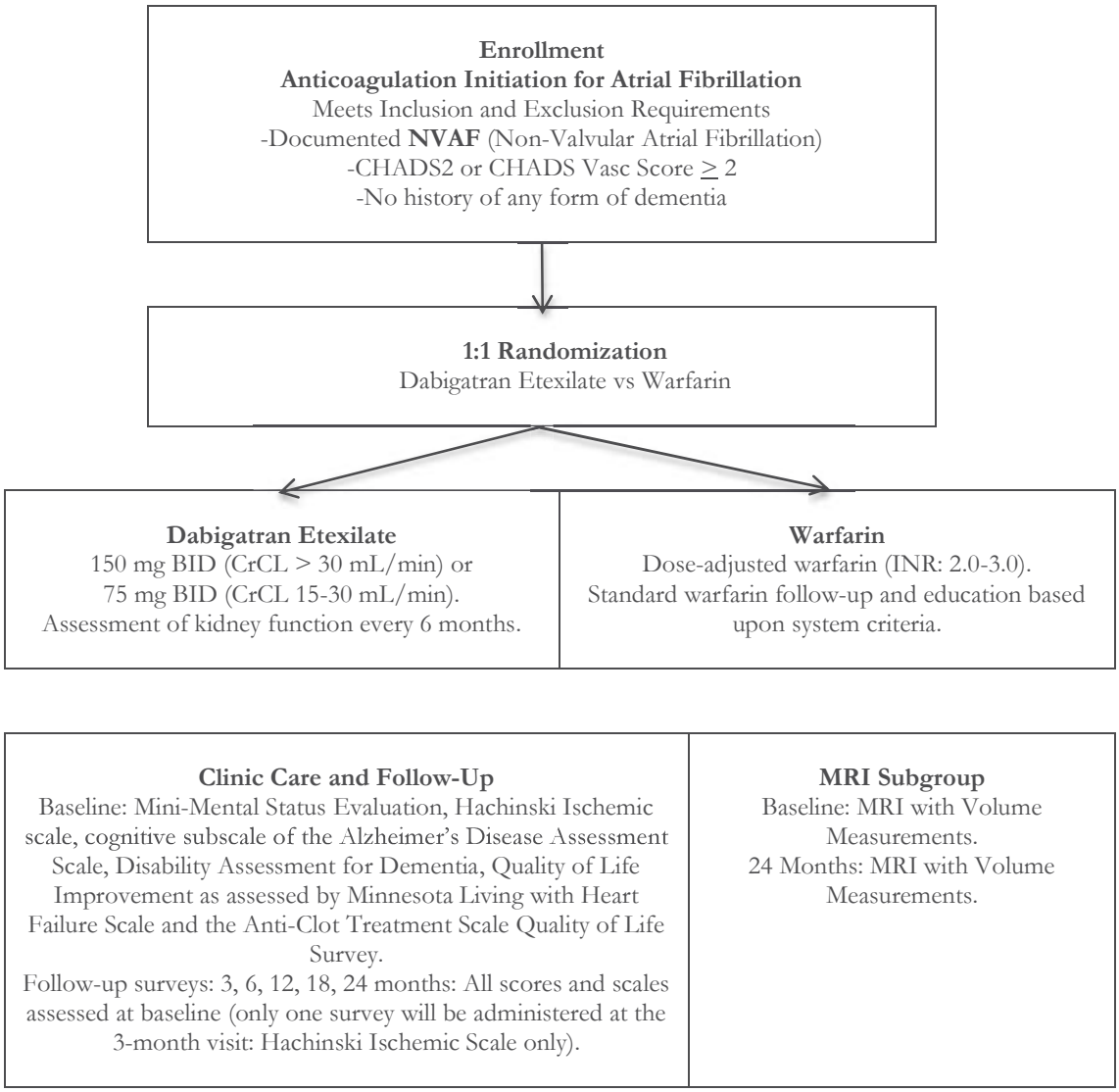
A final purpose of this study is to determine trends of cognition in the prospective study design that include incidence of dementia and the percent of patients that develop moderate decline in each study group to compare amongst the rates observed in the general population, the feasibility of recruitment, study design and subject retention, budget adherence and likelihood of obtaining the desired outcomes for potential future trial design and planning.

3.0 STUDY DESIGN AND SCOPE

This is a randomized, prospective clinical study designed to evaluate whether administration of dabigatran etexilate compared to warfarin in moderate- to high-risk non-valvular AF patients will reduce cognitive decline and dementia incidence at 24 months. The study will be filed under a physician IND (investigation new drug) application.

As a vanguard study, two potential stages of patient enrollment exist. The study is conducted with a total of 120 subjects at Intermountain Facilities in the U.S. (Intermountain Healthcare) to evaluate the primary and secondary study endpoints, feasibility of recruitment, study design and subject retention, budget adherence and likelihood of obtaining the desired outcomes from the pre-specified power analysis, safety and identification of adverse events.

Study Flow Diagram:



3.1 Study Duration

The study will last for approximately 36 to 48 months (a target of up to 24 months to recruit the required subjects, with 24 months of follow-up to complete the study for each subject). It is estimated that 1,100 patients with NVAF are seen at the EPS (electrophysiology) Clinic and 40 patients at the CPAS Clinics, per month. Following screening and recruitment into the study, study subjects will have follow-up visits at within the first 4 weeks, and at 3, 6, 12, 18 and 24 months after the start of anti-coagulation.

A minimum 24 months follow-up will occur for all subjects enrolled. Prior studies of cognitive testing using questionnaires suggest that at minimum 12 months of follow-up is required. Two years will meet this need and also allow separation in treatment arms based upon our data derived from incident dementia rates in warfarin-managed subjects. Restriction to two years will also lower study-related costs.

3.2 Number of Subjects

Approximately 120 subjects will be enrolled in this study (1:1 ratio; see Section 4.2 for details). This number of subjects reflects 10% of the required complete multicenter population sample size estimate. The expected drop-out rate for this study is 25%, which is accounted for in the total population estimate. Hence, it is expected that 150 NVAF patients will be screened in order to enroll the target 120 subjects. The sample size calculation is described in Section 8.2 of this document. Long-term drop out rates are anticipated at 20%.

3.3 Screening of Subjects

Patients will be screened at Intermountain facilities and at Intermountain-affiliated anticoagulation clinics. Patients with NVAF who are seen at the EPS and CPAS clinics of the Intermountain facilities, and other referring clinics, will be considered for this study. The Principal Investigator(s) will confirm the presence of NVAF, based on established and agreed criteria. The Principal Investigator(s), Co-Investigator(s) and/or the designated Clinical Research Coordinator will review the patient's history and medical records. Data gathered is used to evaluate the patient in relation to the inclusion and exclusion criteria listed in Sections 3.5.1 and 3.5.2. It may be necessary to exclude subjects based on this assessment.

A patient evaluation log will be maintained throughout the study. The log will record all subjects considered for enrollment in the trial and indicate whether they were enrolled or not enrolled. In the case of non-enrollment, an explanation will be provided on the log as to the reason for their exclusion.

3.4 Selection of Subjects

Patients who meet eligibility criteria (see Sections 3.5.1 and 3.5.2) and agree to participate will be enrolled in this study. Written informed consent will be obtained by the Principal Investigator(s) or designated personnel prior to subject enrollment, i.e. prior to study inclusion, signed by the subject, using a form that is approved by the Intermountain IRB, and which must be maintained on file by the Principal Investigator(s) or their delegate. The informed consent process is described in more detail in Section 3.5.3.

The study team will attempt to recruit any patient who meets the inclusion criteria for study enrollment, regardless of gender. The study requirements, including required testing, will be discussed with the patient. Patients who are unwilling to agree to the requirements of the study will be excluded from participation.

In addition to selection of 120 subjects for this study, a total of 10 subjects in each treatment arm (see Section 4.2) who are willing and able to undergo the procedure will be invited to participate in the MRI substudy (as described in Section 4.1, subheading "MRI Subgroup").

3.5 Subject Selection Criteria

3.5.1 Inclusion Criteria

Eligible patients must meet all of the following criteria:

1. Male or female ≥65 years of age.
2. Non-valvular atrial fibrillation documented by electrocardiogram, ambulatory event monitor, telemetry, or medical records within 12 months of enrollment.
3. Moderate risk of thromboembolism based upon a CHADS score or CHADS2 Vasc score of ≥2.
4. Ability to complete a mini-mental status evaluation
5. Ability to independently comprehend and complete a quality of life and dementia questionnaires.
6. Ability to provide informed consent for study participation.
7. Willing and able to comply with the prescribed follow-up tests and schedule of evaluations.

3.5.2 Exclusion Criteria

Patients will be excluded if they meet any of the following:

1. Inability to take an anticoagulant due to known or perceived bleeding risk.
2. Have a known coagulopathy that may impact the choice, duration, efficacy and safety of anticoagulation therapy.
3. Atrial Fibrillation in the setting of valvular heart disease. Valvular heart disease defined as any surgical valve or moderate-severe valvular heart disease.
4. Severe renal dysfunction, defined as a creatinine clearance <15 mL/min (documented within the last 3 months).
5. Have a history of any form of dementia.
6. Have a life expectancy less than 24 months.
7. Are unable to comply with the follow-up schedule.
8. Are currently participating in a clinical investigation that includes an active pharmacologic treatment arm.
9. An upper age limit not to be used if participation inclusion criteria are met.
10. Participation in any other clinical trials involving investigational or marketed products within 30 days prior to entry in the study.
11. Other conditions that in the opinion of the Principal Investigator(s) may increase risk to the subject and/or compromise the quality of the clinical trial.
12. Concurrent pharmacologic treatment that is required to treat a condition long-term in which concurrent use of dabigatran etexilate is contraindicated.
13. Have received any anticoagulant drug for stroke prevention for more than 90 days.
    - Aspirin and P2Y12 inhibitors (e.g. clopidogrel (Plavix), or prasugrel (Effient)) are not considered anticoagulant drugs.
    - If a patient has received any anticoagulant drug for stroke prevention for less than 90 days, the Principal Investigator(s) or a Co-Investigator will decide the patient's eligibility for this study
14. The Principal Investigator(s) determine(s) that the patient is not eligible for participation in this research study.

3.5.3 Informed Consent

Written informed consent will be obtained prior to study inclusion, signed by the subject, in accordance with ICH GCP guidelines, CFR regulations and Intermountain Healthcare research policies, and using a form that is approved by the Intermountain IRB. The informed consent process will be conducted within an Intermountain facility.

Subjects may choose to include an involved caregiver in the informed consent process or have them informed of their study participation. If subject gives permission for a caregiver to be involved, the caregivers name will be documented in their study files. The caregiver may aid in providing support (i.e. rides to study related visits, pill organization, etc.) to the subject throughout the study.

For subjects who are diagnosed with dementia during their study participation, the Principal Investigator(s) will document their cognitive capabilities and note if they are able to continue making decisions or if a Legally Authorized Representative (LAR) should be contacted. The Principal Investigator(s) will ask who can be contacted if an LAR needs to be contacted during their participation. The Principal Investigator(s) will continue to document the subject's decision making ability during routine visits.

Following assessment of qualification for study participation as per inclusion/exclusion criteria, eligible patients will be presented with protocol information and will be invited to participate in this study. Patients will be provided sufficient time to consider participation, and to obtain satisfactory answers to their questions.

Patients will be asked to provide written consent by signing an informed consent document previously approved by the Intermountain IRB. The Principal Investigator(s), or an appropriately delegated member of the study team under his/her supervision, will administer the informed consent.

As indicated in Section 3.4 (Selection of Subjects), a total of 10 subjects in each treatment arm who are willing and able to undergo the procedure will have the opportunity to participate in the MRI sub-study (as described in Section 4.1, subheading "MRI Subgroup"). Subjects will be able to opt in or opt out of participation in the MRI sub-study without affecting their ability to participate in the study, and this will be documented on the informed consent form.

4.0 STUDY PROCEDURES

This study will be conducted in accordance with the ICH Good Clinical Practice guidelines (E6), the Code of Federal Regulations (CFR), and the Declaration of Helsinki (see Appendix E).

4.1 Investigational Diagnostic Test Description

Patients will be consented and screened for eligibility per inclusion and exclusion criteria in Sections 3.5.1 and 3.5.2 respectively.

The following information will be obtained from each subject's medical records that was collected as part of usual medical care, preferably within 6 months prior to enrollment (but not limited to):

- Age, gender, height, weight
- Medical history, including any hospitalizations
- Nature of atrial fibrillation
- Vital signs
- Renal function status (creatinine clearance)
- Echocardiogram to determine the presence of valvular heart disease
- Results of prior cardiac and neurological tests
- List of medications you are currently taking
- Other information that the Principal Investigator(s) may require

If this information is not available in the subject's medical records, a member of the research staff may verbally request the subject for this information. If there are tests that were not done within 6 months prior to enrollment, the Principal Investigator(s) may decide to have the tests done or repeated. The cost of such study-required tests will be paid for by the study budget.

The 6 questionnaires listed below will be administered at the baseline visit, and repeated at the 6-, 12-, 18- and 24-month visits as indicated in the Time and Events Schedule below. No questionnaires will be administered at the first follow-up visit. At the 3-month visit, only one questionnaire will be conducted (i.e., the Hachinski Ischemic Scale). The links and references for description and purpose of these questionnaires are indicated in Appendix A3 (Study Tools) of this document.

- Mini-Mental Status Evaluation
- Hachinski Ischemic Scale
- Cognitive Subscale of Alzheimer's Disease Assessment Scale
- Disability Assessment for dementia
- Quality of life improvement as assessed by:
    - Minnesota Living with Heart Failure Scale
    - Anti-Clot Treatment Scale (ACTS) Quality of Life Survey

At the first follow-up visit after the start of anti-coagulation, the following will be done, and repeated at the 3-, 6-, 12-, 18- and 24- month visits:

- CBC (complete blood count)
- Protime/INR (international normalized ratio) (warfarin arm only)
- BMP (basic metabolic profile)
- Review of cardiac medications list
- Review of adverse events and hospitalizations

The questionnaires and laboratory tests are done to guide subject status, drug dosing and to assure safety, and will be performed at Intermountain hospitals and/or clinical facilities. INR/Protime values will not be measured in the group receiving dabigatran etexilate if not clinically indicated. The research staff will keep a portion of the blood that can be used for future study and it will be maintained in the Intermountain repository. Biological samples may be used in current and future research tests multiple times, or until the sample is consumed.

MRI Subgroup:
In each group, 10 subjects will be selected to undergo a cranial MRI at baseline to determine brain volume and characteristic changes representative of microbleeding, with a repeat MRI at 24 months. If a subject withdraws for any reason, or is unable or unwilling to complete their MRI (baseline and/or 24-month), they will be replaced by another willing and able subject.. These subjects will be selected at time of enrollment or within 30 days of signing consent until all slots have been filled (i.e., first 10 subjects in each treatment arm who are willing and able to undergo the procedure). The baseline and 24 month MRIs are done for research purposes only and will be paid by the study. Brain volume will be defined as per routine description (18-20). MRI techniques that provide high contrast between brain parenchyma and highly paramagnetic materials (e.g. deoxyhemoglobin, superparamagnetic hemosiderin, and diamagnetic calcium) which are sensitive to rupture of blood vessels as small as 200 μm in diameter are favorable. All MRIs will be performed using the same technology and the same machine as is foreseeably feasible. An MRI protocol that uses T2* Gradient-Recall Echo (T2*GRE) and Susceptibility-Weighted (SWI) MRI techniques to establish baseline imaging evidence of microbleeds and follow-up studies has been shown to achieve these goals (18-20). While we acknowledge that the discipline of neuroimaging to explicitly defining microbleeds is evolving, we intend to use a standardized approach to image acquisition (all study imaging will be performed on one MRI machine) and interpretation. This approach will limit inter-observer variability and allow for future replicability and more broad applicability. We will specifically adopt a rating scale as described by others that will take into consideration whether lesions are certain or uncertain, and consider them present only if they are observed on serial images (21-23). Subjects enrolled in the imaging sub-study cannot have exclusions to undergo standard MRI imaging.

Additional Serum Tests at Baseline:
Additional tests that have been linked to the development of stroke, intracranial bleed, and dementia in AF patients, may be performed on all 120 subjects at enrollment and the 24 month visit. These tests are not standard-of-care and will be done in a research setting and paid for by the study. These include the following: BNP, troponin, GDF-15, cystatin-C, D-dimer, MMP-9, chemokine ligand 23 (CCL23), ESAM, plasma vonWilebrand factor, CRP, prothrombin fragment 1+2, P-selectin, factor VIII, protein C, protein S, anti-thrombin III, anti-beta-2 glycoprotein-1 IgG and IgM, anticardiolipin IgG and IgM, and lupus anticoagulant panel. Because the most common gene polymorphism associated with sporadic microbleeds is the Apolipoprotein E (APOE) gene on chromosome 19, to control for this variable we will test for this gene as well as and the APOE ε2 and ε4 alleles which have each been independently associated with lobar microbleeds (9, 24, 25). We will also test for neprilysin (a proteolytic enzyme responsible for Aβ catabolism) and the single-nucleotide polymorphism rs6656401 within the Complement Receptor-1gene given that upon genome-wide association studies these are identified risk genes for more severe cerebral amyloid angiopathy

(a well described risk factor for intracranial hemorrhage) (26, 27). Some of these unique tests may need to be sent to an external laboratory, if not possible to do at Intermountain.

The cost of the baseline and 24 month MRIs and the above additional serum tests that are not standard-of-care will be paid for by the study budget. The contract and financial agreements will be available in a separate document.

4.2 Study Treatments

After verifying study eligibility and a written informed consent has been obtained, subjects will be randomized using the permuted block design to receive dabigatran etexilate or warfarin in a 1:1 ratio, as indicated in the Treatment Arm/Intervention Table below. Dabigatran etexilate will be provided by Boehringer Ingelheim , at no cost to the subjects randomized to this treatment arm. Warfarin dispensation and warfarin management will be done per routine clinical care at the expense of the subject or the subject's insurer. Boehringer Ingelheim will not provide warfarin or materials required for warfarin testing.

Treatment Arm	Intervention
Dabigatran etexilate capsules	150 mg BID (CrCL > 30 mL/min) or 75 mg BID (CrCL > 15 to 30 mL/min); Assessment of kidney function every 6 months.
Warfarin tablets	Dose-adjusted (INR 2.0 – 3.0); Standard warfarin follow-up and education based upon system criteria.

Direct Anticoagulant Description:
Dabigatran etexilate is an oral direct thrombin inhibitor. Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed forming the active moiety dabigatran. Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran etexilate is 80% of total clearance. The half-life of dabigatran etexilate in healthy subjects is 12 to 17 hours. The half-life is significantly prolonged with worsening renal function and dose adjustment is required (Table).

RENAL FUNCTION	CRCL (ML/MIN)	INCREASE IN AUC	INCREASE IN C_{MAX}	$t_{½}$ (H)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe	15-30	6.3x	2.1x	27

Dabigatran Etexilate Dosing:
Only currently FDA-approved dabigatran etexilate dosing (150 mg BID and 75 mg BID) will be administered in this study, based upon baseline creatinine clearance. Dose adjustments will be made by the Principal Investigator(s) during the study, should renal function change. For a creatinine clearance of ≥30 mL/min, 150 mg orally twice a day will be used. For a creatinine clearance of 15 to 30 mL/m in, 75 mg orally twice a day will be used. For a creatinine clearance of <15 mL/min dabigatran will be discontinued and anticoagulation will be administered per clinical care. The decision to crossover to warfarin, or to start another anticoagulation agent, will be at the discretion of the Principal Investigator(s) and in agreement with the subject's primary care physician.

Warfarin Dosing:

Warfarin administration and dosing will be considered standard of care for management of non-valvular atrial fibrillation. Dose adjustments as well as frequency of anticoagulant effect will be managed through the CPAS. Since this arm is considered standard of care, neither warfarin nor routine warfarin management will be provided by the sponsor or study. The event rates used for the power analysis were from CPAS directed warfarin therapy for atrial fibrillation.

Risks of Treatment with Dabigatran etexilate:
The currently known risks of dabigatran etexilate include:

Common more than one in 100 (1%) but less than one in 10 (10%) adult patients):

- Anemia (a condition that develops when your blood does not contain enough red blood cells or hemoglobin); symptoms may include tiredness or weakness
- Nose bleed
- Bleeding of the digestive tract (mouth, throat, stomach or bowel).
- Bleeding from the penis, vagina or urinary tract. Blood in urine may stain the urine pink or red
- Bleeding from the skin
- Belly ache or stomach ache
- Indigestion, "heartburn"
- Diarrhea (Frequent, loose or liquid bowel movements)
- Feeling sick (unease and discomfort in the stomach area)
- Abnormal liver function

Uncommon (more than one in 1,000 (0.1%) but less than one in 100 (1%) adult patients):

- Bleeding in the skull or the brain
- Bruising
- Bleeding into a joint
- Coughing up blood
- Lowering in the number of platelets in the blood
- Allergic reaction
- Itching
- Rash
- Inflammation of the stomach and/or esophagus "food pipe"
- Ulcer of the digestive tract (e.g. esophagus or "food pipe", stomach or intestine), can be associated with bleeding and/or black tarry stool as a result of blood in the intestine.
- Acid reflux, a disorder where stomach acid backs up into your esophagus, associated with heartburn
- Being sick, retching, throwing up
- Difficulty or discomfort with swallowing
- Bleeding from a wound or surgical site
- Bleeding or bruising after a procedure
- Wound oozing at the site of a procedure
- Bleeding after injury
- Weeping or seeping wound
- Bleeding

Rare (more than one in 10,000 (0.01%) but less than one in 1,000 (0.1%) adult patients):

- Bleeding at sites of blood draw injection or surgical incision

- Anemia after a surgical procedure (a condition that develops when your blood does not contain enough healthy red blood cells or hemoglobin); symptoms may include tiredness or weakness following operation
- Hives/ Nettle rash (rash with raised red, itchy bumps)
- Serious allergic reaction associated with swelling of face, throat or other locations
- Bloody discharge
- Discharge from wound
- Discharge (secretion) after a procedure

Unknown (frequency based available data):

- Serious and immediate allergic reaction which may cause itchy rash, throat swelling, difficulty breathing and low blood pressure
- Allergic reaction causing difficulty in breathing due to airway contractions

Risks of Treatment with Warfarin:
The currently known risks of warfarin include:
This drug may cause some unwanted side effects. If these side effects do occur, then you may need medical attention.

Major Risk:
- Bleeding, even if warfarin therapy is well controlled through frequent blood testing.
- Gastro-intestinal bleeding (bleeding in the stomach), even if warfarin therapy is well controlled, can indicate the presence of an underlying bleeding condition which may require further study.
- Life threatening or fatal bleeding, particularly if the therapy is not well controlled by the INR blood tests (overdosed).
- Other types of bleeding you might experience are the passage of black, tarry stools, vomiting blood, blood in urine, bleeding from the nose, bleeding around the heart and lungs and bleeding under the skin (black and blue). A decrease in the number of red blood cells may be indicative of bleeding.

Other Side effects:
- Fever
- Nausea and vomiting
- Inflammation of the pancreas
- Diarrhea
- Purple toes syndrome (painful, blue-purple colored toes)
- Increased sensitivity, skin rashes
- Jaundice and liver dysfunction
- Hair loss
- Skin necrosis within a few days of starting warfarin has been reported (death of the skin tissue).The first sign is red swollen patches on the skin.

Risks of Magnetic Resonance Imaging (MRI):
It is commonly acknowledged that if done correctly, there is minimal risk of the , itself. This minimal risk includes the following:
- Magnet effect on patients with artificial heart valves, metallic ear implants, bullet fragments, artificial joints, metallic bone plates, prosthetic devices, and chemotherapy or insulin pumps;
- Risk to a fetus in the first 12 weeks of pregnancy;
- Skin or eye irritation caused by iron pigments in tattoos or tattooed eyeliner;

- Medication patch burns; and
- Allergic reactions or slight risk of infection, if contrast material is used during the MRI.

4.3 Study Visits

Following the baseline visit for obtaining informed consent and conduct of baseline procedures (see Time and Events Schedule table below), subjects will be required to return to clinic within the first 4 weeks, and at 3, 6, 12, 18 and 24 months after the start of anticoagulation. Visit windows will be allowed for the follow-up visits, as follows: first follow-up visit expected within the 4 weeks as directed by routine care from the CPAS service, and plus/minus 30 days for the remaining follow-up visits.

4.4 Study Evaluations

All required study procedures at each specified interval are outlined in the Table below, and are further described in Section 4.1 and Appendix A3 of this protocol. In addition, the Study Coordinator will keep an INR Log on all subjects.

Time and Events Schedule:

Evaluation	Enrollment	*	1-4 weeks****	3 months ± 30 days	6 months ± 30 days	12 months ± 30 days	18 months ± 30 days	24 months ± 30 days
Inclusion/Exclusion	✓							
Demographics, Medical History	✓							
Height, Weight, Vital Signs	✓							
MMSE	✓				✓	✓	✓	✓
Hachinski Ischemic Scale	✓			✓	✓	✓	✓	✓
ACTS QOL Survey	✓				✓	✓	✓	✓
Minnesota Living with Heart Failure	✓				✓	✓	✓	✓
Alzheimers Disease Assessment Scale	✓				✓	✓	✓	✓
Disability Assessment for Dementia	✓				✓	✓	✓	✓
Protime/INR (warfarin arm only)	✓		✓	✓	✓	✓	✓	✓
Additional blood drawn for Serum Tests conducted in a research laboratory**	✓							✓
CBC/ BMP	✓		✓	✓	✓	✓	✓	✓
Cardiac Medication List	✓		✓	✓	✓	✓	✓	✓
Adverse Events and Hospitalizations	✓		✓	✓	✓	✓	✓	✓
MRI***	✓							✓

Table Legend:

*****Start of anticoagulation; ACTS: Anti-Clot Treatment Scale; APOE: Apolipoprotein E; BMP: Basic metabolic profile; CBC: complete blood count; INR: International normalized ratio; MMSE- Mini-Mental Status Evaluation; MRI: Magnetic Resonance Imaging; QOL: Quality of Life.*

***Additional Serum Tests: BNP, troponin, GDF-15, cystatin-C, D-dimer, MMP-9, chemokine ligand 23 (CCL23), ESAM, plasma vonWilebrand factor, CRP, prothrombin fragment 1+2, P-selectin, factor VIII, protein C, protein S, anti-thrombin III, anti-beta-2 glycoprotein-1 IgG and IgM, anticardiolipin IgG and IgM, neprilysn, ApoE2,Apo E4,and lupus anticoagulant panel.*

****Only for 10 subjects in each treatment arm selected for participation in the MRI Subgroup.*

*****The first serum assessment of anticoagulant effect of warfarin will be ordered based upon standard protocol of the CPAS clinic. This will vary based upon individual characteristics but is anticipated to be within 4 weeks.*

4.5 Initial and Potential Subsequent Trials

Based upon the power analysis to detect a difference in the primary endpoint, 1,100 subjects are required for enrollment. However, this analysis was done for dementia alone and this study will also include serial

neurocognitive testing to look for cognitive decline. For this study we will enroll 120 subjects. This number of subjects will give a more precise understanding of the incidence of both dementia and moderate cognitive decline in each anticoagulation group. This data, although intentionally underpowered at this time, will help in answering the primary endpoint as well as important other study questions regarding enrollment, retention, and study feasibility. All of this data will be used and incorporated into a larger study if this is pursed after completion of this initial study.

5.0 CONCOMITANT MEDICAL THERAPY

5.1 Pre-testing Medications

There will be no pre-testing medications administered to subjects in this study.

5.2 Peri-Procedure Medications

Subjects who qualify for this study as per inclusion and exclusion criteria (see Sections 3.5.1 and 3.5.2) will continue their standard of care treatment for any underlying medical conditions, as per discretion of the Principal Investigator(s), and in agreement with the subject's primary care physician. Treatment for non-valvular atrial fibrillation will be given to study-eligible subjects as described in Section 4.2.

5.3 Post-Procedure Medications

Following the subject's completion of this study, there will be no post-procedure medications administered, other than standard medical care as assessed by the Principal Investigator(s), in agreement with the subject's primary care physician. Dabigatran etexilate or warfarin will be continued as part of the subjects' standard medical care, as assessed and decided by their cardiologist and/or primary care physician.

6.0 CLINICAL LABORATORY PARAMETERS

Laboratory Testing Requirements

See Section 4.1 and the Time and Events Schedule table above for specific laboratory tests to be obtained at each visit.

7.0 SAFETY REPORTING

7.1 Serious and Non-serious Adverse Events

Assessment of adverse events

Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site,). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

• Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

• Moderate: Enough discomfort to cause interference with usual activity

• Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the Principal Investigator(s) or a Co-Investigator.

Responsibilities for SAE reporting to Boehringer-Ingelheim (BI)

The Sponsor shall report, i.e., from signing the informed consent onwards through the trial defined follow-up period which is completion of all study participants that do not withdraw to their last follow-up at 24 months, all SAEs and non-serious AEs that is relevant to a reported SAE by fax or other secure method to the BI Unique Entry Point as specified in pharmacovigilance agreement.

BI Unique Entry Point:
Boehringer Inglehiem Pharmaceuticals, Inc
Fax: 1-203-837-4329

For each adverse event, the investigator(s) will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The Principal Investigator(s) or a Co-Investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure or US Package Insert for the Product.
The investigator(s) does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator(s) becomes aware of an SAE(s) that occurred after the patient has

completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if the investigator(s) consider(s) it as relevant to the BI study drug.

This is a randomized clinical treatment trial using 2 FDA-approved drugs. It is expected that no significant and/or unexpected safety issues will arise. In order to guarantee the best possible protection of enrolled subjects, the study will only be initiated after appropriate IRB approval is obtained. Additionally, a qualified Data Safety Monitoring Board will be established to monitor the outcomes of the study. Serious and non-serious adverse events will be reported in accordance with ICH GCP, U.S. CFR, Intermountain policies and all other applicable regulatory requirements. All safety-related data for this study will be collected on standardized Case Report Forms as described in this protocol. See Appendix B, D and F for further guidance.

7.2 Subject Withdrawal

Subjects shall have the ability to withdraw consent for study participation and/or the use of their clinical information and test results at any time by contacting the Principal Investigator(s) without penalty, preferably in writing, addressed to the Principal Investigator(s) at the address indicated on the cover page of this protocol.

In the event of study withdrawal in a participant receiving dabigatran etexilate, the patient will be either treated by CPAS to receive standard of care warfarin, or referred to their primary care physician or cardiologist to start another DOAC. In the event of a study withdrawal in a participant receiving warfarin, the patient will be either treated by CPAS to continue to receive standard of care warfarin or referred to their primary care physician or cardiologist to start another DOAC.

Management of Data Already Collected on Subjects Who Withdraw Consent:

In the case a subject enrolled in this study decides to withdraw from the research, or an Investigator decides to terminate a subject's participation, the study investigator(s) must follow accepted standard practices regarding the management of collected data about these subjects, as follows:

- Investigators must document in the research record each instance of a subject's withdrawal, including the reasons for the withdrawal, if known.
- Previously-collected blood samples, information that has been gathered, and all material from the subject's identifiable samples that they have at the time of the subject's withdrawal from the study will remain in the study to maintain the integrity of the research, in accordance with current FDA regulations.
- The investigator(s) and/or their delegates may ask the subject whether he/she will agree to continued follow-up and further collection of clinical information following his/her withdrawal. The subject's agreement/disagreement for this continued collection of information will be documented appropriately in the subject's research study file.
  If the subject withdraws and does not consent to continued follow-up and collection of clinical information, the investigator(s) will discontinue access to the subject¹s medical record or other confidential records, for purposes related to the study.

7.3 Lost to Follow-Up Subjects

Because this is a 2-year study, with periods of time between research-related interactions, retention of participating subjects until study completion could be a challenging element. In order to facilitate subject retention, specific information will be obtained during the first research encounter and updated at all subsequent encounters. Although critically important to the successful completion of the study, if a

participant expresses concern and/or refuses to provide this information, they will not be excluded from the research. The following specific information will be collected and used for this purpose:

- Contact information of the participant (i.e. address, phone number, email)
- Contact information of one or more contact persons (close friend or family member) not living with the participant

In the event that a research participant becomes lost to follow-up, the research team will contact the subject or designated individuals named by the participant. A maximum of 3 telephone calls will be attempted. If there is no response, a letter signed by the Principal Investigator(s) requesting for a response may be sent. Once contact is reestablished, interest in continued participation will be verbally confirmed and documented, and the participant will return to active study participation as appropriate, based on their status/time point in the research.

8.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

8.1 Data Collection and Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs), to be created by a Clinical Research Coordinator (CRC) or a designated member of the IHI Cardiovascular Research team (see Appendix F). A duly-assigned CRC will perform primary data collection drawn from review of source-documents (hospital charts) and from on-going study procedures.

Internal monitoring of the study, including source document verification, will be done by a delegated and qualified member of the IHI CVR team who is not directly affiliated with the study, as per departmental SOP on monitoring of studies.

8.2 Sample Size Calculation

Estimates of potential cognition benefit are derived from our prior work on percent TTR and dementia (11). In this study, all patients will have had no history of dementia and were closely managed at the CPAS clinics at the time of enrollment. In this regard, we anticipate the dementia outcomes to represent best-case scenario with warfarin and may be worse in standard management settings.

In this study, the percent TTR averaged 62.7±22.9%, with the percent of INRs being <2.0 was 25.9±19.7% and the percent of INRs being >3.0 was 16.0±14.6%. We anticipate that dabigatran etexilate will have cognitive outcomes as good or better than the best managed warfarin patients. Using these patients that had a percent TTR >75% the estimated dementia risk is 1.9%. Within our population of AF patients managed by CPAS the distribution of patients in each category of percent TTR were: ≤25%: 215 (8.0%), 26-50%: 403 (15.0%), 51-75%: 1283 (47.6%), >75%: 792 (29.4%). Given this distribution, the estimated dementia risk of the entire population is from 4.9-5.5%. In those with concurrent use of an antiplatelet this risk increases slightly to 5.8%. Therefore, we anticipate the dabigatran etexilate group will have a two-year dementia rate of 1.9% versus 5.2% in the dose adjusted warfarin population. We acknowledge that superior TTR has been associated with a suspected diminution in benefit of the target-specific oral anticoagulants compared with warfarin for the outcome of major bleeding (17) and thus believe that the high quality of INR management provided by CPAS serves as a meaningful comparator to dabigatran etexilate.

The study will enroll approximately 10% of the subjects needed for potential larger study based upon the power analysis. As such we do not anticipating finding a significant difference in the primary endpoints. However, these data will assess the primary and secondary endpoints, including trends of cognition decline by serial cognitive testing over time as well as incident dementia rates in the prospective study design, and the

feasibility of recruitment, study subject retention, budget adherence and likelihood of obtaining the desired outcomes from the pre-specified power analysis, safety, and identify adverse effects. Evaluation Endpoints

8.3 Evaluation Endpoints

8.3.1 Primary Endpoint

1. The primary functional endpoint of this study is to demonstrate that with long-term anticoagulation therapy with dabigatran etexilate (150 mg BID or 75 mg BID, dose based upon renal clearance) will reduce incident dementia and worsening cognitive decline compared to dose-adjusted warfarin.
    a. Evaluating the difference of incident dementia between the treatment arms. Incident dementia will be defined as a formal diagnosis of dementia by a neurologist. In subjects that receive a MMSE score of <24 and report memory impact on quality of life will be referred to neurology for further evaluation of dementia.
    b. Change in cognitive decline. This endpoint will be determined by measuring the change from baseline to study conclusion on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment) and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment). An increase in ADAS-cog11 of >30% is considered significant for moderate cognitive decline. In subjects that score <50% on the DAD, there is a direct correlation with global deterioration scales and scores. Subjects with a 30% decrease in DAD score or those with a score <50% will be consider to have moderate cognitive decline.
2. The primary anatomic endpoint of this study is to demonstrate that with long-term anticoagulation therapy with dabigatran etexilate will reduce micro- and macro-cerebral ischemic events (both bleeds and clots) on compared to dose-adjusted warfarin

8.3.2 Secondary Endpoints

1. Stroke or Transient ischemic attack (TIA), intracranial bleed
2. Changes from baseline scores on the mini-mental status evaluation and the Hachinski Ischemic Scale
3. Since the sample size of 120 subjects will be potentially too small for meaningful data analysis of this study, there are minimal secondary outcomes planned for this study. Secondary outcomes include those required to proceed with a potential future larger study will be obtained. These include the following:

- Enrollment potential
- Feasibility
- Adherence and dropout rate
- Drug tolerability

8.4 Statistical Analysis

The study is a 1:1 randomized prospective trial. The subjects, physicians, and pharmacists will not be blinded to the assigned therapy.

The sample size of 120 subjects for the study will be potentially too small for meaningful data analysis, other than a description of trends and to assess the feasibility of recruitment, study subject retention, budget adherence and likelihood of obtaining the desired outcomes from the pre-specified power analysis, safety, and identification of adverse effects.

General baseline characteristics of the study participants for each of the aims will be described using means and standard deviations for continuous variables, and proportions for discrete and categorical variables.

Variables to be described include age, sex, and standard cardiac risk factors. Baseline characteristics will be compared between randomization groups to provide validation of the successful balance of study variables and potential confounders between the groups by the study randomization procedure administered at the time of study enrollment.

For the primary outcomes, two year incident dementia will be evaluated using the chi-square statistic. Odd ratios will be determined by Logistic regression. The chi-square statistic will also be utilized to evaluate whether there was a significant change in ADAS-cog11 (increase of >30%) and DAD (score <50% and/or a 30% decrease) scores. In addition, change scores for ADAS-cog11 and DAD (two-year survey score minus baseline survey score) will utilize the student's *t*-test. Comparisons of change scores between baseline and other time points (i.e., 6, 12, and 18 months) will also use the student's *t*-test to determine significant differences at these time points.

Subject clinical outcomes between the arms will be evaluated to determine differences for the other endpoints. As appropriate, the student's *t*-test and chi-square statistic will be utilized for continuous and discrete outcomes. Logistic regression will also to be utilized for binary outcomes to calculate odd ratios so that the odds of experiencing an event between arms can be determined. Kaplan-Meier survival estimate and log-rank test will be utilized to determine time to events stratified by arm. Regression analysis will also be utilized to identify clinical and procedural factors that are predictive of the outcomes. Analyses will be performed on an intention-to-treat basis.

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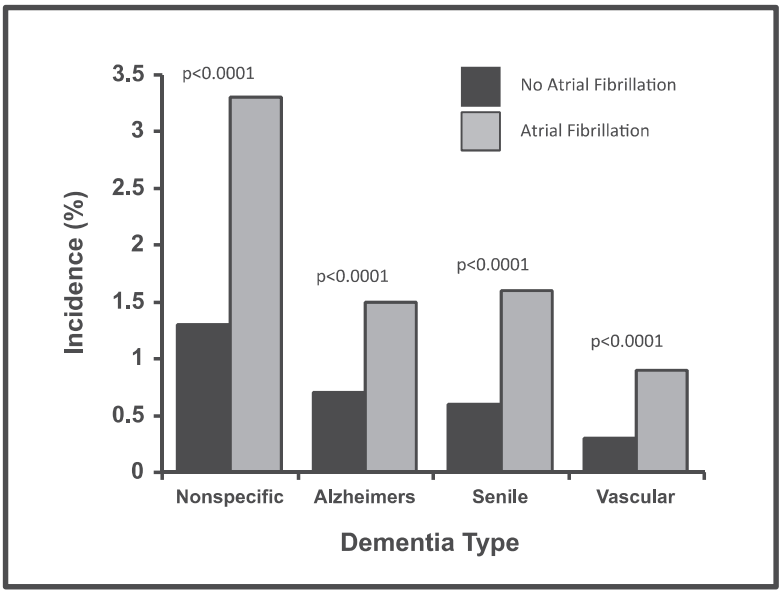
10.0 APPENDICES

APPENDIX A: PROTOCOL FIGURES, INVESTIGATIONAL PRODUCT INFORMATION AND STUDY TOOLS

Appendix A1: Protocol Figures

FIGURE 1: Incidences of different types of dementia in patients with atrial fibrillation and no atrial fibrillation.



Atrial fibrillation contributes to all types of dementia.

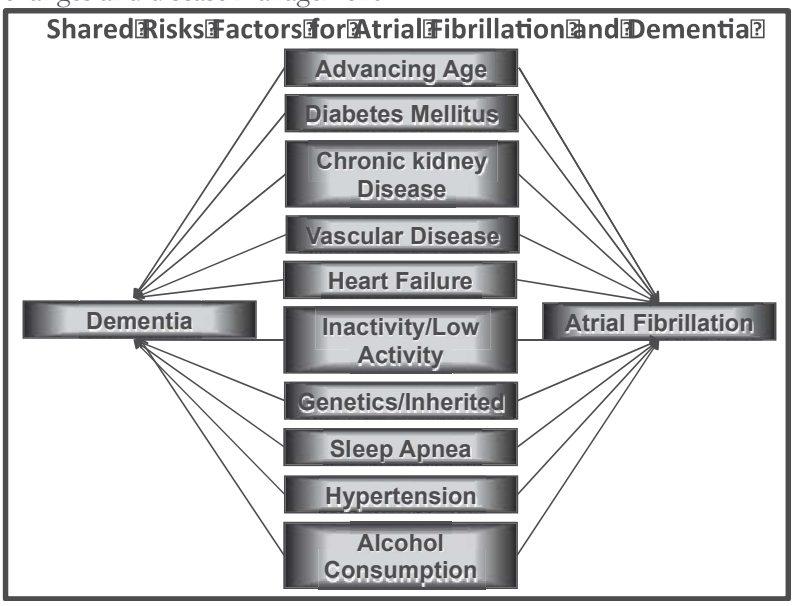
FIGURE 2: Odds Ratios for Association of Atrial Fibrillation based on Age and Dementia Type.

Odds Ratios for Association of AF based on Age and Dementia Type

Dementia	Overall	≤70	70-79	80-89	≥90
Vascular	1.73 p=0.001	2.22 p=0.004	1.68 p=0.02	1.31 p=0.45	------
Senile	1.39 p=0.005	3.34 p<0.0001	1.60 p<0.0001	0.93 p=0.004	0.54 p=0.41
Alzheimers	1.06 p=0.59	2.30 p=0.001	1.07 p=0.68	0.81 p=0.29	0.81 p=0.37
Nonspecific	1.44 p<0.0001	2.87 p<0.0001	1.49 p=0.001	0.96 p=0.77	0.60 p=0.44

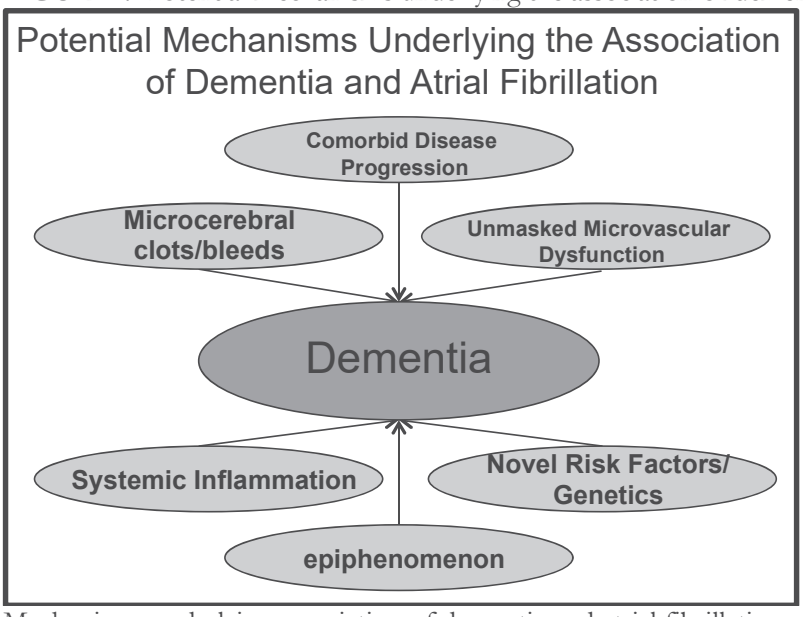
Association of atrial fibrillation and dementia based on age.

FIGURE 3: The figure displays common risk factors for both atrial fibrillation and dementia. Outside of aging and genetic/inherited variables, the majority of them are potentially modifiable with early lifestyle changes and disease management.



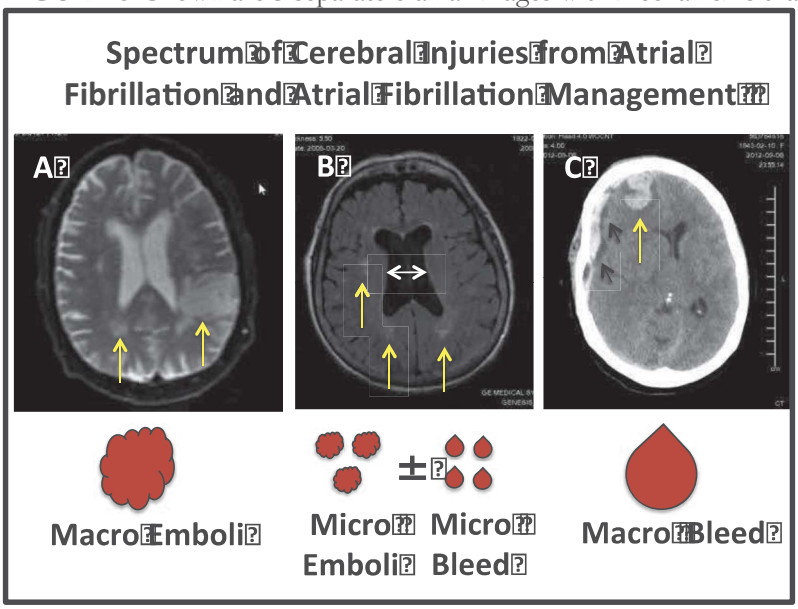
Common risk factors for both atrial fibrillation and dementia.

FIGURE 4: Potential mechanisms underlying the association of dementia and atrial fibrillation.



Mechanisms underlying association of dementia and atrial fibrillation.

FIGURE 5: Shown are 3 separate cranial images with mechanisms that impact cognition.



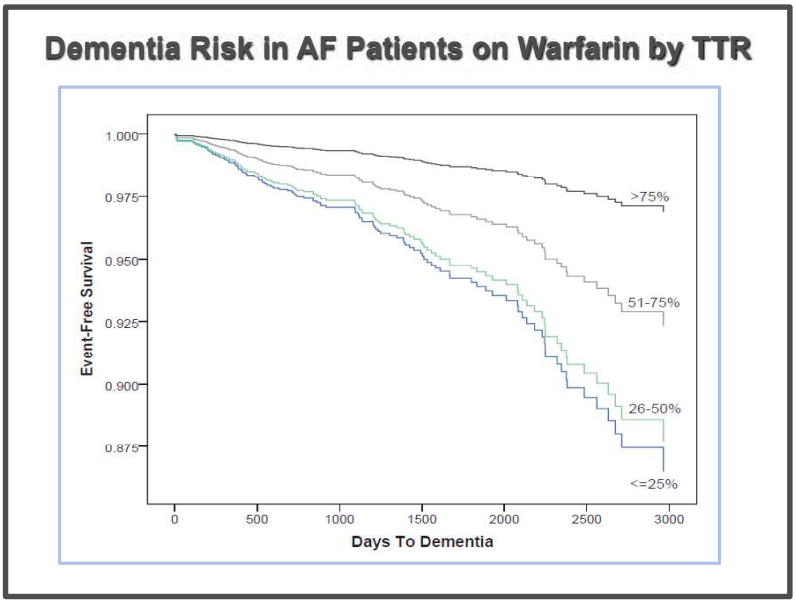
Mechanisms that impact cognition

A: Diffusion weighted axial MRI images of a patient that developed a large stroke after a cardioversoin. A large ischemic injury is noted in the left posterior parietal lobe (yellow arrow). A second injury is also noted on the left (yellow area) consistent with multiple emboli.

B. Axial MRI image of a patient with cognitive decline. The ventricles and cortical sulci demonstrate generalized atrophy and resultant enlargement in cerebral spinal fluid spaces (white arrows). Periventricular T2 hyperintensity consistent with white matter disease (yellow arrows).

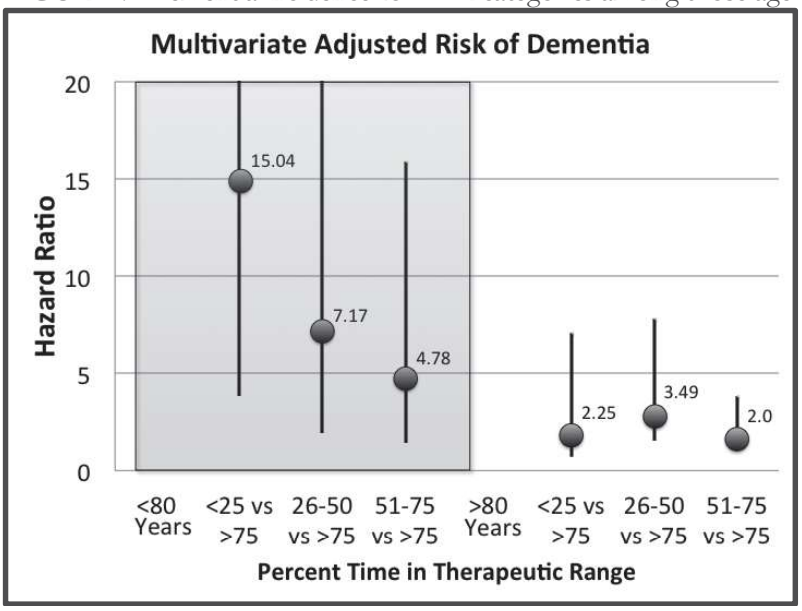
C. Noncontrast CT scan of in an AF patient on warfarin that fell striking her head. Black arrows highlight a subdural hematoma. The yellow arrow highlights intraparenchymal hemorrhage.

FIGURE 6: Event-free survival estimates for dementia incidence among categories of percent TTR.



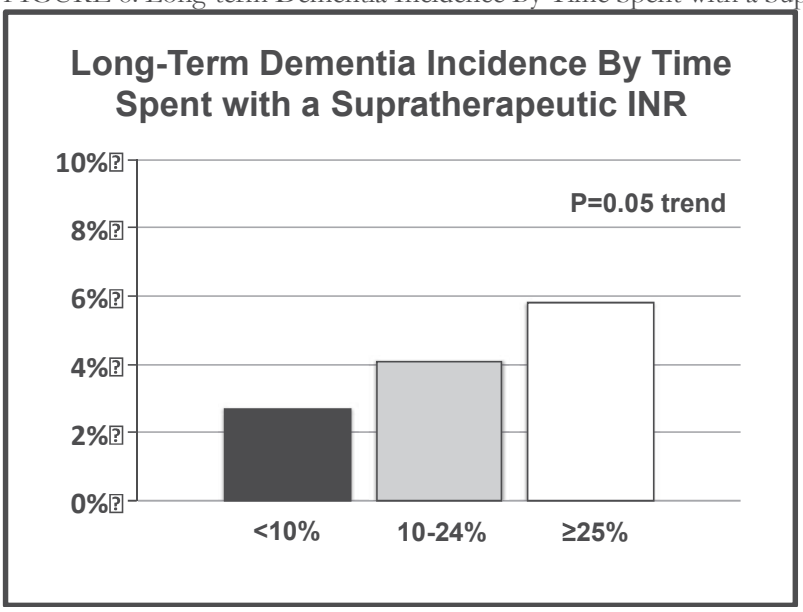
Over and under-anticoagulation contributes to the increased risk of dementia.

FIGURE 7: Dementia incidence for TTR categories among those age <80 and age ≥80 years.



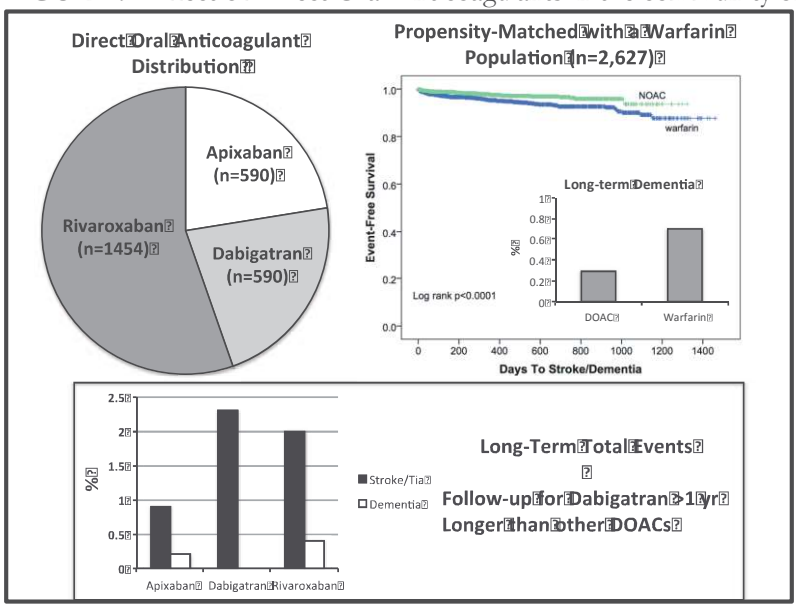
Low time in therapeutic range is associated with highest risk of dementia.

FIGURE 8: Long-term Dementia Incidence By Time Spent with a Supratherapeutic INR.



Patients who are taking antiplatelet drugs and are over-anticoagulated are more likely to develop dementia.

FIGURE 9: Effect of Direct Oral Anticoagulants in the community on stroke and dementia rates.



Dementia incidences were lower in the direct oral anticoagulant group when compared to warfarin.

A2: Investigational Product Information

1. Pradaxa (dabigatran etexilate mesylate) capsules

http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf

2. Warfarin sodium tablets

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

A3: Study Tools
Six questionnaires will be administered at the baseline visit, and repeated at the 6-, 12-, 18- and 24-month visits. The questionnaires and their purpose are described below.

1. Mini-Mental Status Evaluation
http://www.dhs.state.mn.us/main/groups/county_access/documents/pub/dhs16_159601.pdf

2. Hachinski Ischemic Scale
http://www.strokecenter.org/wp-content/uploads/2011/08/hachinski.pdf

3. Cognitive Subscale of Alzheimer's Disease Assessment Scale
http://www.dementia-assessment.com.au/cognitive/ADAS_Packet.pdf

4. Disability Assessment for dementia
http://www.dementia-assessment.com.au/function/DAD_Scale.pdf

5. Minnesota Living with Heart Failure Scale
http://www.queri.research.va.gov/chf/products/hf_toolkit/Minnesota-HF-Questionnaire_Rector.pdf

6. Anti-Clot Treatment Scale (ACTS) Quality of Life Survey
http://hqlo.biomedcentral.com/articles/10.1186/1477-7525-10-120

APPENDIX B: SAFETY-RELATED EVENTS

Safety-related events information, as defined by ICH Good Clinical Practice guidelines (E6) (ICH GCP E6), the Code of Federal Regulations (CFR), Intermountain research policy, and Intermountain Heart Institute Cardiovascular Research (IHI CVR) standard operating procedures (SOPs), will be collected throughout the study and will be reported using the appropriate case report forms, in accordance with relevant regulations/guidelines and Intermountain policy. See Section 7 for safety reporting processes.

APPENDIX C: INVESTIGATOR RESPONSIBILITIES

Study Conduct
The Principal Investigator(s) must ensure that all work and services described in the protocol are conducted in accordance with the investigator responsibilities described by ICH GCP E6, CFR, Intermountain policy and IHI CVR SOPs. The Principal Investigator(s) will provide copies of the current study protocol to all Co-Investigators and other staff responsible for study conduct. Each investigator (Principal and Co-Investigators) will sign an Investigator Agreement in which responsibilities to the Sponsor, Intermountain, and FDA are defined.

Institutional Review Board (IRB)
The Principal Investigator(s) must submit the protocol and informed consent document to the Intermountain IRB and obtain IRB written approval before initiation of the study. The Principal Investigator(s) may delegate this task to the IHI CVR Regulatory Specialist or other member(s) of the Study Team. These delegates and their assigned tasks must be documented on the study-specific Delegation of Responsibility log.

Patient Recruitment and the Informed Consent Process
Recruitment of subjects for this trial will be done in accordance with ICH GCP E6, CFR, Intermountain Research Policy and IHI CVR SOPs. The process for obtaining individual patient's consent will be documented on the CRF. An Informed Consent Form (ICF) that has been approved by the Intermountain IRB will be used to document the patient's agreement (via his/her dated signature) to participate in this research study.

Record Retention
The Principal Investigator(s) and his/her designated research staff are responsible for maintaining accurate, complete, and current records relating to the conduct of the investigation, in accordance with ICH Good Clinical Practice guidelines (E6) and the Code of Federal Regulations (CFR) (refer to ICH GCP 8.1 to 8.4 for a list of essential documents for retention).

In addition, the Principal Investigator(s) and his/her designated research staff are responsible for retaining any additional documents as required by Intermountain Heart Institute (IHI) or Intermountain Medical Center (IMC), in accordance with departmental and/or institutional records retention policy.

In the event that there is inadequate records storage space at IHI and/or IMC, all or part of the clinical study records can be sent to an IHI-approved archival storage facility that has a duly-executed service contract with IHI. As appropriate, the study Sponsor and other Stakeholders will be notified.

In the event that the Principal Investigator(s) transfers custody of all or part of the clinical study records to another person or entity, the IRB must be notified within 10 working days after the transfer occurs. In addition, and as appropriate, the study Sponsor and other Stakeholders will be notified.

Confidentiality of Patient Records
The IHI Regulatory Specialists and Clinical Research Coordinators will maintain all patients' information supplied by the clinical investigators in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) and IHC's guidelines for compliance and privacy. The subjects' files will be secured at Intermountain Medical Center, using alphanumeric codes to identify each subject (e.g., 1st 3 letters of last name, 1st 2 letters of first name + sequential number: LLLFF-001).

APPENDIX D: OTHER OVERSIGHT

Data and Safety Monitoring Board

The Principal Investigator(s) and his research team will monitor subject safety in accordance with ICH GCP E6, CFR, Declaration of Helsinki, Intermountain policies, IHI CVR SOPs, and all applicable local regulations.

A Data Safety Monitoring Board (DSMB) will be assembled to evaluate futility/superiority, adverse events, and study feasibility. Exact criteria will be set forth in the DSMB charter, to be created upon approval of this protocol by the Intermountain Institutional Review Board (IRB). Criteria will be based on a combination of incident dementia and/or moderate decline in cognitive testing.

Executive Operations Committee

The Intermountain Heart Institute (IHI) Executive Committee will be responsible for the day-to-day administrative management of the trial. This committee will meet periodically to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. A list of current members of the Executive Committee is available upon request from the office of the Director of Cardiovascular Research, Intermountain Heart Institute.

APPENDIX E: DECLARATION OF HELSINKI

WMA Declaration of Helsinki –
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to

participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX F: CASE REPORT FORMS

Case report forms (CRF) will be developed by the designated Clinical Research Coordinator, in collaboration with the Principal Investigator(s) and the research team at Intermountain Heart Institute.

11.0 PROTOCOL SIGNATURE PAGE

PROTOCOL IDENTIFICATION

Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients with Non-Valvular Atrial Fibrillation (Cognition Anticoagulation Trial)

PRINCIPAL INVESTIGATOR AGREEMENT

I agree to conduct this clinical trial/research study in accordance with the design and specific provisions of this protocol. Deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment and approval by the Institutional Review Board (IRB). I also agree to report all information or data in accordance with the protocol. In particular, I agree to report any serious adverse experiences as defined in the Safety Reporting section of this protocol to the Intermountain IRB, and in accordance with the IRB's reporting requirements. I also agree to handle all clinical supplies provided by the Sponsor, and collect and handle all biological specimens, in accordance with the protocol.

_____	_____
Site Principal Investigator (Printed Name)	Site Principal Investigator (Printed Name)
_____	_____
Site Principal Investigator (Signature)	Site Principal Investigator (Signature)
_____	_____
Date	Date