Catheter **Ab**lation Versus **An**tiarrhythmic Drug Therapy for **A**trial Fibrillation Trial

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Protocol Synopsis

SPONSOR	National Heart Lung and Blood Institute
PROTOCOL TITLE	**C**atheter **Ab**lation Versus **An**tiarrhythmic Drug Therapy for **A**trial Fibrillation Trial (CABANA)
PROTOCOL TYPE	Investigator Initiated IDE: G050233 NCT: 00911508 EudraCT-Number: 2011-002532-12
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Subjects who have new onset or under-treated paroxysmal, persistent, or longstanding persistent AF who ***warrant therapy*** for their arrhythmia, that (1) Over the preceding **6** months have: a) ≥2 paroxysmal episodes (***electrocardiographic documentation*** of at least 1 episode) lasting ≥1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48h of AF onset) b) ***electrocardiographic documentation*** of 1 persistent AF episode: (sustained for ≥7 days **or** cardioversion is performed more than 48h after AF onset); c) ***electrocardiographic documentation*** of 1 longstanding persistent AF episode: (continuous AF of duration >1 year). (2) are eligible for catheter ablation, (3) are eligible for ≥2 membrane active drugs and/or ≥2 rate control drugs, and (4) are ≥65 yrs of age or <65 yrs with one or more risk factors for stroke (hypertension, diabetes, heart failure, prior stroke or TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), or left atrial diameter ≥ 5.0 cm or left atrial volume ≥ 40 cc/m^2). Eligible subjects with persistent or long-standing persistent AF will require at least 1 documented episode. See main protocol for complete inclusion/exclusion criteria.
STUDY HYPOTHESIS	The treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing a) the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (primary endpoint; previously the key secondary endpoint) and decreasing total mortality (secondary endpoint; previously the primary endpoint) in subjects with untreated or incompletely

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	treated AF warranting therapy.
STUDY DESIGN	Multicenter, prospective, randomized, open-label clinical trial.
TREATMENT REGIMEN(S)	One-half of the subjects will be randomly allocated to treatment with catheter ablation and one-half will be allocated to drug therapy for either rate control or rhythm control.
DURATION OF STUDY PARTICIPATION	Enrollment will occur over approximately 4 years, and subjects will be followed for an average of approximately 5 years.
NUMBER OF SUBJECTS	2000-2200 with a 1:1 randomization ratio
NUMBER OF SITES	Total number: approximately 180 North American Sites: approximately 120 Non-North American Sites: approximately 60
PRIMARY ENDPOINT	Composite of: 1) total mortality, 2) disabling stroke, 3) serious bleeding, or 4) cardiac arrest.
SECONDARY OUTCOMES	Total mortality, Total mortality or cardiovascular hospitalization, Total mortality or stroke or cardiovascular hospitalization, Cardiovascular death, Cardiovascular death or disabling stroke, Arrhythmic death or cardiac arrest, Heart failure death, Freedom from recurrent AF, Cardiovascular hospitalization, Medical costs and resource use and cost effectiveness, Quality of life, Composite adverse events, LA size, morphology and function.
INTERIM ANALYSES	An interim examination of key safety and endpoint data will be performed at regular intervals during the course of the trial. The primary objective of these analyses will be to evaluate the accumulating data for a high frequency of negative clinical outcomes. The interim monitoring will also involve a review of the control arm event rates, patient recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study.

Investigator Statement

I have read the protocol, including all appendices and agree that it contains all necessary details for me and my staff to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the Sponsor and or designee. I will discuss this material with them to ensure that they are fully informed about the conduct of the study in general. I am aware that, prior to the commencement of this study, the Institutional Review Board responsible for such matters must approve this protocol in the clinical facility where it will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol.

I agree to provide all subjects with informed consent forms, as required by government and International Conference of Harmonization regulations. I further agree to report any adverse experiences in accordance with the terms of this protocol and FDA regulation 21 CFR 812 (Subpart E).

_____ _____

(Signature of Principal Investigator) (Date)

_____

(Please Print: Principal Investigator)

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1.0 Introduction

This protocol describes The Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial which has the overall goal of establishing the appropriate roles for medical and ablative intervention for atrial fibrillation (AF) in patients who require AF treatment and are at an increased risk for mortality, stroke and other health-related complications associated with AF. The trial aims to enroll a sufficiently broad spectrum of patients to allow far-reaching applicability of the results to the dramatically increasing numbers of patients with this arrhythmia. AF specifically affects patients of advancing age, and is an escalating burden to the health care system. This trial arises out of the AFFIRM, RACE, STAF, and AF CHF investigations of rate vs. rhythm control therapy and the International AF Ablation Registry. An ablation trial evaluating overall mortality and major AF related events, conducted within a population at increased risk, will provide the most compelling evidence for guiding the therapy of this malady. The completion of the 60 patient CABANA Pilot Study provides solid evidence of the feasibility of this landmark study. The primary aim of the CABANA Trial is to test the hypothesis that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing: 1) total mortality, disabling stroke, serious bleeding, or cardiac arrest as the primary endpoint and 2) total mortality as the secondary endpoint in patients with untreated or incompletely treated AF.

This project is a collaborative effort sponsored by the National Heart, Lung, and Blood Institute and involving the following organizational units:

- Mayo Clinic, Rochester, MN, Douglas L. Packer MD, [Clinical/Admin Coordinating Center]
- Duke Clinical Research Institute (DCRI), Durham, NC, Kerry L. Lee PhD, [Statistics and Data Coordinating Center]
- Duke Clinical Research Institute (DCRI), Durham, NC, Daniel B. Mark MD, [Economics and Quality of Life Coordinating Center]
- Mayo Biomedical Imaging Resource Center, Rochester, MN, Richard Robb PhD, [CT/MR Image Analysis]
- University of Washington/Seattle Institute Cardiac Research (SICR), Seattle WA, Jeanne Poole MD, [ECG/EGM Core Lab]
- International CABANA Investigators involving approximately 180 enrolling centers.

CABANA Trial Organization and Process Flow

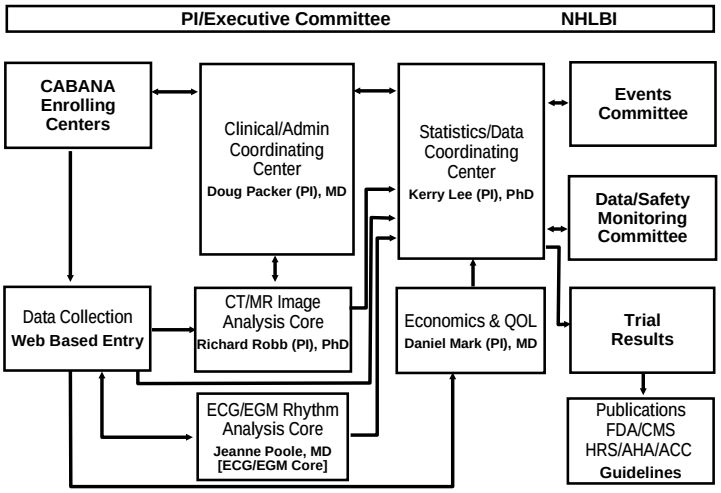

Figure 1

1.1 Background

Atrial Fibrillation: The Problem

1.1.1 Increasing Incidence and Prevalence

In the past 15 years, AF has emerged as the leading arrhythmic malady in terms of both numbers and sequelae. Several studies have documented a 1% incidence of AF in 60 year olds, with an increase to 8-12% in octogenarians [1]. This translates into a prevalence of 2.3 million patients, with a projected increase to 5.6 million by the year 2050 [1-3]. The prevalence of AF in the setting of heart failure is even higher, with up to 45% of patients with class IV heart failure suffering from this arrhythmia [4-6].

1.1.2 Progression of AF

While many patients with paroxysmal AF show little propensity for arrhythmia progression, the majority of studies have document a transition to more persistent AF in a substantial proportion of patients. The Canadian Registry of AF (CARAF) showed that 63% of 757 patients with paroxysmal AF had recurrent arrhythmia over a 5 year period, with progression to permanent AF seen in 25% [7]. Similar numbers have been documented by others [8, 9]. Although progression to chronic AF in patients with little underlying heart disease may be as low as 31% over 3 decades [10], other reports document progression to chronic AF in 48-77% of patients over 8-14 years[11,12]. These differences are due, in part, to the extent of underlying disease [13, 14]**.**

There is also reason to anticipate an increasing impact of this arrhythmia on mortality, stroke, bleeding and cardiac arrest. In the Framingham study [15], both men and women between 55 and 75 years of age with AF showed a near doubling of mortality over the course of 10 years. Within that time frame, the overall death rate was approximately 15% in patients without and 55% in those with AF. This rate is further incremented in those individuals between the ages of 75 and 94 years, in whom the mortality rate increased from 30% to nearly 70% in the presence of AF [15]. Up to 50% of individuals with a new stroke in both population-based and cohort studies have underlying, potentially related, AF [16-18]. This risk increases from an attributable risk of 1.5% in the 6th decade of life to 23.5% in 80-89 year olds [18]. The problem of AF

associated stroke is corroborated by another population-based study from Olmsted County demonstrating an increasing prevalence of stroke related to AF over the past 3 decades, perhaps due to increasing AF occurrence [19].

1.1.3 Health Care Costs of AF

AF related illness is a rapidly increasing burden on the global health care system. Data from the 2003 National Discharge Survey in the US, used to estimate the annual number and prevalence of hospitalizations, showed an increase from 154,086 to 376,487 admissions for AF as the first listed diagnosis and from 787,750 to 2,283,673 for any AF diagnosis [20]. Other studies document an increase in hospitalizations and nursing home need because of this arrhythmia [20, 21]. A recent study suggested that the excess annual health care cost in the US is also 5 times greater in patients with, than without AF [22]. An additional four-fold increase in expense has also been reported in patients with multiple yearly AF recurrences [23]**.** Similarly, the cost of AF-related care in the UK rose from 244,000,000 Pounds in 1995 to 459,000,000 Pounds in 2000[24]. The cost of AF hospitalization, the foremost driver of AF-related expense, is likewise increasing [24-25], presaging even greater increases in health care costs in the future.

1.2 Clinical Experience with Drug Therapy

The medical approach to patients with AF by definition requires poly-pharmacy. Many patients with recurrent AF require rate control therapy. Others, in whom sinus rhythm is desirable, require treatment with an anti-arrhythmic drug, while patients with risk factors for stroke or peripheral thromboembolic events require anti-thrombotic therapy. Many health care providers also remain unenthusiastic about the limited efficacy and increased proarrhythmic risks of membrane-active agents for AF control.

1.2.1 Anti-Thrombotic Therapy

The importance of anti-thrombotic therapy in the management of patients with AF has been established by the AFASAK, SPAF, BAATAF, EAFT, CAFA and other trials demonstrating a reduction in stroke risk with warfarin [26]. The response to aspirin or clopidogrel and aspirin has been disappointing, as shown in these and the recent ACTIVE Trial [27]. Both the AFFIRM and RACE trials also clearly demonstrated excess stroke morbidity in patients discontinuing anticoagulation and in those with inappropriate INRs [28, 29]. This finding may be related to the occurrence of asymptomatic AF seen in 40-60% of patients [30-33]. Perhaps the most crucial contribution of these trials is the clarion call to maintain anticoagulation, even if sinus rhythm has been restored. It remains unclear whether these data apply to post-ablation patients.

1.2.2 Drug Therapy for Rate Control

In many patients with new onset AF, therapy with single or combination rate control agents can be valuable [34]. Agents such as beta- or calcium channel blockers, or even digitalis may control heart rate in the many patients treated aggressively. The AFFIRM trial demonstrated that 65% of patients so treated had appropriate rate control at 1 year, with 70% at 2 years, and 75% at 3 years [28]. Comparable findings were seen in the RACE trial [29]. Nevertheless, these patients may have a variety of other drug-related side effects.

1.2.3 Drug Therapy for Maintaining Sinus Rhythm

Multiple small observational studies demonstrate a 40-50% chance of maintaining sinus rhythm with membrane active anti-arrhythmic drugs over the course of one year. These data have been validated by recent larger comparative clinical trials. In AFFIRM, 82.4% of patients treated with rhythm control drugs were in sinus rhythm at the end of 1 year, 73.3% at 3 years, and 62.6% at 5 years [28]. This is in comparison with the 43% prevalence of sinus rhythm at 1 year,

which decremented to 34.6% at 5 years in those receiving AV Nodal blocking agents alone. Many of these patients in sinus rhythm at the time of follow-up had recurrent arrhythmia during the time between these evaluations. In the AFFIRM First Drug Study, 33% of patients taking amiodarone had an AF recurrence by 1 year, with 50% by 3 years. This was significantly better than the 52% AF recurrence in sotalol-treated patients at 1 year, and 71% recurrence at 3 years [35]. The findings were similar in RACE, with only 39% remaining in sinus rhythm at the end of the trial [29] and only 38% of patients at 2 years in the STAF Trial [36]. Overall improvements in quality of life (QO) were comparable in rate and rhythm control patients in AFFIRM [28, 37]. Rate control therapy was also more cost effective in these comparative studies [37, 38, 39, 40, 41]. In addition to an increase in morbidity and mortality risk with rhythm control therapy attributable to pro-arrhythmia, AFFIRM rhythm control patients also had excess non-cardiac mortality compared to their rate control counterparts.

1.2.4 Mortality Benefit of Drug Therapy in Randomized Trials

The morbidity and mortality response to drug therapy for AF seen in these studies has been disappointing [28, 29, 36, 38, 42]. In the AFFIRM Trial, conducted in patients at increased risk because of age or the presence of risk factors for stroke, there was no statistically significant difference in mortality outcomes with rate (21.3%) and rhythm (23.8%) control strategies at 5 yrs [hazard ratio 1.15 (0.99-1.34) for rhythm control therapy; p=0.08] [28]. Patients treated with rhythm control were more likely to require rehospitalization (80.1%) than rate control patients (73.0%) [p<0.001] and rhythm control therapy was more expensive [43]. The outcome of the secondary endpoint of death, disabling stroke or anoxic encephalopathy, major bleed, or cardiac arrest was also similar in the two arms. Importantly, similar trends of mortality and composite endpoints were seen in RACE [29], PIAF [38]**,** and STAF [36]. As suggested by accompanying editorial opinion, only 40 to 50% of eligible patients were enrolled in these trials, in part because of bias toward rhythm control in highly symptomatic patients. These data may not be directly applicable to younger patients without heart disease.

The outcomes of rate vs. rhythm control management strategies were also recently examined in patients with underlying heart failure. The AF CHF Trial [42] enrolled 1376 patients with one AF episode in 6 months and either Class II-IV CHF and an EF ≤35%, or Class I CHF with a CHF hospitalization, or an EF ≤25%. 682 patients were randomized to rhythm control (Amiodarone in 82%) versus 694 to rate control (beta blockers in 88% and Digoxin in 75%) [42]. Thirty-one percent had paroxysmal while 69% had persistent AF, and 31% had Class III or IV CHF. There was no difference in the primary endpoint of CV death in rhythm (26.7%) vs. rate control patients (25.2%) [HR=1.06, CI=0.86-1.30, p= 0.59] over 37 months of follow-up. There was no difference in total mortality (31.8% vs. 32.9%, p=0.73), stroke risk (2.6% vs. 3.6%, p=0.32), worsening CHF (27.6% vs. 38.8%, p=0.17) or the composite of CV death, stroke, or worsening CHF (42.7% vs. 45.8%, p=0.20). Bradycardia was more common in those treated to maintain sinus rhythm (8.5% vs. 4.9%, p=0.007) and 21% of patients crossed over from rhythm to rate control therapy.

The findings of this trial, along with AFFIRM, RACE and STAF raise important questions regarding the quest for maintaining sinus rhythm in patients with AF. These studies can be interpreted as supporting the thesis that the restoration and maintenance of sinus rhythm does not alter over-all outcome. If true, this would indicate that 1) other factors are responsible for morbidity and mortality in AF patients, 2) AF is not a risk factor for either total or CV mortality, or 3) this arrhythmia is simply a marker of CV risk related to underlying disease. Alternatively, there may be significant benefit to sinus rhythm, which is offset in these trials by the pro-arrhythmia, heart failure, or organ toxicity attending anti-arrhythmic drug therapy. Disappointing efficacy of drugs in maintaining sinus rhythm would further diminish their appeal.

Any recommendation for rhythm control must be tempered by a consideration of pro-arrhythmic risk and occurrence of intolerable side effects. In AFFIRM, 5% of patients had a pro-arrhythmic event [44], with drug discontinuation because of side effects in 10% of rate control and 30% of rhythm control patients [28, 29]. In addition to poor efficacy, there also may be an inadequate AF gradient between groups of patients due to appreciable undetected AF and accompanying risk in rhythm control patients or unexpectedly common sinus rhythm in rate control patients, both limiting discernible differences between groups. Of note, 31% of patients in AFFIRM had paroxysmal AF and many of the rate control patients had sinus rhythm.

Despite the pessimism potentially generated by these issues, the results of the recent ATHENA trial have provided incentive for the reconsideration of drug therapy for AF [45]. In comparing the class III antiarrhythmic agent dronedarone in 2327 patients against placebo given to 2301 individuals, this study showed a 24% reduction in cardiovascular hospitalization or mortality (p,0.0001), a 29% decreased in cardiovascular mortality (p= 0.03), and a 26% decrease in cardiovascular hospitalization(p ≤0.0001) with active therapy at 22±5 months of follow-up. There were also significantly lower ACS and stroke rates with dronedarone therapy, in the setting of low proarrhythmia and heart failure rates. These data support the potential for cancelation of benefit from drug therapy by untoward toxicities of drug interventions.

1.3 Clinical Experience with Catheter Ablation

1.3.1 Single Center Ablation Success Rates

While these trials have established the benefit/risk ratios of pharmacologic rate and rhythm control therapies, in the absence of longer-term studies, the comparative long-term outcomes of ablative intervention remain unclear. This is particularly true in patients with advancing age or underlying disease. Still, the outcome of the AF CHF trial, viewed within the context of AFFIRM, RACE, and STAF, argues strongly for alternative catheter-based or surgical intervention for AF elimination. The efficacy and safety outcomes of catheter ablation for AF are available in the form of observational studies from individual centers [46-51]. These issues have been reviewed in detail in the recent AF Ablation Consensus Statement [50] and the Venice Chart International Consensus Document on AF Ablation [51]. These clinical studies document AF elimination rates of 55-80% with lasso-guided ablation of paroxysmal AF [46], with a 70-90% success rate using more aggressive wide area circumferential or high frequency, complex electrogram-guided ablative approaches [47,48]. The mechanism of beneficial effect is not completely established but likely includes the isolation of AF-initiating triggers arising within pulmonary veins (PVs), the alteration of parasympathetic and sympathetic nerve ganglia in the posterior LA, and the disruption of candidate initiation and substrate-mediated maintenance mechanisms of AF [47]. These studies have several limitations including absence of randomized enrollment, variability in techniques, differences in end points, the inconsistent use of blanking periods, and an uncertain number of redo procedures. Moreover, the 60-70% ablation success rate seen in the recent International AF Ablation Registry detailing outcome, suggests that the efficacy rate of ablation may be less than seen in earlier observational studies [49]. Furthermore, recent data have suggested an increased recurrence rate 2-3 years after ablation [52].

The complication rates of ablative intervention have been inadequately documented. While recent studies demonstrate a 1% stroke rate and a reduced PV stenosis rate down to 1-2% with ablative intervention, the same International AF Ablation Registry suggested that serious ablation events occur in up to 6% of patients [49]. The occurrence of stroke, PV stenosis, tamponade, and the recently reported lethal atrial-esophageal fistulae [53] indicate that the true complication rates of AF ablation have yet to be established.

Smaller, randomized ablation vs. drug studies include the CACAF [54], RAAFT [55], APAF [56], and A4 [57] Trials. These trials randomized 67-198 patients to rhythm control therapy vs. primary AF ablation. Over a 12-month follow-up period, a 76% average recurrence rate was seen in drug treated patients, which was greater than the 24% recurrence rate in ablated patients [54-57]. These studies also provide additional preliminary information. In the CACAF Trial [54], 1 of the ablation patients (1.5%) and one patient in the control group (1.5%) sustained a stroke, and 2 patients (3%) in the drug control group died over the course of follow-up. In the RAAFT Trial [55], re-hospitalization was required in 19 (54%) of anti-arrhythmic drug-treated patients compared with only 3 (9%) of those ablated ($p<0.001$). No mortality was seen in either treatment group. In these studies, 20-73% of drug treated patients crossed over to ablative therapy. Since patients over the age of 75 years were largely excluded, these early trial results may not apply to the increasing elderly population of patients at risk for untoward AF-related morbidity and mortality. Nevertheless, these data show similar rates of AF elimination, all favoring ablative intervention.

At least 4 studies have assessed the outcome of catheter ablation for AF occurring in the setting of ventricular dysfunction [58-61]. In contrast to the AF CHF Trial, these studies show a substantial improvement in EF/CHF class in patients in whom sinus rhythm was restored and maintained by intervention. Accompanying data suggest that this is more likely in patients with non-ischemic than ischemic cardiomyopathy. Short follow-up periods in these studies make it impossible to draw conclusions regarding mortality and/or morbidity benefit, however.

1.3.2 CABANA Pilot Study

Sixty patients were enrolled in 10 centers and randomized to AF ablation versus drug therapy, indicating the feasibility of randomizing patients with CABANA characteristics [62]. Of the patients enrolled, 77% were men and 23% women. The average age was 59 years (37% $\geq$65 yrs). Among the 60 patients, 80% had hypertension, 71% had 2 or more co-morbidities, 28% had sleep apnea and 25% had a family history of AF. Thirty two percent of patients had paroxysmal, 37% persistent, and 32% longstanding persistent AF. This pilot experience suggests that the Pivotal study will provide relevant information for a broad spectrum of AF patients. Only 7% of the pilot study patients had Canadian class 0 (asymptomatic) AF, 12% class I, 19% class II, 51% class III, and 11% had class IV symptoms [63]. Twelve percent had class I CHF symptoms, 31% were class II, and 5% had class III CHF. Twenty five percent had been on a single rhythm control drug, and 97% on rate control. Of these patients, 47% had required prior hospitalization for AF and 47% had been previously cardioverted. These patient characteristics are similar to AFFIRM patients and are very different from the typical catheter company PMA patients with paroxysmal AF and no other heart disease.

Twenty-nine patients (48%) were randomized to ablation and 28 of them underwent ablation. All 31 patients (52%) randomized to drug therapy were treated with rate or rhythm control agents. 13% of patients have been treated with rate-control only, 16% with rhythm control agents only, and both in 71%. The overall enrollment rate in this start-up pilot study exceeded the 0.7 patients/center/month needed to complete the pivotal study. In addition, following the change in focus from ablation expert-driven enrollment to non-ablationist co-PI recruitment, enrollment increased to 1.1 patients/site/month. The pilot study demonstrated the feasibility of recruiting and enrolling patients, identified the expected demographics of Pivotal Trial subjects, and has been very helpful in optimizing the study design of the Pivotal Trial.

1.4 Rationale For Maintaining Sinus Rhythm

None of the trials to date address the far-reaching question of the merit of maintaining sinus rhythm for reducing morbidity and mortality. Recent data from the AFFIRM trial provide a glimpse into this issue. In a post-hoc, time-dependent covariate assessment of the relationship between cardiac rhythm and survival, warfarin and sinus rhythm were associated with a lower risk of death [HR=0.53 CI=0.39-0.72 ($p< 0.0001$)] [64]. Similarly, 18 of 19 primary endpoint events in the STAF trial occurred in those patients remaining in AF [36]. Nearly identical findings were seen in patients in the DIAMOND studies, which reviewed the effect of dofetilide on total mortality in the setting of a prior MI or CHF [65]. The probability of survival in patients treated with dofetilide, who remained in sinus rhythm, was 60% at 36 months as compared to 30% in those remaining in AF, an effect also seen in the placebo group. Pappone et al [48] in his comparative report noted that 72% of all adverse events were observed in patients remaining in AF. In contrast, patients maintaining sinus rhythm in the RACE trial did not show improved survival [66]. It remains unknown whether the ability to maintain sinus rhythm is a marker of improved outcome, or whether sinus rhythm *per se* confers a mortality benefit. The post-hoc nature of the analyses limit the value of these results for guiding clinical practice.

The data from Nademanee and coworkers [67] also bear directly on the feasibility of the CABANA trial. Their study examined mortality and stroke outcomes in 540 patients with AFFIRM characteristics (age >65 or the presence of hypertension, diabetes, atrial enlargement or ventricular dysfunction in patients <65yrs). Their mean age was 69 years, with 165 patients $\geq$75 years of age, and 124 with an EF<40%. Fourty% had paroxysmal, 26% had persistent, and 34% had permanent AF. Each patient underwent ablation (once in 374, while 121 underwent 2 sessions, 43 underwent 3 sessions and 2 patients 4 sessions). 492 were followed for 4.2$\pm$1.1 years. The 2.7% long term mortality rate in 431 (86%) patients remaining in sinus rhythm was substantially better than the 16% death rate in the 63 (14%) who remained in AF ($p<0.0001$). Sinus rhythm was the most important independent predictor of survival ($p=0.002$), whereas EF and warfarin had little prognostic value in these patients. These studies taken together, along with data from population-based studies, provide the rationale for a large, multi-center trial to prospectively examine the impact of sinus rhythm on total mortality, disabling stroke, serious bleeding and cardiac arrest in patients with AF. Information from a well-designed randomized mortality trial is critically needed to provide a reasoned basis for the continued application of advanced ablation technology, justifying its concomitant cost, or its earlier application as first line therapy [68].

1.5 Rationale for Rhythm Monitoring

Most studies examining outcomes of drug and ablative therapy use symptomatic episodes of AF for establishing endpoints. While this allows assessment of AF burden and quality of life, it is an inadequate basis for making critical decisions regarding ongoing anticoagulation. Presumably, AFFIRM patients demonstrating excess morbidity after discontinuation of warfarin were felt to have complete control of their AF by anti-arrhythmic drug therapy [28]. Their subsequent events may have been due to undetected silent AF or some other underlying factor. Other studies have documented a moderate prevalence of asymptomatic or “silent” AF in other settings [30-33, 70-72]. Additionally, 10-40% of successfully ablated, asymptomatic patients may have silent AF [71, 72], which raises the possibility of continuing stroke risk or other morbidity, even though symptoms are eliminated [73]. Of note, others have reported far lower asymptomatic AF rates [48, 74, 75]. In addition, patients with asymptomatic AF may be at equivalent risk as their symptomatic counterparts. These issues, and the need to establish simple treatment efficacy, provide a clear rationale for careful monitoring to establish treatment efficacy.

1.6 Rationale for Cost and Quality of Life Investigations

AF is responsible for almost 500,000 in-patient hospitalizations in the US every year [20-21]. The direct medical costs associated with AF account for several billion dollars of excess health care spending per year in this country. At the individual level, AF increases medical spending from 9 to 22 times that for similar patients without AF. The cost effectiveness of ablation has been evaluated in preliminary studies only [76, 77]. Although case control studies have suggested that AF-related impairment of QoL is between that of having an MI and heart failure, improvement is expected with treatment [28, 29, 26, 38, 78-80]. Preliminary data suggest that AF ablation can restore QoL to levels comparable to age/sex matched general populations [81, 82]. Given the epidemic growth of this arrhythmia in the aging US population, more effective therapy offers the potential of relieving suffering in a growing number of citizens. As part of the CABANA research program, we plan to examine economic and QoL outcomes comprehensively using state-of-the-art tools and techniques used in recent or ongoing trials (OAT, STICH and SCD-HeFT).

1.7 Rationale for Cardiac Imaging Studies

Atrial remodeling, occurring with AF has been well documented, although it is difficult to know whether changes in atrial structure precede or follow this arrhythmia or are simply triggered by underlying disease. It also remains uncertain whether a reversal of atrial dysfunction occurs following ablation. In theory, elimination of AF should produce both electrical and anatomic remodeling, regardless of the therapy employed. At present, LA size and function outcomes following ablation are contradictory [83-88]. These data suggest an improvement in LA size and function following more limited PV isolation, although this might be offset by the scarring produced by more aggressive intervention. We also have preliminary data suggesting that LA dysfunction remains beyond the typical 1-2 month time frame used in deciding to stop anti-coagulation after restoring sinus rhythm [89]. CT / MR Image Analysis will be required to document the occurrence of LA remodeling following AF elimination with ablation or drug therapy and establish its impact on overall outcome, stroke risk, and the need for post-ablation anti-coagulation. The real-life prevalence of catastrophic atrial-esophageal fistula formation and PV stenosis will also be established. *While some of this desired information could be obtained echocardiographically, this approach is problematic given difficulties in standardizing image acquisition and interpretation. Furthermore, the echo approach cannot be used to assess pulmonary vein or esophageal status. CT or MR imaging can be standardized both in terms of acquisition and interpretation.*

1.8 Significance of the Trial

This trial is of substantial importance at multiple levels. Clinically, the trial will establish whether the emerging role of aggressive catheter ablation in the treatment of AF is justified by patient outcomes. This is an expensive approach, potentially complicated by life threatening events, which is now performed in thousands of patients without clear evidence of long-term benefit. The issues raised above have not been settled for “curative ablation”. The impact of age, AF type, and underlying disease on the outcome of ablation and drug therapy remain unclear. This study will answer these questions, will document the effect of ablation on AF recurrence and specifically examine health care costs, cost effectiveness, and quality of life outcomes. This study will also assess the role of earlier therapy for AF and the related utility of ablation as first line therapy in patients warranting treatment.

Scientifically, the trial will determine whether the attainment of normal sinus rhythm is a mortality and stroke advantage. No trial to date has prospectively addressed this issue, nor will any currently envisioned 1-2 yr study be sufficiently powered for this purpose. The trial should also

provide outcomes-based support for the role of AF as a modifiable risk factor of increased morbidity and mortality. The trial will also establish the determinants of ablation outcome. The CT/MR Imaging will also elucidate the structural abnormalities contributing to the occurrence of AF in a diverse population of patients and the modulation of those factors by drug or ablative intervention.

From a health care policy standpoint, this trial will help establish the place for medical and non-pharmacologic therapies for this escalating national healthcare dilemma. Aggressive intervention in an increasing number of patients and resulting mushrooming financial burden to society is already taking place at a time of increasingly constrained funding for health care. The Quality of Life and cost components of the trial will firmly establish whether AF ablation represents good value for the money and is an efficient way of improving health in the affected population relative to alternative health care expenditures. It will also allow much better estimation of the impact of the diffusion of ablation technology into the overall health care system. A critical window of opportunity for a randomized trial is now present, and the outcome of this landmark trial will likely shape therapy decisions and health care policy for years to come.

2.0 Objectives

Changes to the Protocol from the Original Study Design

Although CABANA was originally mandated to be a mortality trial, a careful assessment of the progress of the trial was undertaken by the study leadership in early 2013. Completely blinded to any treatment-specific outcome data, the two major issues addressed by the leadership group were (1) a lower than expected aggregated mortality rate, and (2) accrual of patients at a slower rate than projected. Careful consideration of these issues led to a decision to (a) change the primary endpoint of the trial from total mortality to the original key secondary endpoint consisting of the composite of death, disabling stroke, serious bleeding, or cardiac arrest, and (b) reduce the sample size to a number that was consistent with the new primary endpoint and more realistically achievable. There may still be a mortality difference between treatment groups. This was not revealed in the interim review. These changes will be highlighted in the sections of the protocol that follow.

2.1 Primary Objective and Hypothesis

The primary hypothesis of the CABANA trial is that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art medical therapy with either rate control or rhythm control drugs for decreasing the incidence of the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (primary endpoint) and reducing total mortality (key secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy. The study is powered to detect treatment with percutaneous left atrial catheter ablation will reduce the incidence of this endpoint by $\geq$30% compared to drug therapy. To properly interpret this composite endpoint, the incidence of each of the individual components will also be descriptively examined to assess its relative contribution to the overall composite outcome. The primary endpoint and all secondary endpoints will be carefully assessed and analyzed on an intention to treat basis.

2.2 Secondary Endpoints/Objectives

1. Total mortality
2. Total mortality or cardiovascular hospitalization

3. Total mortality, stroke, or CV hospitalization (for heart failure or acute ischemic events)
4. Cardiovascular death
5. Cardiovascular death or disabling stroke
6. Arrhythmic death or cardiac arrest
7. Heart failure death
8. Freedom from recurrent AF
9. Cardiovascular hospitalization
10. Medical costs, resource utilization, and cost effectiveness
11. Quality of Life
12. Composite adverse events
13. LA size, morphology and function

2.2.1 Total Mortality

Because of the vital importance of assessing the impact of left atrial catheter ablation on total mortality, this endpoint (which is a component of the primary endpoint) will be a specific secondary endpoint in the trial.
Hypothesis: Catheter ablation for AF will reduce total mortality by ≥30% compared to state-of-the-art pharmacologic therapy.

2.2.2 Composite Mortality / Cardiovascular Hospitalization

By reducing the recurrence of AF, the proposed therapies should also reduce cardiovascular hospitalization. Additional secondary endpoints, including cardiovascular hospitalization and the composite of total mortality and cardiovascular hospitalization, will therefore be examined. The composite of total mortality, stroke or cardiovascular hospitalization will also be assessed. *Hypothesis*: Catheter ablation for AF will be significantly (≥25%) more effective than pharmacologic therapy, in reducing cardiovascular hospitalization, the composite of total mortality or cardiovascular hospitalization, and the composite of total mortality, stroke or cardiovascular hospitalization.

2.2.3 Freedom from Heart Failure Mortality

AF may be seen in 40-50% of heart failure patients. Furthermore, heart failure may occur because of uncontrolled ventricular response rates or as an adverse consequence of drug therapy. Heart failure related mortality may be affected differently by the ablative elimination of AF than by ongoing pharmacologic treatment.

2.2.4 Freedom from Recurrent Atrial Fibrillation

The purpose of therapy is to eliminate accompanying symptoms in affected individuals. An additional secondary endpoint will be the elimination of AF, comparing complete freedom from and time to recurrent AF outcomes of ablation and drug therapy. Time to second AF recurrence and AF burden will also be established. Freedom from AF after each ablation performed in an individual subject will be separately tracked.

2.2.5 Cost / Economic Impact

AF is responsible for almost 500,000 in-patient hospitalizations in the US every year and several billion dollars of excess health care expenditures. For patients, AF increases medical spending from 9-22 times that of comparable patients without AF, and this effect is likely to have even greater impact on health care spending in the future given the growth in number of AF patients expected and the increasingly complicated therapies used for these patients. As part of CABANA, we will examine the economic impact of AF ablation using state-of-the-art techniques.

2.2.6 Quality of Life

AF also causes significant impairment of quality of life, at a level between that of an MI and heart failure. Preliminary case control data further suggest that ablative therapy for AF can restore QOL to levels comparable to age and sex matched general populations. Given the epidemic growth of this arrhythmia in an aging population, a more effective therapy offers the potential to relieve suffering in a growing number of US citizens. Therefore, QOL assessment must be included in this trial.

2.2.7 Adverse Events

This trial must provide a clear delineation of the "down side" of therapy and track serious untoward events unique to each approach. Although strict comparisons will be difficult because of therapy-specific adverse events, additional analyses will look at each event type descriptively. With drug therapy, unanticipated heart failure hospitalization, pro-arrhythmic events, amiodarone pulmonary toxicity, and disabling stroke remain most concerning. For AF ablation the adverse events of greatest concern include pulmonary vein (PV) stenosis, atrial-esophageal fistula formation, and disabling stroke occurrence with ablative therapy. Of note, we will also track descriptively other complications and adverse events of both therapies and these will be recorded. We anticipate that the rate of serious adverse events will be similar in both treatment arms, although the specific complications will vary in type and extent.

2.2.8 LA Size and Function

The impact of long-term drug or ablative therapy on LA size and function is unknown [83-89]. Further, the relationship between structure and function measures and morbidity and mortality have not been examined. In addition to screening for PV stenosis, the CT / MR studies will examine these questions in both drug and ablation patients and provide mechanistic information above and beyond descriptive long-term outcomes data.

3.0 Subject Selection

The intent of the CABANA trial is to enroll patients who have new onset or under-treated paroxysmal, persistent, or longstanding persistent AF who ***warrant therapy*** for their arrhythmia. The vast majority of patients will be sufficiently symptomatic to cross the "therapy threshold" to active rate or rhythm control. Asymptomatic patients will be less common, but may be enrolled, if their AF is jeopardizing ventricular function, felt to be aggravating underlying disease, or requiring therapy to prevent sequelae of AF. Each patient will be screened for the inclusion/exclusion criteria listed below, which are similar to those of the AFFIRM trial [64].

3.1 Inclusion Criteria

To be eligible for the trial, subjects must meet all of the following criteria:

1. Over the preceding **6** months have:
   a) ≥2 paroxysmal (***electrocardiographic documentation*** of at least 1) AF episodes lasting ≥1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48h of AF onset): or
   b) ***electrocardiographic documentation*** of 1 persistent AF episode: (sustained for ≥7 days or cardioversion is performed more than 48h after AF onset): or
   c) ***electrocardiographic documentation*** of 1 longstanding persistent AF episode: (continuous AF of duration >1 year).
2. Warrant active therapy (within the past 3 months) beyond simple ongoing observation
3. Be eligible for catheter ablation and ≥2 sequential rhythm control and/or ≥2 rate control drugs.

4. Be ≥65 yrs of age, or <65 yrs with **one or more** of the following risk factors for stroke: Hypertension (treated and/or defined as a BP >140/90 mmHg) [90], Diabetes (treated and/or defined as a fasting glucose ≥126 mg/dl) [91], Congestive heart failure (including systolic or diastolic heart failure), Prior stroke, TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size >5.0 cm (or volume index ≥40 cc/m^2), or EF ≤35. Subjects <65 yrs of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify.
5. Have the capacity to understand and sign an informed consent form.
6. Be ≥18 years of age.

NOTE: Subjects may have recent onset AF (in the past 4-6 months), AF present for a longer time period, or may have been treated with a single anti-arrhythmic drug, providing they remain realistically eligible for ≥2 membrane active drugs and/or ≥2 rate control agents. Patients receiving new drug therapy initiated within the previous 3 months may continue that therapy if randomized to the drug therapy arm. Reasonable expectation of a response to therapy must be present. Subjects will not be excluded because of advancing age or underlying heart disease. Subjects with a history of a single episode of paroxysmal AF do not meet the "crossing the threshold/warranting therapy" litmus test. Subjects with persistent or long-standing persistent AF will require at least 1 documented episode, if it is of sufficient clinical importance that drug or ablative therapy is warranted. Subjects can be randomized before cardioversion, even if restoration of sinus rhythm is a desired endpoint of therapy. Patients may have documented atrial flutter in addition to atrial fibrillation and remain eligible for enrollment.

3.2 Exclusion Criteria

If a subject has ***any*** of the following criteria, he or she may not be enrolled in the study:

1. Lone AF in the absence of risk factors for stroke in patients <65 years of age
2. Patients who in the opinion of the managing clinician should not yet receive any therapy for AF
3. Patients who have failed ≥2 *membrane active* anti-arrhythmic drugs at a therapeutic dose due to inefficacy or side effects (Table 5.2.2)
4. An efficacy failure of full dose amiodarone treatment ≥8 weeks duration at any time
5. Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma
6. Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months
7. Hypertrophic obstructive cardiomyopathy (outflow track)
8. Class IV angina or Class IV CHF (including past or planned heart transplantation)
9. Other arrhythmias mandating anti-arrhythmic drug therapy (i.e. VT, VF)
10. Heritable arrhythmias or increased risk for torsade de pointes with class I or III drugs
11. Prior LA catheter ablation with the intention of treating AF
12. Prior surgical interventions for AF such as the MAZE procedure
13. Prior AV nodal ablation
14. Patients with other arrhythmias requiring ablative therapy
15. Contraindication to appropriate anti-coagulation therapy
16. Renal failure requiring dialysis
17. Medical conditions limiting expected survival to <1 year
18. Women of childbearing potential (unless post-menopausal or surgically sterile)
19. Participation in any other clinical mortality trial (Participation in other non-mortality trials should be reviewed with the clinical trial management center)
20. Unable to give informed consent

NOTE: Exclusion Criterion #3 includes failed membrane active antiarrhythmic drugs started within 3 months prior to enrollment. Prior ablation of the cavo-tricuspid isthmus alone is not an exclusion if the patient develops subsequent recurrent AF. Planned atrial flutter ablation in combination with the left atrial ablation is not an exclusion.

4.0 Overview of Study

4.1 Trial Design and Time Line

This multi-center study will randomize 2000-2200 patients in a 1:1 fashion to a strategy of catheter ablation vs. state-of-the-art drug therapy with either rate or rhythm control, as outlined in Figure 2. Each patient will have untreated or incompletely treated AF, which in the opinion of the investigator warrants therapy. CABANA enrollment will occur over approximately 4 years.. All CABANA patients will be followed an average of approximately 5 years. Assuming criteria for early termination are not reached, the major trial results are expected to be reported in early 2018.

This study will be conducted in accordance with current United States Food and Drug Administration (FDA) Regulations and guidelines, the European Clinical Trials Directive and associated guidelines, International Conference on Harmonization guidelines on Good Clinical Practice, the principles of the Declaration of Helsinki, as well as all other applicable national and local laws and regulations.

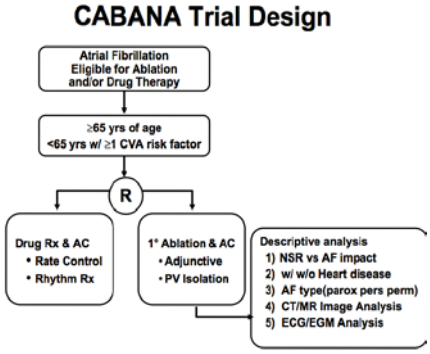

Figure 2

4.2 Screening and Pre-randomization Procedures

Study personnel will assess each subject against each inclusion and each exclusion criterion and the Investigator will determine the subject's eligibility for study participation. The principal investigator or documented members of the research team approved by local Institutional Review Board (IRB) or Ethics Committee (EC) will discuss the underlying rationale for the study, the procedures to be followed, the potential benefits and risks, and other issues mandated by the consent process. The informed consent process and all assessments will be documented in the subject's medical record or comparable source document. Baseline functional status, economic data (including two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer" and asking 5 brief questions), and quality of life data (including a Baseline Questionnaire of validated scales, ie, SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, AF Effects on QOL (AFEQT), Work Productivity and Activity Impairment Instrument (WPAI), Stanford Presenteeism scale and Mayo AF Symptom Index (MAFSI)) will be collected by the Site Coordinator via structured interview prior to randomization.

4.3 Enrollment and Randomization

Eligible patients, who have given written, informed consent and meet all inclusion with no exclusion criterion will undergo 1:1 randomization in an unblinded, parallel arm treatment format to a strategy of drug therapy for rate or rhythm control vs. catheter ablation. Randomization will be accomplished by telephone or internet using a centralized, interactive voice and web

randomization system (IXRS). The enrollment scheme is based on permuted block randomization with stratification by clinical site.

4.4 Post Randomization Procedures

For morbidity and mortality end points, intention-to-treat analysis will begin at randomization. All therapies will be established and optimized in a 3-month treatment initiation period, during which patients may receive alternative drugs or undergo repeat ablation if AF recurs. The duration of this "blanking period" is derived from standard clinical practice and the AF Ablation Consensus Document [50, 51]. Thereafter, therapy will be administered and patients followed for an average of approximately 5 years. Efficacy, (i.e. absence of AF recurrence) will be established by long-term follow-up beginning after the 3-month therapy initiation phase. Any AF occurring after the 3-month blanking period will be considered a treatment failure for the AF recurrence secondary endpoint. Patients will be followed at 6 and 12-month intervals from randomization throughout the trial.

4.4.1 Baseline Testing

Defining the eligibility of patients for the CABANA Trial will require information generated during the course of routine clinical care as dictated by their attending physician. This information should be, consistent with established guidelines, consensus documents, and good clinical practice. Selected baseline testing data will be collected in order to characterize the type, cause and severity of the patient's AF and the treatments received prior to enrollment. The baseline data will include information from the following clinical evaluations:

1. Relevant medical history including prior and current drug treatment of AF
2. Relevant physical examination
3. 12 lead ECG prior to treatment
4. Blood Tests (INR, creatinine, hemoglobin / hematocrit) (pre-treatment)
5. Trans-thoracic 2-D echocardiography

The trans-thoracic echocardiographic (TTE) data will be used to characterize the substrate underlying the patient's AF, establishing the presence of LV dysfunction (LVEF), hypertrophy, diastolic dysfunction, or other structural abnormalities. The TTE will also assess LA size and volume, and provide measures of atrial function.

Following a recommended approach consistent with established guidelines, consensus documents, and good clinical practice, a trans-esophageal echocardiographic (TEE) study will be performed within 24 hours prior to ablation in patients with *persistent or longstanding persistent* AF. The TEE may be performed up to 48 hours before the procedure in patients on continuous anticoagulation therapy, such as warfarin at a therapeutic INR or in those appropriately bridged with intravenous un-fractionated or low molecular weight heparin.

The performance of a pre-treatment TEE in patients with *paroxysmal* AF is left to the discretion of the investigator (5.4.4), but is not required in CABANA. Data on the performance and results of all TEEs performed as part of routine care will be collected in the eCRF, however. TEE data may also be used to confirm atrial size and morphology. The approach to cardioversion in drug treated patients should follow the recommendations of AF Treatment Guidelines [92].

In those centers where routine clinical practice includes the performance of pre-ablation and post-ablation CT/MR studies, relevant data from these studies will be collected to serve as a baseline for comparative quantitative LA size, morphology, and function studies, as well as

subsequent follow-up PV and esophageal investigations. In addition at those centers, up to 150 patients randomized to drug therapy will be asked to undergo one research CT/MR scan prior to initiating therapy. This will allow the CABANA study to evaluate and compare atrial structure and function in response to drug or ablative therapy. These drug-treated patients will be recruited from selected centers that are committed to CT/MR assessment of all enrolled patients (both study arms). Since randomization is performed (stratified) within each site, this component of the study will still benefit from the overall study randomization. Optimally, the pre-therapy scans performed in all patients should be within 4 months prior to treatment.

In addition to these clinically dictated studies, baseline economic and QOL data will be obtained after informed consent is obtained, but before randomization occurs.

4.4.2 Patient Follow Up

Follow-up in all patients will occur at 3, 6, and 12 months following randomization during the first year and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below. Economic and QOL data, including a full follow-up questionnaire of validated scales, ie, SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, AF Effects on QOL (AFEQT), Work Productivity and Activity Impairment Instrument (WPAI), Stanford Presenteeism scale, will be repeated by trained telephone interviewer staff from the EQOL Coordinating Center (EQOL CC) for patients enrolled in North America and by the Site Coordinator in sites outside North America.

Follow-up visits/calls at 3 and 6 months should be completed within 30 days +/- of the due date (Ex: 3 month visit: completed between 60 days and 120 days of randomization).

Follow-up visits/calls at 12 months and every 6 months thereafter should be completed within 60 days +/- of the due date (Ex: 12 month visit: completed between 300 days and 420 days of randomization).

Medical bills for patients enrolled at US sites will be collected throughout the trial by the EQOL Coordinating Center economic team. The Site Coordinators will complete a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim hospitalizations and/or ER visits since last contact. These forms will be forwarded to the EQOL Coordinating Center for processing. As part of the economic and QOL data in CABANA, two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer", asking 5 brief questions and Mayo Atrial Fibrillation Symptom Index (MAFSI) will be collected by the Site Coordinator at 3 and 12 months following randomization during the first year and yearly thereafter throughout the trial and entered into the e-CRF.

After enrollment, subjects will either receive a single 'CABANA Box' recording system to be used throughout the entire study, or will be followed using ambulatory event and Holter ECG monitoring as generated during the course of routine clinical care as dictated by their attending physician.

At sites where the 'CABANA Box' has received appropriate approval, all patients enrolled will receive a single 'CABANA Box' recording system to be used for both patient activated event monitoring (throughout the trial), 24 hour autodetect/autocapture (AD:AC) event monitoring and 96 hour full disclosure Holter monitoring throughout the study. During year one, subjects will be asked to record their heart rhythm each month. After the first year, they will be asked for a 24 hour recording twice a year and a 96 hour recording twice a year. Fingertip recordings as well as AD:AC recordings can be transferred via telephone download from the patient's home to the

CABANA monitoring center. Holter recordings will require downloading of information at the enrolling site for data transfer to the CABANA monitoring center. All recordings will be made available to the enrolling center for use in clinical practice.

Follow up monitoring with an alternative system will be required in centers unable to use the "CABANA Box".

CT/MR imaging studies will be performed where clinically indicated or otherwise part of routine clinical care on ablation subjects after ablation therapy (between 90 days post ablation and the 6 month follow-up) and as indicated for PV stenosis management throughout the trial. The 150 drug therapy patients that received the CT/MR scan prior to initiating drug therapy, will also undergo one research CT/MR scan after therapy is fully established (between 90 days post drug treatment initiation and the 6 month follow-up). CT/MR data will be electronically transferred to a server at the Mayo Biomedical Imaging Resource, the CABANA Trial Image Analysis Lab. Scans will be anonymized at the site using a software tool provided by the Imaging Center. Each clinical center will also perform standard site radiology evaluation and assessment of the CT/MR images according to the sites' standard clinical practice.

After completion of the 60 month follow-up, subjects will be asked to extend their participation. If agreed upon, subjects will be asked about their current state of health and any clinical events every 6 months by telephone until the last subject enrolled reaches approximately 36 months follow-up.

Follow-up data will also be obtained at the time of treatment discontinuation, with a crossover in treatment strategy, and at the emergence of any primary or secondary endpoints.

4.4.3 Schedule of Assessment

Assessments	Baseline	Post Therapy	Mo 3	Mo 6	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36	Mo 42	Mo 48	Mo 54	Mo 60	Extended every 6 months
			(+/-) 30 days		(+/-) 60 days									(+/-) 60 days
Medical history Office visit	X		X		X		X		X		X		X	
Medical history Office visit OR phone follow-up				X		X		X		X		X		X
Review Past/Current Medications	X	X(5)	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X			X		X		X		X		X		
Blood Tests (INR, creatinine, hemoglobin, hematocrit)	X													
12 Lead Electrocardiogram (ECG)	X	X(5)												
Transthoracic 2-D Echocardiogram	X													
Trans-esophageal Echocardiogram (1) (2)	X													

Assessments	Baseline	Post Therapy	Mo 3	Mo 6	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36	Mo 42	Mo 48	Mo 54	Mo 60	Extended every 6 months
			(+/-) 30 days		(+/-) 60 days									(+/-) 60 days
CT/MR Evaluation (1) (3)	X		X(4)											
CABANA Box/Ambulatory Monitor Symptom Event Recording		Throughout the 60 month follow-up periods when Atrial Fibrillation symptoms are present												
CABANA Box/Ambulatory Monitor 24-Hour Holter / AC;FD (monthly during Year 1)	X	Monthly / 1,2,3,4,5,7,8,9,10,11				Every 6 months / 15,21,27,33,39,45,51,57								
CABANA Box/Ambulatory Monitor 96-Hour Holter				X	X	X	X	X	X	X	X	X	X	
Economic and QOL Survey SF36, DASI,	X		X		X		X		X		X		X	X
Economic and QOL Survey Toronto AF Severity Scale AFEQT, WPAI, Stanford Presenteeism	X			X		X		X		X		X		X
AF Severity/Symptom Check List MAFSI, EQ5D	X		X		X		X		X		X			X
Review Adverse Events	X	X(5)	X	X	X	X	X	X	X	X	X	X	X	X

(1) Ablation therapy subjects;
(2) Or as warranted throughout trial;
(3) 150 subjects randomized to Drug Therapy;
(4) 3 months following therapy initiation = end of blanking period. Or as indicated for PV stenosis
(5) Hospital discharge or following Drug Therapy initiation

All procedures and laboratory tests during follow-up should be performed whether or not a subject receives treatment according to the protocol.

5.0 Treatment Arms

5.1 Description of Treatment Arms

5.1.1 Treatment Strategies

Rather than comparing a specific drug therapy against any specific ablative intervention, CABANA compares two treatment strategies. The first is that of medical therapy with the intention of controlling AF rhythm or rate. The second strategy is that of ablative intervention designed to eliminate AF. The following guidelines will shape therapy selection and implementation.

5.2 Pharmacologic Approach to AF (Drug Therapy)

It is recommended that drug treatment patients first receive rate control medication and the effect on ventricular response during the blanking period documented. Medication use must conform to the Guidelines for Management of Subjects with AF published in 2006 by the ACC/AHA/ESC [92]. Approved drugs and minimum dosing guidelines are as specified below.

5.2.1 Drugs Approved for Rate Control

Drug	Administration	Minimum recommended daily dosage
Digoxin (Lanoxin)	Oral	0.125-0.25 mg
Beta Blockers		
Metoprolol (Toprol)	Oral	50-100 mg
Atenolol (Tenormin)	Oral	50-100 mg
Propranolol (Inderal)	Oral	40-80 mg
Acebutolol (Sectral)	Oral	200-300 mg
Carvedilol (Coreg)	Oral	6.25-25 mg
Nebivolol (Bystolic)	Oral	5-40 mg
Bisoprolol (Monocor)	Oral	2.5-20 mg
Ca Channel Blockers		
Diltiazem (Cardizem)	Oral	180-240 mg
Verapamil (Calan)	Oral	180-240 mg

Patients without other heart disease receive beta or calcium channel blockers as first line rate control therapy [95]. Patients with coronary artery disease or heart failure will receive beta-blockers. Patients with ventricular hypertrophy not warranting exclusion would receive either beta- or calcium channel blockers, while patients with heart failure will receive carvedilol, bisoprolol, or metoprolol. Rate control medications may be used in combination and doses adjusted to achieve resting heart rates <80 bpm and exercise heart rates on 6 minute walk or Holter monitoring <110 bpm [28, 92]. These criteria will also be insured by clinical activity assessment in patients capable of exercise, as monitored by the patient's clinical cardiologist.

5.2.2 Drugs Approved for Maintenance of Sinus Rhythm

Drug	Administration	Minimum recommended daily dosage	Type/Level
Propafenone (Rhythmol)	Oral	450-625 mg	1C/B
Flecainide (Tambocor)	Oral	200-300 mg	1C/B
Sotalol (Betapace)	Oral	240-320 mg	Class III/ A
Dofetilide (Tikosyn)	Oral	500-1000 mcg	Class III/A
Amiodarone (Cordarone)	Oral	200-400 mg	Class III/B
Quinidine (Quinaglute/ dex)	Oral	600-900 mcg	Class I, III/B
Dronedarone (Multaq)	Oral	800 mg	Class III

At the documentation of failure of rate control using AFFIRM [28] and AF CHF [43] criteria, or if the patient has previously failed rate control by these criteria or remains symptomatic despite AV nodal blockers, rhythm control may be started using a membrane active drug in an approach consistent with the recommended Guidelines for Management of Subjects with AF [92]. Each patient will be placed on an anti-arrhythmic drug for an appropriate period and cardioverted to sinus rhythm if necessary. During the 3 month therapy initiation period, dosage adjustments can be made or the drug replaced with a different rhythm control drug. In general, patients with no other heart disease may be treated with propafenone, flecainide, sotalol or dofetilide. Patients with underlying ischemic heart disease or isolated diastolic dysfunction may/can be treated with sotalol, dofetilide, or amiodarone. Patients with underlying heart failure can be treated with dofetilide or amiodarone. Multaq (dronedarone) should not be used in patients with NYHA IV heart failure, or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. Background therapy with upstream

ACE-I / ARBs, statins, fish oil, and aldosterone antagonists will also be encouraged and tracked at each follow-up.

5.2.3 Drugs for Future Consideration

It is anticipated that other rate control agents and membrane-active anti-arrhythmic drugs may become available over the course of the trial. Since a chief aim of the trial is to provide relevant, up-to-date information for guiding drug and ablative therapy for AF, these new treatment strategies will be incorporated in CABANA once approved by the CABANA Innovative Drug Therapy and Executive Committees. Drugs which have been approved by appropriate regulatory agencies outside of the United States may be used within that jurisdiction.

5.2.4 AV Nodal Ablation

Ablation of the AV conduction system may be considered as an alternate measure in patients with inadequate rate control refractory to at least 3 rate control agents or 2 membrane-active anti-arrhythmic drugs.

5.2.5 Changing Drug Therapy

During follow-up, patients may have recurrent AF, which constitutes an endpoint for the AF Recurrence secondary endpoint. Nevertheless, these patients will continue to be followed throughout the study to establish the occurrence of the primary and the secondary composite endpoints. These patients may require other drug therapy, which can be instituted during follow-up, without patient withdrawal from the trial.

5.2.6 Cross-Over to Ablative Therapy

During follow-up, drug arm patients with recurrences may be treated with additional anti-arrhythmic drugs or alternative rate control agents. Of note, most patients included to date in single center trials were treated for over one year before undergoing ablation. Thus, it is anticipated that most patients will be treated for at least 12 months in the drug therapy arm and that patients will be fully informed of this at the time of the consent process. Cross over ablative intervention is strongly discouraged. **Crossovers must be approved by the CABANA Trial Administrative Center. Before approval is granted for a patient randomized to drug therapy to be crossed over to ablation,** sites will be required to provide rationale and documentation that drug therapy options have been exhausted.

5.2.7 Compliance with Treatment Protocols /Site Performance

The success of the trial will be enhanced by careful consideration of 1) participating Site Qualification, 2) Procedure Standardization, 3) Site performance, and 4) Follow-up tracking. High standards in each of these areas will provide the greatest assurance that optimal, protocol-dictated therapy is being delivered and that patients have the best opportunity of responding to it. Each site will be required to provide documentation of expertise in the medical management of AF, including at least 2 of the following: 1) successful participation in AFFIRM, RACE, STAF, PIAF or other multi-center clinical trials; 2) medical management of at least 30 patients with AF; 3) site expertise in clinical practice, research, or quality assurance registries or databases; 4) an active AF clinic; or 5) treatment of >20 patients with sotalol, dofetilide or amiodarone. Patient compliance with medical therapy in rate control patients will be judged from achievement and maintenance of rate control targets noted in Section 5.2. Rates of sinus rhythm among rhythm control patients in the medical arm will be monitored and benchmarked against recent clinical trials including AFFIRM, AF CHF and ATHENA. Frequent phone contacts and newsletters will encourage compliance during the therapy initiation phase. These communications will then be continued regularly during the follow-up phase. Since we desire participation by a true cross section of individuals with AF, enrollment will not be based on availability of health insurance.

The IDE: G050233 approval establishes the approach of this trial as a CMS B2 therapy. As has been seen in the Pilot Study, the therapies in this trial can be billed to Medicare/3rd party payers.

5.3 Primary Catheter Ablation for AF (Ablation Therapy)

5.3.1 Pre-ablation Assessment

Pre-ablation assessment using standard practice patterns as outlined in the AF Ablation Consensus and Venice Chart Documents [50,51], will provide baseline data for safety and efficacy outcomes analyses. All patients who are randomized to ablative intervention will also undergo baseline CT or MR scanning. These studies will form the basis for comparisons of change in LA function with ablative or drug therapy.

5.3.2 Ablation Therapies

A potential limitation of any trial examining ablative intervention for AF is the number of different methodologies used for the primary curative ablation. The NHLBI Work Group on AF Ablation, the AF Ablation Consensus [50] and the Venice Chart [50] documents all agreed that pulmonary vein (PV) isolation is the starting point for AF ablation. PV isolation is therefore the minimum required ablation procedure for every patient in the trial. This may be a variation of: 1) Circular mapping catheter-guided ablation as described by Haissaguerre et al. [50, 93, 94], 2) Antral Isolation using a circular-guided approach as described by Natale et al. [95, 96], or 3) Wide area circumferential ablation [48, 97, 98]. As described in the AF Ablation Consensus Documents [50, 51], the approach in most expert ablation centers has evolved toward larger circumferential ablation outside the PVs. The selection of ablation guidance systems (circular mapping catheters, fluoroscopy, mapping systems and intracardiac ultrasound) is left to the discretion of the site PI, providing that site has performed at least 100 AF ablation cases with that approach. The acute endpoint of ablation is the isolation of all PVs.

Adjunctive procedures such as enlarging the field of ablation for the targeting of complex fractionated atrial electrograms [47], sites of apparent ganglia [99], or the use of additional linear lesions is allowed, but only after wider area or antral PV isolation. The methods for each of these are as outlined in the AF Ablation Consensus Document [50]. Each ablative approach and adjunctive measures will be carefully tracked to establish overall contribution to outcomes. Additional factors such as 1) termination of AF with ablation, 2) non-inducibility with atrial stimulation, and 3) absence of immediately recurrent AF with 10-20 mcg/min of isoproterenol, although controversial, will be tracked. Of note: ablation of the AV conduction system is not considered an alternative for primary ablative intervention.

5.3.3 Approved Ablation Devices

The specific choice of ablation catheters is left to the investigator, but must be one or more of the catheters listed below (see also Appendix B). Catheters which have been approved by appropriate regulatory agencies outside of the United States may be used within that jurisdiction.

Manufacturer	Catheter	Reference#
St. Jude Medical	Livewire TC™ XLS™	P960016
St. Jude Medical	Therapy™ Dual / Thermocouple	P040014
St. Jude Medical	Therapy Cool Path	P060019
Biosense Webster	NAVI-STAR / NAVI-STAR DS	P990025 / P010068
Biosense Webster	Celsius Braided Tip / Long Reach	P950005
Biosense Webster	NAVI-STAR Thermo-Cool	P030031
CryoCath	Freezor® / FreezorMax	P020045

Manufacturer	Catheter	Reference#
Bard	Stinger	P000020
Boston Scientific	Blazer II RF / RPM / SteeroCath /XP	P920047 / P020025
Boston Scientific	Chilli Cooled	P980003

5.3.4 Approaches for Future Consideration

Undoubtedly, primary ablative intervention for AF will evolve over the course of this trial. In order to maximize the potential for the generalizability of CABANA findings to the broader area of AF ablation, newly evolving methods or devices will be permitted, as approved by the Innovative Ablation Therapies / Executive Committees.

5.3.5 Cross-over to Drug Therapy

Patients with recurrent AF during the blanking period can be maintained on anti-arrhythmic drug therapy, although this should be discontinued by the end of the 90-day monitoring period. Subsequent AF recurrence will be considered an endpoint for the AF freedom endpoint. Those who are highly symptomatic may subsequently receive anti-arrhythmic drug therapy, but will be followed on an intention-to-treat basis as part of the ablation treatment group for primary and secondary endpoint assessments.

5.3.6 Compliance with Treatment Protocols /Site Performance

CABANA ablation sites must be pre-qualified for participation by 1) demonstration that each site has performed $\geq$100 primary AF ablations and 2) satisfactory completion of review of performance-confirming site data by the CABANA Ablation Therapies Committee including: 1) 5 prior ablation reports; 2) demonstration of an adequate prior ablation database to establish the CABANA patient's position in the site's overall series; 3) evidence of acceptable standard follow-up practices and data collection methods; 4) 5 pre and post lasso electrograms establishing acute PV isolation success; and 5) 5 prior Carto/NavX maps showing mapping proficiency. Taken together, these will provide validation of AF ablation expertise.

Site ablation performance will be tracked throughout the trial. Ablation data including ongoing acute success rates in achieving PV isolation, ablation time, fluoroscopy time, and ablation methods captured by ablation eCRFs will be tabulated by the Data Coordinating center. Outliers will be identified for special review. Exact ablation methods, complications, and compliance with the protocol will be reviewed by the DCRI monitors and a member of the Ablation Therapy Committee. Timeliness and accuracy of eCRF data entry will also be monitored.

5.4 Guidelines for Anti-thrombotic Therapy

5.4.1 Guidelines for Anticoagulation in Drug Treated Patients

Patients with risk factors for CVA or peripheral thromboembolic events at the time of enrollment, treated with rate control agents alone, will remain on active anticoagulation therapy (warfarin, dabigatran, rivaroxiban or apixaban) throughout the duration of the trial [92]. Unlike the AFFIRM trial, patients receiving rhythm control therapy will also be required to receive adequate anticoagulation (warfarin, dabigatran, rivaroxiban or apixaban) for the duration of the trial. In the use of warfarin therapy, target INRs of 2 to 3 will be required, unless higher INRs are mandated because of underlying disease.

5.4.2 Guidelines for Anticoagulation Therapy in Ablation Patients

Anticoagulation before, during, and after the ablative intervention will follow the guidelines of the AF Ablation Consensus Document [50]. Prior to the ablative intervention, patients with persistent and long-standing persistent AF should receive adequate anticoagulation (i.e. at least

one month of warfarin anticoagulation (INRs: 2-3)), or have a TEE excluding intra-atrial thrombus at the time of the intervention. During the ablative intervention, maintaining an ACT between 300 and 400 seconds is strongly recommended. Following the ablative intervention, patients will be started on IV heparin or subcutaneous injections of low molecular weight heparin beginning 4 to 6 hours after all sheaths are removed, and appropriate anticoagulation reinstituted the evening of the intervention. Thereafter, low molecular weight heparin is to be maintained until anticoagulated appropriately or standard dose warfarin achieves a target INR of 2 to 3, unless the ablation was performed at a therapeutic INR in patients maintained on warfarin through the ablation. One month following the ablation, dabigatran, rivaroxiban or apixaban may be substituted for warfarin, following recently written guidelines. Three to six months after ablation, warfarin may be replaced by full dose aspirin in patients with a CHADs score $\leq$1. This would include patients with hypertension without hypertrophy, or those <65 years of age, providing 1) atrial size and function are normal and 2) there is no symptomatic or asymptomatic AF by standard or full-disclosure monitoring. In those patients with a CHADs score $\geq$2, adequate anticoagulation is to be continued throughout the trial. Randomization of warfarin discontinuation is precluded by the low post-ablation stroke rates that would require at least 10,000 patients for detecting differences in stroke prevalence. Nevertheless, the characteristics, follow-up monitoring results, and long-term anticoagulation status of ablation patients will be compared to descriptively identify predictors of events and profiles of patients at high risk for warfarin discontinuation. The utility of trans-telephonic, auto-detection / full disclosure, and Holter monitoring, as a future aid in the decision to discontinue anticoagulation will also be critically examined.

5.4.3 Newer Antithrombotic Therapies

It is likely during the course of the trial that newer antithrombotic therapies non-inferior to warfarin or dabigatran will be approved. These agents may be used as replacement therapy for warfarin on approval of local regulatory agencies and the Innovative Antithrombotic Therapies/Executive Committees.

5.4.4 Items Left to the Discretion of the Physician

Specific items left to the investigators discretion include: 1) specific choice of rate control vs. rhythm control drug therapy and specific drugs to be used; 2) hospitalization to initiate anti-arrhythmic drug therapy; 3) choice of TEE guided direct current cardioversion (DCCV) vs. DCCV after 4 weeks of appropriate anticoagulation therapy, such as warfarin to an INR of 2-3; 4) pre-ablation TEE assessment in patients with simple paroxysmal AF and hypertension without hypertrophy; 5) continuation of warfarin to maintain a therapeutic INR at the time of catheter ablation; 6) selection of warfarin versus dabigatran, rivaroxiban or apixaban.

5.5 Management of Arrhythmia Recurrences During Follow-Up

During the 3 months of “therapy initiation”, patients randomized to drug therapy may receive alternative drugs. Patients in the ablation arm may undergo repeat ablation in those cases where the recurrent arrhythmia is not felt to be due to the irritation and inflammation of the ablative intervention. These patients may also be treated with rhythm control drug therapy, providing it is discontinued by the end of the blanking or “therapy initiation phase”. Any event occurring during this period will be tracked as an “Early Event”. Long-term follow-up with respect to efficacy will begin 3 months after the initiation of drug therapy or ablation therapy. These events will be used for the determination of overall freedom from recurrent AF, but will not be of sufficient importance to remove the patient from the trial. Patients achieving a secondary endpoint through non-fatal events will be followed throughout the remaining follow-up period.

6.0 Definitions & Adjudication for Study Endpoints

6.1 Primary Endpoints

The primary endpoint is the composite of total mortality, disabling stroke, serious bleeding or cardiac arrest. All components will be adjudicated by an independent Clinical Events Committee (CEC) and the most proximate cause of the event established. A Disabling Stroke will be considered present using a modification of a Rankin Stroke score [100], and will be adjudicated by a Neurologic Events Committee. Serious (or Life-threatening) bleeding will be considered present using a modification of the GUSTO bleeding Scale adapted for use in catheter ablation [101]. These events will be tracked regardless of treatment randomization. The definition for each of these events is listed in the CEC Charter. When there is disagreement between the CEC and the principal investigator, the CEC's decision will be considered final. Procedures for adjudicating events are described in the CEC Charter, which is available upon request. The CEC will also confirm whether a death is cardiac/vascular/non-cardiovascular in origin; as well as witnessed/un-witnessed; or sudden/non-sudden. Cardiac mortality will be further categorized as tachyarrhythmic, bradyarrhythmic, heart failure, or due to other cardiac causes using the events adjudication form. Hospitalization will also be tracked with specific reason for admission (heart failure, acute ischemic event, etc.) determined by the site principal investigator as reported in the eCRF.

6.2 Secondary Endpoints & Safety Endpoints

Secondary endpoint events, including total mortality and a composite of total mortality or cardiovascular hospitalization will be confirmed.
While hospitalization for any atrial fibrillation, atrial flutter or atrial tachycardia in both treatment arms will be carefully tracked and compared, it will be considered as an "*AF recurrence"* and counted against efficacy, not safety. Therefore, *AF recurrence and/or worsening of AF* ***need not*** *be reported as an adverse event.*

7.0 Adverse Events

Adverse events, defined as any undesirable medical occurrence in a clinical study patient which occurs during the course of the study and can be attributed to a device, procedure, or medications required *by a procedure, protocol, or trial* will be tracked throughout the study.

An adverse event (AE) will be considered present if 1) there are untoward signs, symptoms, illnesses, or other medical events that develop or worsen in severity during the course of the study, 2) they are clinically relevant *and* if they are clinically related to the study. Note: Disease, signs symptoms, and or laboratory abnormalities already existing at randomization are not considered adverse events unless they represent an intensity or frequency exacerbation. An adverse event designation should reflect the reason for a diagnosis or abnormal measurement. Procedures planned prior to randomization and the conditions leading to these measures are not adverse events.

An event inherent to an intervention/medication that is expected to occur for a projected duration in some or all subjects is considered unavoidable. Unavoidable adverse events will not be tracked during the trial (*examples: pain at catheter insertion sites during and after a procedure; pain at injection sites; palpitations; nausea due to anesthesia, etc*.).

The DCRI will evaluate any safety information that is spontaneously reported in the time frame specified in the protocol. For each subject, adverse events occurring after randomization must be recorded on the applicable Adverse Events page(s) in the electronic Case Report Form (eCRF). Recording should be done in a concise manner using standard, acceptable medical terms. The adverse event recorded should not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. It is the responsibility of the Principal Investigator to oversee the safety of the patients enrolled in the study at his/her site. This responsibility includes careful assessment and appropriate reporting of adverse events. The primary mechanism for reporting adverse events in CABANA is for study personnel at the clinical sites to enter the relevant information and the details and description of each event using the adverse event forms that are part of the InForm electronic data capture (EDC) system being used in the trial.

Again, *AF recurrence and/or worsening of AF* ***need not*** *be reported as an adverse event.*

7.1 Adverse Event Classification

The investigator will evaluate all AEs with respect to seriousness, severity (intensity), and causality (relationship to study therapy or device) according to the following definitions and guidelines:

7.1.1 Anticipated Adverse Events

An anticipated event is one that has been identified in previous studies, published literature, or product labeling to be related to the disease state or therapies. A listing of commonly occurring 'anticipated/expected' events in the population being studied can be found in Appendix A. An unanticipated/unexpected adverse event is any adverse event that has not been reported in previous studies, published literature, product labeling, or which is not anticipated in the population being studied (see appendix A).

7.1.2 Serious Adverse Event

An adverse event that warrants additional action, includes *any* untoward event that:

1. Is fatal
2. Is life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization >48 hours. Exceptions- therefore not reportable:
    a. Preplanned (prior to the study) hospital admissions unless the hospitalization is prolonged >48 hours beyond the anticipated length of stay.
    b. Planned admissions (as part of a study – e.g. admission for drug change or titration for treatment of atrial fibrillation)
    c. 23 hour hospitalizations OR observation.
    d. Hospitalization for elective procedure (e.g. cardioversion).
    e. Emergency room visits that do not result in hospitalization.
    f. Hospitalization to titrate or optimize medical therapy to treat recurrence of atrial fibrillation.
4. Results in persistent or significant disability or incapacity.
5. Results in a congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life-threatening, or require inpatient hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3 Adverse Event Intensity or Severity Classification

The intensity or severity of each AE will be classified according to the following guidelines:

1. **Mild**: Any event that results in minimal transient impairment of a body function and does not threaten damage to a body structure, and/or does not require intervention other than monitoring (easily tolerated).
2. **Moderate**: Any event which results in moderate transient impairment of a body function or damage to a body structure, or which requires intervention.
3. **Severe**: Any event which is life threatening, results or could result in significant permanent impairment of a body function or damage to a body structure, requires significant and timely intervention to prevent permanent impairment of a body function or damage to a body structure, or which is intolerable or places the subject at immediate risk of harm.

7.1.4 Causal Relationship to Medical or Ablative Therapy

The International Council of Harmonization (ICH) Guidelines (1995) indicate that "reasonable causal relationship" means that "there are facts [evidence] or arguments to suggest a causal relationship." The causality assessment must be made by the investigator based on information available at the time that the adverse event eCRF is completed. The initial causality assessment may be revised as new information becomes available.

1. **Definitely related**: there is a reasonable temporal relationship to study therapy or device
    a. follows a known response pattern (e.g., study drug, treatment or device is known to cause this AE)
    b. there is no alternative etiology or explanation for the event
2. **Probably related**: there is a reasonable temporal relationship which
    a. follows a suspected response pattern
    b. no evidence for a more likely alternative etiology though could be unrelated
3. **Possibly related:** there is a reasonable temporal relationship but
    a. equivocal evidence that the event is study related as opposed to an alternative etiology
4. **Probably not related:** there is not a reasonable temporal relationship OR
    a. good evidence for a more likely alternative etiology
5. **Not related:** there is not a temporal relationship OR
    a. clear and compelling evidence that the event is due to an alternative etiology

7.1.5 Device Related Adverse Events

1. **Device-related:** any adverse event for which a causal relationship between the device and the event is a reasonable possibility. The likelihood that the event is device related will also be sub-classified using the approach in 7.1.4 above. The event will be further classified as whether it is a device failure or malfunction (7.1.5.2) and whether it is unanticipated (7.1.5.3), as described in these sections.
2. **Device Failure or Malfunction:** a device has failed if it is used in accordance with the Instructions for Use, but does not perform or function according to Instructions for Use and negatively impacts the treatment by preventing treatment as intended. Such a failure does not necessarily result in significant adverse outcome.
3. **Unanticipated Adverse Device Effect (UADE):** any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or prior medical literature, or any other unanticipated serious problem

associated with a device that relates to the rights, safety, or welfare of subjects. This event needs to be entered into the eCRF SAE pages within 24 hours of the site's knowledge.

7.2 Adverse Event Reporting

The goal is to have an adverse event reporting process that is (a) clear and simple for site investigators and study coordinators to understand and implement, (b) satisfies all regulatory reporting requirements, (c) eliminates any duplication in data collection and reporting, and (d) has a balanced focus on both the drug and ablation arms of the trial.

All related adverse events, serious and non-serious, that occur between the time of randomization and the last study-related procedure/visit will be followed until resolution, stabilization, or to trial completion. Adverse events for subjects who discontinue study participation at any time during the study should be collected/reported through at least the time of discontinuation. In addition, the required Institutional reporting structure will be followed and/or as described in this protocol.

7.3 Serious Adverse Event Reporting

Regardless of causality, the investigator will record all serious adverse events occurring between randomization and the last study-related procedure/visit or completion of the trial into the electronic database within 24 hours of knowledge of the event. DCRI will report all unanticipated/unexpected study related serious adverse events to Mayo Clinic, NHLBI and the DSMB chair within 2 business days of receipt.

The investigator must update the eCRF SAE when important follow-up information (final diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial entry. Follow-up information should be entered within forty eight (48) hours of knowledge. All reportable events will be followed until resolution, stabilization, or to trial completion, whichever occurs first. In addition, the required Institutional reporting structure will be followed and/or as described in this protocol.

7.4 Expedited Event Reporting

Specified events as listed below that meet ***serious*** criteria (see section 7.1.2 of the protocol), are ***related (***possibly/probably/definitely) to either study drug or the ablation device or procedure, and are ***unanticipated/unexpected*** if occurring between randomization through completion of follow-up (end of trial) require ***expedited*** reporting to the DCRI and in turn to the appropriate regulatory agencies.

7.4.1 Expedited events include:

1. Unexpected, SAE related to study drug
2. Unanticipated ablation procedure related events
3. Unanticipated Adverse Device Effect (UADEs)
4. Device failures or malfunctions
5. **Events of Interest (EOI)**: Drug or ablation therapy or ablation procedure related events (index and/or follow-up): The related events that resulted in death, and the following events if they are life-threatening or severe in nature; pro-arrhythmic events, myocardial perforation / tamponade requiring intervention, esophageal atrial fistula, and/or severe pulmonary vein stenosis that were life threatening or classified as severe in nature.

7.5 Adverse Event Documentation

All AEs and SAEs must be documented on the appropriate eCRF. The outcome of each AE and SAEs will be tracked through the major endpoints of the trial, if present. Otherwise these events will be tabulated and addressed descriptively, as gleaned from the eCRF.

Expedited Events must be entered on the appropriate eCRF pages or if the electronic database is unavailable for more than 24 hours, the event would be reported on an *Expedited Event Form* and faxed/emailed to DCRI Safety Surveillance within 24 hours of knowledge of the event. When available, the event must be entered into the electronic data base.

DCRI Safety Surveillance

Telephone: 1-919-668-8624

Toll Free: 1-866-668-7799

Email: Safetysurveillance@mc.duke.edu

Fax: 1-919-668-7138

Toll Free Fax: 1-866-668-7138

It is understood that complete information about the event may not be known at the time the initial report is submitted. The investigator must assess the relationship of the event to the study device or study therapy and should make every attempt to obtain as much information as possible concerning the event. Additional information pertaining to an expedited event should be submitted to DCRI Safety Surveillance as it becomes available. All reported events will be followed until resolution, stabilization, or until the trial completion whichever occurs first.

7.6 Reporting to Regulatory Authorities

7.6.1 Physician Reporting of Drug or Device Adverse Events

Physician reporting of drug or device-related unexpected/unanticipated serious adverse events (as mandated by regulatory authorities) using MedWatch or Council for International Organizations of Medical Sciences (CIOMS) forms, should continue independently of any CABANA reporting.

It is anticipated that pphysicians and/or the appropriate healthcare professional will complete this reporting by, 1) MedWatch- submit form 3500 for drug or device via the FDA's MedWatch Adverse Event Reporting program online at www.fda.gov/MedWatch/report.htm, by phone 1-00-FDA-1088, or by returning the postage-paid FDA form 3500 downloaded from ww.fda.gov/MedWatch/getforms.htm by mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787 or fax 1-800-FDA-0178, 2) CIOMS- using http://www.cioms.ch/index.htm, postal address: c/- World Health Organization, Avenue Appia, 20 CH - 1211 Geneve, 27 Switzerland, telephone: +41 (0) 22 791 34 13 or fax: +41 (0) 22 791 42 86.

7.6.2 CABANA Reporting of Drug or Device Adverse Events

For CABANA trial purposes, adverse events will be reported through the eCRF submission process designed to facilitate notification to DCRI Safety Surveillance and/or their designee. DCRI Safety Surveillance will review and code all SAEs.

The Safety Surveillance Medical Monitor (a physician trained and experienced in safety reporting) will review Events of Interest, and unexpected/unanticipated SAEs related to ablation

therapy or CABANA approved rate or rhythm control drugs. The decision regarding ultimate classification will be made by **individuals within CABANA Leadership** with expertise in antiarrhythmia and ablation therapies and clinical trial experience.

DCRI Safety Surveillance will notify the NHLBI and Mayo within 1-2 business days of an unexpectedness/unanticipated event determined to be related to the drug, device, and/or therapy. The final report will be submitted to the Regulatory Authorities and all participating investigators per regulations. Investigators are responsible for reporting trial unexpectedness/unanticipated events to their reviewing IRB within 10 working days of first learning of the event.

DCRI Safety Surveillance will notify the NHLBI within 5 business days of all reported Events of Interest (as identified above).

7.6.3 Criteria for Withdrawal of Subjects from Study

No subjects will be removed from the study, and attempts will be made to collect follow-up information for all subjects except those who specifically withdraw consent for release of such information.

8.0 Statistical Considerations

8.1 Sample Size and Power Considerations

In initially planning the CABANA trial, several design factors and research objectives were considered in developing an appropriate sample size for the study. First, the number of patients was determined so there would be a sufficient number of endpoints to provide a high degree of confidence (power $\geq$ 90%) for testing the primary hypothesis. Second, important secondary endpoints were considered. Third, it was considered important for the overall sample to be large enough to permit a prudent examination of treatment effects in selected subgroups of patients where AF ablation might be particularly advantageous, or where the question of a treatment benefit from this invasive procedure is particularly relevant. Important pre-specified subgroups of interest in this study include those defined by age, gender, race, AF type (paroxysmal, persistent, or long-standing persistent), AF duration, heart failure class, presence/absence of underlying structural heart disease, presence/absence of hypertension, and ejection fraction. Finally, the sample size was determined to provide a reasonable level of confidence of detecting clinically important therapeutic effects even if current projections of event rates and treatment differences prove to be optimistic.

As described in Section 2.0, the study was originally designed with total mortality as the primary endpoint. However, in early 2013 a careful assessment of the progress of the trial was undertaken by the study leadership. Completely blinded to any treatment-specific outcome data, the two major issues addressed by the leadership group were (1) a lower than expected aggregated mortality rate, and (2) accrual of patients at a rate much slower than projected. Careful consideration of these issues led to a decision to (a) change the primary endpoint of the trial from total mortality to the key secondary endpoint consisting of the composite of death, disabling stroke, serious bleeding, or cardiac arrest, and (b) reduce the sample size to a number that was consistent with the new primary endpoint. The following paragraphs, which outlined the key considerations in determining the original sample size, are also relevant for the revised sample size.

A combination of data from recent AF trials that reflect patient outcomes when treated with drug therapy (rate control or rhythm control) provide useful information on the range of outcomes that would be expected among the patients enrolled in the drug arm of CABANA. These studies include AFFIRM, RACE, STAF, PIAF and AF CHF. Since the study population in CABANA will be most like patients enrolled in the AFFIRM trial, the most reliable estimates of mortality and other endpoint events applicable to the drug arm of CABANA can be obtained from the AFFIRM data. The five-year mortality in AFFIRM was 23.8% in patients assigned to receive rhythm control drugs and 21.3% in patients assigned to rate control drugs. The crude death rate based on a mean follow-up of 3.5 years was 16.4%. However, the Kaplan-Meier curves in the primary AFFIRM publication reflect mortality rates at 3 years of 13% in the rhythm control arm and 11% in the rate control arm. At 3.5 years, mortality was approximately 16% in the rhythm control arm and 14% in the rate control arm. Based on this information, the mortality rate in the drug-treated arm of CABANA was projected to be approximately 12% after 3 years of follow-up and 15% after 3.5 years of follow-up (3.5 years is the average duration of follow-up originally projected for CABANA). With the original secondary endpoint elevated to become the primary endpoint, the incidence of the new primary endpoint is expected to be higher than the mortality rates.

In addition to the control (drug) arm event rate, a key driver of the sample size is the magnitude of the treatment effect (i.e., the reduction in the primary endpoint expected in the ablation arm). A synthesis of information from multiple published sources [48, 58-61, 67] suggests that the event rate in ablation-treated patients has been relatively low (less than 3% per year), which translates to a projected 3-year event rate of 8-9 % or a 3.5 year rate of 10% or less in the ablation arm of the trial (i.e., a reduction by one-third compared to the drug arm).

Another important factor that must be considered in sample size calculations is the extent to which patients randomized to the drug arm may **cross over** to receive an ablation during the course of their follow-up (if the AF and its symptoms are not adequately controlled by drugs). Although there are strict guidelines regarding changes to a patient's assigned therapy, in certain instances a downstream change may be clinically indicated. All crossovers and reasons for them must be carefully documented. However, crossovers of drug-arm patients to receive ablation will have the impact of reducing the event rate of patients randomized to drug therapy (assuming ablation is effective), and diminishing the magnitude of the treatment effect. Allowance for these crossovers is essential in determining the appropriate sample size. It is possible that up to 25-30% of patients randomized to the drug arm will cross over to ablation at some point during follow-up. Although the length of follow-up in the CABANA Pilot study was only 1 year, the rate of crossover to ablation of patients randomized to drug therapy was only 9.7%.

In addition to drug-arm patients crossing over to ablation, there may also be patients randomized to the ablation arm who require drug therapy. The number of patients randomized to ablation, that following randomization decline the procedure and are treated with drugs, is expected to be small and inconsequential in the sample size calculations. However, there will be patients randomized to ablation that during the course of their follow-up after the ablation are treated with drugs, including in some cases membrane-active antiarrhythmic drugs. For purposes of sample size calculations, these patients are assumed to receive the full benefit of ablation in reducing clinical outcomes, although one might argue that antiarrhythmic drugs, with their possible proarrhythmic effects, might attenuate the clinical benefits of the ablation.

Since the primary treatment comparisons in this study will be based on time-to-event methodology using the log-rank test [102] or equivalently, the Cox proportional hazards model

[103], the approach used for calculating sample size requirements for CABANA was based on the method of Schoenfeld [104] developed for the proportional hazards model.

To provide an adequate number of patients in the trial that will be relatively robust under various assumptions regarding the control-arm event rates and the magnitude of the treatment benefit, 2,000-2,200 patients will be enrolled. With a minimum follow-up of 3 years (amounting to an average follow-up of approximately 5 years), 2,200 patients will provide 90% power for detecting a 30% reduction in the new primary endpoint, and 2,000 patients will provide 88% power, assuming a 3-year event rate in the drug arm of 12% and allowing for a 2% loss to follow-up. Thus, the study will have high power for detecting an important benefit if the control arm event rate is consistent with the rate expected based on previous studies. A sample size in this range will also provide acceptable power (86% with 2200 patients and 82% with 2000 patients) for detecting a 25% reduction with ablation in the primary endpoint if the 3-year drug arm event rate is 15%. Thus we will have good power for detecting a more conservative estimate of the benefit in the composite endpoint if the control arm event rate is higher, but still consistent with previous studies. A 25-30% reduction in primary events will be highly important from a clinical and public health standpoint, given the large population of patients in this country and throughout the world who suffer from AF.

This number of patients (2,000-2,200) will also provide adequate power for detecting a 25% reduction in other important secondary composite endpoints listed in section 2.2 such as the endpoints that involve cardiovascular hospitalization where the incidence is expected to be higher than for the primary endpoint.

8.2 Statistical Analysis

Statistical analyses will be performed by the Coordinating Center. All major treatment comparisons will be performed by intention to treat, and endpoints will be attributed to the treatment arm to which the patients were randomized, regardless of treatment crossover or post-randomization medical care. Statistical comparisons will be performed using two-sided significance tests.

8.2.1 Analysis of the Primary Endpoint

The log-rank test will be the primary analytic tool for comparing outcome differences between the two therapies. Kaplan-Meier estimates of cumulative event rates as a function of follow-up time will be calculated and displayed. Relative risks will be expressed as hazard ratios with 95% confidence intervals generated using the Cox proportional hazards model.

Supplementary analysis involving covariate adjustment will be performed with the Cox model. Such adjustment will be limited to a relatively small, prospectively defined set of patient characteristics that are known *a priori* to have a strong prognostic relationship with the primary endpoint. The covariate-adjusted analysis will serve as a prelude to supplementary analyses examining differential treatment effects. The covariates will include age, sex, race, heart failure class, presence/absence of structural heart disease, whether the patients' AF is paroxysmal, persistent or long-standing persistent, duration of AF, presence/absence of hypertension, and ejection fraction. Cox model analyses may also be performed using appropriate groupings of sites as a stratification factor.

If the data provide evidence of an overall difference in outcome between treatment groups, an assessment will be made of whether the therapeutic effect is similar for all patients, or whether it varies according to specific patient characteristics. This analysis will focus on whether the

relative therapeutic benefit differs according to patient age, sex, race, type of AF, duration of AF, heart failure class, presence/absence of structural heart disease, presence/absence of hypertension, and ejection fraction. These analyses will utilize the Cox model by testing for interactions between treatment and these specific baseline variables. In addition to the formal assessment of treatment interactions, treatment effects characterized by a hazard ratio (with 95% confidence interval) will be calculated and displayed for prospectively-defined subgroups of patients defined by the variables listed above. These descriptive hazard ratios will be carefully interpreted in conjunction with the formal interaction tests.

8.2.2 Analysis of Secondary Endpoints

Secondary endpoints, including total mortality and secondary endpoints 2 through 9 listed in Section 2.2, will all involve time-to-event analyses and thus will be analyzed similar to the primary endpoint using the log-rank test, Cox model, and Kaplan-Meier event-rate estimates.

8.2.3 Analysis of Morbidity (Adverse Events)

Statistical comparisons of major adverse events are challenging in this trial because of therapy-specific differences in the nature of the adverse events. For drug therapy, the major events include unanticipated hospitalizations for heart failure, drug-related proarrhythmic events, and pulmonary toxicity from amiodarone. For the ablation arm, the major events include myocardial perforation with tamponade requiring resuscitation, symptomatic pulmonary vein stenosis requiring intervention, and atrial-esophageal fistula formation. The frequency with which these events (and other serious adverse events) occur will be descriptively tabulated. Treatment comparisons with respect to these serious adverse events will of necessity be more informal rather than statistically rigorous (since different adverse events are expected in the two arms), bringing to bear clinical judgment as to the relative seriousness of these various adverse events. Adverse complications or adverse events of either therapy will be carefully tabulated and descriptively summarized, using statistical comparisons of the treatment groups where appropriate, and interpreting such comparisons in the context of treatment differences in the primary and major secondary clinical endpoints.

8.2.4 Analysis of Core Lab Measures of LA Size, Morphology, and Function

Patients enrolled at a subset of the clinical sites will undergo baseline and follow-up CT/MR imaging studies, and core lab measures of left atrial size, morphology, and function will be examined. Of interest will be the change in atrial size (volume) and function (i.e., atrial ejection fraction) from the baseline to the follow-up study within each treatment arm, and then importantly, a comparison of whether the change in size and function in the patients randomized to ablation therapy differs from the change in size and function of the patients randomized to drug therapy.

The distribution of these measures from the baseline and follow-up studies in each treatment arm will be descriptively characterized using univariate descriptive statistics and graphical tools such as box and whisker plots. The statistical significance of the changes in left atrial size and function from baseline to follow-up within each treatment arm will be assessed using a paired-sample test such as the paired-t test. A two-sample comparison of the two groups with respect to changes in size and function will be performed using general linear models, including the baseline value as a covariate, and assessing treatment group differences. This comparison will be performed for the changes in atrial size (left atrial volume) and also for atrial function (atrial ejection fraction).

In dealing with this type of data, the completeness of which is dependent on obtaining both the baseline and follow-up studies, there will inherently be missing data resulting from patients in

whom it is not possible to obtain both studies (because they die or fail to return for other reasons to enable the follow-up measurements to be made). Every effort will be made to minimize the amount of missing data. However, because some data are expected to be missing, several missing data strategies will be employed in order to assess the sensitivity of the conclusions to the approach used. The approaches that will be considered include (1) analyzing only patients with complete data; (2) assigning "worst case" scores to missing observations; (3) carry forward previously observed data to the observation period missed; and (4) use of likelihood-based methods to impute missing data. By synthesizing the results from these different but complementary approaches, it will be possible to provide a comprehensive assessment with respect to these key mechanistic data.

8.2.5 "On-Treatment" Analysis

Although the intention to treat analyses will serve as the standard for interpreting treatment differences in the key clinical outcomes and constitute the primary analyses in the trial, because a number of patients from the drug arm may cross over to receive ablation during the trial, we will supplement the intent to treat comparisons with "on-treatment" comparisons. The "on-treatment" analysis will involve a comparison of patients who received ablation (even if originally assigned to the drug arm) versus those who did not. Statistically, this will be accomplished using the Cox proportional hazards model with ablation included in the analysis as a time-dependent covariate. Thus, event-free follow-up time for a patient in the drug arm who later crosses over to ablation would be credited to the drug arm until the time of crossover, and at that point, the patient would be shifted to the ablation group. Because treatment assignment is no longer random, results can be biased by an association between the likelihood of treatment change and the risk of a clinical event (i.e., factors that make a patient more likely to cross over may also make them more likely to have an event). Thus such analyses should be cautiously interpreted. The "on-treatment" analyses will also include an assessment of freedom from AF in ablation patients after each ablation performed, including those undertaken after the end of the blanking period.

An analysis using a time-dependent covariate with the Cox model will also be conducted to examine the prognostic relationships of sinus rhythm with clinical outcomes. The analyses described in this section will be covariate adjusted for baseline prognostic factors that are related to the clinical outcomes of interest. These analyses will be strictly exploratory and supplementary to the primary intent to treat analyses.

8.2.6 Interim Analyses

For ethical reasons, an interim examination of key safety and endpoint data will be performed at regular intervals during the course of the trial. The primary objective of these analyses will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in any of the treatment arms. In addition, the interim monitoring will also involve a review of the control arm event rates, patient recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study. The results of the interim analyses and status reports will be carefully and confidentially reviewed by an NHLBI-appointed Data and Safety Monitoring Board (DSMB).

The DSMB will meet at approximately 6-month intervals to review the accumulating data. Prior to each meeting, the Statistical and Data Coordinating Center will conduct the desired statistical analyses and prepare a summary report that will be carefully reviewed by the DSMB. The extracted data files and analysis programs for each DSMB report will be archived and maintained at the Data Coordinating Center for the life of the study. Reports will be presented describing the progress of patient enrollment, the rates of compliance with therapy, and the

frequency of protocol violations. The Data Coordinating Center will also report on the number (status) of data forms completion, the number of outstanding queries, the number of queries completed, and the number of forms reviewed through on-site monitoring.

These interim safety and efficacy reports introduce well-recognized statistical problems related to the multiplicity of statistical tests performed on an accumulating set of data. To properly account for the repeated interim testing in CABANA, a group sequential method similar to that proposed by O'Brien and Fleming [105] as a guide in interpreting interim analyses will be used. This procedure requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final analysis is near the "nominal" critical value. Hence the sample size requirements with this group sequential procedure remain essentially the same as the conventional fixed sample size estimate. The actual method for this interim monitoring that will be employed in CABANA is the “spending function” approach to group sequential testing developed by Lan and DeMets [106]. The Lan-DeMets approach only requires specification of the rate at which the Type I error (which in this trial will be α=0.05 for the primary endpoint) will be "spent". This procedure allows "spending" a portion of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05. One such spending function generates boundaries that are nearly identical to the O'Brien-Fleming boundaries. It is this approach that will be used in CABANA, namely two-sided, symmetric O'Brien-Fleming type boundaries generated using the flexible Lan-DeMets approach to group sequential testing. Since the number of looks and the increments between looks need not be predetermined, it allows flexibility in the monitoring process for accommodating additional comparative examinations of the data in response to concerns of the DSMB that may arise during the course of the trial.

The analytic approach that will be used at the interim analyses for assessing treatment differences will be the time-to-event analysis methods described previously, except that interpretation of statistical significance associated with treatment comparisons will be guided using the group sequential monitoring boundaries outlined above.

Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the originally projected sample size. As an aid in this latter assessment, the Coordinating Center will supplement the group sequential analyses outlined above with calculations of conditional power, namely the conditional probability that the treatment comparison will be significant at the end of the trial at the α level used in the design, given the hypothesized treatment difference and the data observed to date. After approximately 50% of the total events have occurred, conditional power for the primary treatment comparison will be computed and provided to the DSMB as part of the interim study reports.

8.2.7 Multiple Comparisons

With the primary hypothesis and the various secondary endpoints that have been outlined, there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one of the comparisons could be "significant" by chance. Although adjustments (e.g., based on the Bonferroni inequality) could be used to preserve the overall type I error level, to adjust for the effects of the repeated significance testing that will occur as part of the interim monitoring (discussed above), plus adjust for the multiplicity of secondary endpoints, would require that very small significance levels be used for every comparison. Although the overall level of significance for the assessment of the primary composite endpoint will be 0.05, to account in

part for the multiplicity of comparisons involving secondary endpoints, a conservative approach will be taken while interpreting those results, taking into account the degree of significance, and looking for consistency across endpoints. The actual p-value for each comparison will be reported to aid in the overall interpretation.

8.2.8 Health Economics Analyses

The health economic analyses for CABANA will consist of two major parts, an empirical intention to treat cost comparison and a cost effectiveness analysis. Primary statistical comparisons between the two treatment arms of empirical costs will be performed by intention-to-treat. The patients enrolled outside the United States will be excluded from the primary cost intention-to-treat analyses. Confidence limits around the observed cost differences will be constructed using bootstrap methods.

The cost-effectiveness analyses will estimate the incremental cost required to add an extra life year with the investigational ablation arm relative to control medical therapy. In secondary analyses, we will incorporate utility weights to estimate the incremental cost per quality adjusted life year gained with ablation, relative to medical therapy. These analyses will be conducted from a societal perspective and will use a lifetime time horizon so that the estimated incremental cost-effectiveness and cost-utility ratios can be compared with societal benchmarks. We will also calculate within-trial cost-effectiveness/cost-utility ratios, although these ratios are limited in their value due to their failure to account for long-term benefits and costs and the absence of comparative benchmarks. Costs will be adjusted for inflation and both costs and life expectancy will be discounted to present value at a 3% annual discount rate. Adjustments for censored data due to staggered entry will be made following the approach of Bang and Tsiatis [107]. Extensive sensitivity analyses will be performed.

8.2.9 Quality of Life (QOL) Analyses

For each of the QOL measures examined in this study, data analysis will proceed in two stages. First, we will provide simple descriptive and comparative analyses by intention-to-treat. Second, we will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. Since there is currently no consensus in the statistical literature about the best way to deal with the multiple comparisons problem arising from testing each individual scale separately, we propose two complementary approaches. First, we will pre-specify functional status (Duke Activity Status Index), AF symptom burden, and patient utilities (EuroQOL-5-D) as the primary QOL comparisons of interest and assign all other comparisons to a secondary (exploratory) status. Second, we will use the average of post-baseline values in the primary analyses of these 3 endpoints to reduce the problem of comparisons at multiple time points. Statistical power estimates for this part of our analysis show that we should have in excess of 90% power to detect ¼ SD differences in our 3 principal QOL endpoints.

9.0 Data Management and Quality Control

9.1 Study Data Collection -- All Patients

The full study dataset will be collected for subjects who enter the randomized/ treatment phase of the study. The primary data collection system for CABANA is based on the electronic data capture (EDC) system, InForm™. All data collected at any point in the trial, except the economic and quality of life information and core lab data are entered into this system. Data from the CT/MR Imaging Lab, the ECG Core Lab, and the Medicomp Monitoring Core Lab are transferred electronically to the Data Coordinating Center on a regular basis.

9.2 Electronic Case Report Form (eCRF)

This study will use web-based electronic CRFs (e-CRFs) developed through a validated, Electronic Record, Electronic Signatures (ERES) compliant platform (21 CFR Part 11). Prior to initiation of the trial, each site will be contacted as to computer availability, hardware specifications, and internet connectivity, to evaluate the capacity of the site to use this type of data collection system. Data will be entered into the InForm™ eCRF by personnel at the clinical sites. The Investigator's site staff who will be entering data will receive training on the system, after which, each person will be issued a unique user identification and password. For security reasons, and in compliance with regulatory guidelines, it is imperative that only the person who owns the user identification and password access the system using their own unique access codes. Access codes are non-transferable. Site personnel who have not undergone training may not use the system and will not be issued user identification and password until appropriate training is completed.

During monitoring visits, the site will make their computer and/or high speed Internet access available to the CRA, so that he/she may verify the data entries with the source documentation. At the conclusion of the study, each enrolling site will be provided with a compact disc (CD) containing PDF files of both the individual subject's data and the audit trail (changes made to the database). This will be maintained at the site according to the requirements for records retention.

Components of the eCRF in CABANA include enrollment and demographics form; a form for recording relevant history, symptoms, physical exam, ECG data and other baseline presenting characteristics; forms to document the details of the drug therapy and ablation procedure; follow-up forms for use at the regular follow-up visits and tracking the patient’s clinical course over time; and event forms for recording the circumstances and details surrounding the occurrence of a death, stroke, cardiac arrest, or bleeding event as well as other adverse events. In addition to the eCRF, there are specialized additional forms for collecting various components of the quality of life and health status information. Detailed instructions for completing the various data forms, along with a detailed Manual of Operations will be provided to each of the clinical sites

9.3 Data Management and Quality

Any out-of-range values and missing or inconsistent key variables are flagged and addressed/answered at the site in real time during the data entry process. When a query is generated on a particular variable, a flag is set in a field in the database enabling the system to track the queries and produce reports of outstanding queries. Queries can also be generated from manual review of the data forms. These queries will be entered into the database and tracked in the same manner as the computer-generated queries. At regular intervals, all data will be transferred from InForm™ to SAS for statistical summarization, data description, and data analysis. Further cross-checking of the data is performed in SAS, and discrepant observations flagged and appropriately resolved through a data query system.

The Data Coordinating Center will perform internal database quality-control checks, and data audits throughout the course of the trial. All clinical site patient-related payments are prompted by completion of data forms with appropriate responses to all data elements.

9.4 Economic and Quality of Life (EQOL) Data

For the CABANA study the economic and quality of life studies will be fully integrated into the clinical trial, including their inclusion in the main trial Informed Consent Form. The EQOL data

will be quality controlled and entered into the study data base at the EQOL Coordinating Center. Measurements of utilities by the EQ-5D and 0-100 Thermometer (EuroQoL) will be obtained throughout the trial in the CABANA EDC system. Statistical analysis of the EQOL data by intention-to-treat will be performed by the EQOL Coordinating Center.

10.0 Investigator Responsibility/Performance

By signing this protocol, the clinical site investigators agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Investigator will provide current copies of the study protocol to all Sub-Investigators or other site personnel responsible for study conduct. The investigator must ensure that all site staff involved in the conduct of the trial are familiar with and have appropriate knowledge of the protocol and all study-specific procedures.

The Investigator will provide DCRI and/or their designee with copies of all IRB or EC actions regarding the study.

11.0 Study Data Reporting and Processing

The principal investigator is required to sign the eCRF on the appropriate pages to verify that he/she has accepted responsibility for the recorded data. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties to a sub-investigator will be recorded on the Delegation list (kept on file at the site).

11.1 Site Selection and Monitoring

To qualify as an investigative site, each group must be committed to enrollment and randomization without bias or inclination toward early cross-over from drug to ablative therapy. Each site must also demonstrate the skill and expertise for participating in clinical trials as judged from their past trial performance. A Co-PI approach to the enrollment and treatment of patients will be required. A cardiac electrophysiologist skilled in the art of AF ablation will work closely with a non-interventional clinical cardiologist or internist. This will also help counter potential bias in favor of ablation. The focus of recruitment will be in Primary and Secondary Care clinics, Hospital ERs, and first referrals to ablation centers. Each site will be strongly encouraged to minimize the time between randomization and ablation to <2 weeks, by “holding” ablation slots.

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of Good Clinical Practice and applicable regulations, the Monitoring Plan is being revised with Executive Committee approval. A DCRI study monitor or their designee will no longer perform on-site visits to Active study sites regularly and throughout the study. Rather they will maintain frequent telephone and written communication, as well as perform on-site visits to a subset of sites to ensure data integrity.

The on-site monitoring visits will be made to assure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will assure that the

facilities are still acceptable; the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to DCRI and/or their designee and the IRB/EC, study drug and study drug inventory are controlled and the Investigator is carrying out all agreed activities.

During on-site monitoring visits, the Monitor will perform a review of all Inclusion/Exclusion criteria of selected randomized subjects. Review of informed consent forms, HIPAA Authorization, all events meeting criteria for expedited event reporting as well as selected SAE's and Events of Interest (EOI)'s will be performed. Additional review will be performed on a site-by-site basis, as warranted. Key variables (inclusion/exclusion criteria, adherence to treatment assignment and safety) on the eCRF will be compared with each subject's source documents. Any discrepancies will be noted and resolved.

During monitoring visits, the site will make their computer and/or high speed Internet access available to the CRA, so that he/she may verify the data entries with the source documentation.

11.1.1 Initiating / Training Sites

Over the first year of the trial, sites will come on-line for active participation once all local regulatory requirements have been met. Unconditional IRB/EC approval will be required at each site. Training for data collection and reporting must be completed. Individual sites will also be trained at the time of the first general investigator meeting held at the beginning of the trial. The specific site's ablation and clinical investigators and the clinical study coordinator will be required to attend these meetings.

11.1.2 Terminating a Site

Any activated site may be terminated from the trial for failure to enroll any subjects, within a reasonable period of time. Also, any site may be suspended from active enrollment, if it fails to meet reasonable enrollment goals or comply with study procedures. Specifically, any site consistently failing to provide timely reports or adequate data quality will be withdrawn from active enrollment. A cross-over rate $\geq$10% over any 6 month period will result in a warning to that site. A crossover rate >15% will prompt suspension of enrollment. A 3-month period for resolving any operational difficulties will be required prior to reinstating or permanently terminating a specific site to further enrollment. All subjects randomized must be followed until death or the end of the trial, even if the site has been inactivated due to enrollment or study compliance.

11.1.3 Conflicts of Interest: The two principal investigators from each site, along with additional study staff will be required to disclose any present or potential conflicts of interest following guidelines established by the American College of Cardiology.

12.0 Study Documentation

Study documentation includes all electronic data collection forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents, etc.

The investigator will prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws,

rules and regulations; and, for each subject participating in the study, promptly complete all original case report forms and such other reports as required by this protocol.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed and shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of DCRI and/or their designee or responsible government agencies as required by law.

The investigator agrees to promptly take any reasonable steps that are requested by DCRI and/or their designee as a result of an audit to cure deficiencies in the study documentation and case report forms.

13.0 Source Documentation

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study.
Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data collected on the CRF (eCRF). In order to comply with these regulatory requirements, the following information will be maintained and made available as required by DCRI and/or their designee monitors and/or regulatory inspectors:

1. Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
2. Medical record documenting that informed consent was obtained for the subject's participation in the study
3. Notes for each subject visit including results of examinations.
4. Lab results
5. Dated printouts or reports of special assessments, (e.g., ECG reports).
6. Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study drug or device, outcome and treatment for adverse event).
7. Notes regarding concomitant medications taken during the study (including start and stop dates).
8. Subject's condition upon completion of or withdrawal from the study.

14.0 Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement.

Investigators are required to obtain prior approval from CABANA Administration before initiating deviations from the investigational plan or protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in study files. Unless CABANA Administration has consented to any such deviations in writing, CABANA Administration will not assume any resulting responsibility or

liability. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation.

Deviations will be reported to DCRI and/or their designee regardless of whether medically justifiable, preapproved by CABANA Administration, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the [study specific, e.g., Report of Non-Compliance] Form.

Investigators will maintain documentation of the dates and reasons for each deviation from the protocol, in compliance with the ICH-GCP guidelines, Code of Federal Regulations (CFR) 812.140 and national legislation.

15.0 Data Transmittal and Record Retention

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the subject visit or the availability of test results.

As forms are completed or updated, data will be transmitted via the Internet from investigational sites to a central site utilizing state-of-the-art encryption mechanisms to ensure security and confidentiality.

The investigator takes responsibility for retaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by DCRI and/or their designee as well as the FDA and other regulatory agencies, as provided by law. DCRI and/or their designee will be contacted if the investigator plans to leave the institution so that arrangements can be made for transfer of responsibilities.

16.0 Study Closeout

The end of the trial is defined as the day of the official end of patient follow-up in the trial.

For clinical trial sites located in the EU, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC. For sites located in countries outside the EU, local regulations will be followed.

Upon completion of the study DCRI and/or their designee will notify the site of closeout and a study closeout visit will be performed. The DCRI monitor and/or their designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous correspondences have been resolved. Other issues to be reviewed at the closeout visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

17.0 Audit/Inspections

DCRI Quality Assurance personnel and/or their designee may conduct audits at the study site(s). Audits will include, but not be limited to: audit trail of data handling and processes, SOPs, drug supply, presence of required documents, the informed consent process, and

comparison of case report forms/database with source documents. The investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with governmental (e.g. FDA) audits conducted at a reasonable time in a reasonable manner.

18.0 Informed Consent

The investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all subjects before any study-related procedures are performed or given.

The principal investigator or IRB-documented members of the research team will approach the patient to obtain written informed consent on an informed consent form (ICF) approved by the same IRB/EC responsible for approval of this protocol. The informed consent document will conform to FDA regulations in 21 CFR Part 50, and/or to the national requirements for informed consent. It must include all elements required by law, local regulations, GCP and International Conference on Harmonization guidelines and study specific procedures. The underlying rationale for the study, the procedures to be followed, the potential benefits, risks, alternatives, and other issues mandated by the consent process will be fully disclosed. If new information becomes available during the course of the trial that may be relevant to the subject's consent, the Informed Consent Form will be revised and the revised version will be submitted for EC/IRB approval before use.

The investigator agrees to obtain approval from DCRI and/or their designee of any ICF intended for use in the study, prior to submission for IRB approval.

19.0 Confidentiality of Subjects

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number and subject name code) will be used that allows identification of all data reported for each subject.

Subject information collected in this study and all records will be kept confidential and the subject's name will not be released by study staff at any time.

When requested patient medical records may be examined by authorized monitors (DCRI and/or their designee) or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IRB / IEC members and by domestic and foreign regulatory authorities. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected.

Furthermore; for clinical trial sites located in the US, the NHLBI has issued CABANA a Certificate of Confidentiality to protect the privacy of research subjects by withholding their identifiable information from all persons not connected with this research.

20.0 Authorization for Use and Disclosure of Protected Health Information (HIPAA)

For clinical trial sites located in the US, an Authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule [45 CFR § 164.102 *et seq*] will be obtained from every trial subject prior to, or at the time of, enrollment. It will be presented to, and signed by, the subject at the same time as the Informed Consent Form (ICF). The investigator is responsible for obtaining subjects' authorizations and signatures, and for explaining the elements of the HIPAA Authorization form if necessary.

HIPAA Authorization may either be a separate form or included in the study ICF, dependent upon local requirements. If a separate HIPAA document is signed, the investigator will append one signed original of each executed HIPAA Authorization to the trial subject's signed ICF, and file it in the site's regulatory file. If a second copy of the signed ICF is filed in the subject's medical records, an additional copy of the signed HIPAA Authorization form will be appended. Subjects will be given the other signed duplicate for their personal records.
The HIPAA Authorization form will contain all elements required under the HIPAA Privacy Rule. By law, site IRB approval of the Sponsor-provided Authorization form for use in this study is not required, and no such approval will be sought or requested. However, DCRI or their designee, upon request, will provide advance copies of its HIPAA Authorization form to the investigator or the site's privacy board or privacy official, and will work with the site to eliminate any concerns.
The investigator or the site will promptly inform DCRI or their designee of any restrictions on the use or disclosure of PHI of any subject to which the site or the investigator have agreed under the Privacy Rule. The investigator or the site will also promptly inform DCRI or their designee of any written revocation of any subject's HIPAA Authorization.

21.0 Human Subject Protections

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21.1 Research Subject Selection and Justification of Exclusions

There will be no exclusion from participation in the study on the basis of ethnicity or race. Subjects will undergo a screening process, during which they will have multiple opportunities to ask questions. The Principal Investigator or authorized designee will provide a detailed discussion of the protocol, and answer any questions. The subject will be given time to consider study participation. No coercion or undue influence on this decision will be used. Only those subjects who give written, informed consent and complete enrollment testing will be considered for participation in the study.

22.0 Institutional Review Board/Ethics Committee Review

This study will be initiated only after all required documentation has been reviewed and approved by the respective IRB/EC and competent authority (CA) according to national and international regulations.
The investigator will provide DCRI or their designee with the study approval documentation before the study may begin. The same is applicable for the implementation of changes introduced by amendments.
Where applicable, the investigator must also provide to DCRI and/or their designee the following documentation:

1. A copy of IRB annual re-approval of the protocol per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonization guidelines.

2. IRB approval of revisions to the informed consent documents. Administrative changes (such as a change in address or phone number) must be sent to IRBs/Ethics Committees but do not require their approval.
3. The investigator must submit periodic status reports to their EC as required, as well as notification of completion of the study and a final report where applicable.
4. The investigator will provide DCRI or their designee with documentation of all approvals.

23.0 Publication Policies

Trial results will be released in several manuscripts providing outcomes of the trial as a whole. No details will be released prior to the scheduled presentation of the main trial results. Data summaries will be provided to the DSMB and NHLBI as appropriate for trial regulation. Release of other results, including those generated in any sub-study must be done in a manner so as to protect the integrity of the trial as a whole. Portions of the database will not be released to single or groups of enrolling centers for analysis.

The Publication Committee will receive and review applications and potential authors for sub-studies beyond those comprising main trial results, and make recommendations to the Executive Committee for approval. A detailed list of the sub-studies, the requesting investigators, and the timing of applications will be maintained in anticipation of other publications.

All manuscripts, abstracts and presentations will be reviewed by the Publication Committee for scientific merit, appropriateness of the presentation or manuscript, and for authorship. All presentations or publications of <u>any</u> type are expected to maintain the integrity of the main objectives of the overall project. By agreement of the principal investigators, endpoint data will not be presented prior to the release of main study results. Authorship on ancillary studies will depend on contribution to the trial effort.

24.0 Sub-Studies

All activated <u>sites will be given the opportunity to participate or not participate</u>. All proposed sub-studies will be first submitted for review and approval to the respective IRB/EC and competent authority (CA) based on national and international regulations. It is further acknowledged that <u>subjects enrolled in CABANA will have the choice to participate or to not participate</u> in sub-studies.

24.1 CABANAgene

<u>CABANAgene</u>: a resource that will accumulate DNA samples from CABANA subjects to enable subsequent genotype-phenotype studies.

Appendix C, page 62, the CABANAgene protocol, provides the rationale for studies and approaches that are anticipated. The major goal of CABANAgene is to create the resource. Specific projects to use the samples would require approval of the CABANA study group, and phenotypes to be studied would be those collected by and adjudicated by the CABANA study group. The CABANAgene project is included in the Pharmacogenetics Research Network (PGRN) arrhythmia site renewal. Participation under the PGRN umbrella also provides access to advanced genotyping and genetic statistical methods to investigators accessing the CABANAgene resource.

Examples of issues that CABANAgene could address include: 1) predictors of response to antiarrhythmic or rate control drug therapies; 2) predictors of response to warfarin therapy; 3) predictors of response to ablation therapy and; 4) clinical and genetic approaches to defining AF subtypes.

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Appendix A Adverse Events

The following events have been identified as "Anticipated Events" for subjects randomized to drug or ablation therapy for this study.

CATEGORY	ANTICIPATED EVENT			
CARDIOVASCULAR				
	1	Air embolism	17	Intraventricular conduction delay
	2	Bradycardia	18	Ischemia
	3	Cardiac arrest	19	Left ventricular dysfunction
	4	Cardiac thromboembolic event	20	Myocardial infarction
	5	Chest pain during energy delivery	21	Myocardial perforation
	6	Clinically relevant AV node dysfunction	22	Pacemaker damage
	7	Clinically relevant sinus node block	23	Pericardial effusion
	8	Complete/permanent AV block	24	Pericarditis
	9	Coronary artery dissection	25	Proarrhythmia; new or worsened arrhythmia
	10	Coronary artery occlusion	26	Persistant PFO / iatrogenic ASD
	11	Coronary artery spasm	27	Prolonged QT
	12	Nonsustained VT	28	Sustained VT
	13	Elevated creatinine phosphokinase (CPK)	29	Tamponade
	14	Heart failure (Class I, II, III, IV)	30	Torsade des pointes
	15	Heart valve damage	31	Transient AV block
	16	Hypotension	32	Ventricular fibrillation
ENDOCRINE				
	32	Hyperthyroidism	33	Hypothyroidism
GENERAL				
	34	Allergic reaction (skin rash, SOB)	39	Radiation skin burn
	35	Bluish / gray skin tone	40	Skin rashes
	36	Fatigue	41	Temperature elevation
	37	Photosensitivity	42	Volume overload
	38	Radiation related cancers		
GASTROINTESTINAL				
	43	Constipation	48	Stomach disorder
	44	Diarrhea	49	Nausea
	45	Esophageal atrial fistula	50	Poor appetite
	46	Esophageal disorder	51	Unusual taste (metallic or other)
	47	Gastroesophageal reflux	52	Vomiting
			53	Abnormal liver functions
GENITOURINARY				
	54	Impotence	56	Renal failure
	55	Kidney damage	57	Urinary tract infection
INFECTIOUS				
	58	Infection	59	Sepsis
NEUROLOGIC				
	60	Alteration of color vision	68	Phrenic nerve damage
	61	Blindness	69	Seizure
	62	Blurred / double vision	70	Stroke
	63	Depression	71	Syncope
	64	Deteriorating vision	72	TIA
	65	Dizziness / light headedness	73	Unsteady gait / imbalance
	66	Headache	74	Vasovagal reaction
	67	Pain	75	Visual migraine

Appendix A Adverse Events (continued)

The following events have been identified as "Anticipated Events" for subjects randomized to drug or ablation therapy for this study.

CATEGORY	ANTICIPATED EVENT			
PULMONARY				
	76	Asthma exacerbation	84	Pulmonary hypertension
	77	Hemothorax	85	Pulmonary vein damage/dissection
	78	Lung toxicity	86	Pulmonary vein stenosis
	79	Pleural effusion	87	Pulmonary vein thrombus
	80	Pneumonia	88	Respiratory depression
	81	Pneumothorax	89	Shortness of breath/dyspnea
	82	Pulmonary edema	90	Wheezing
	83	Pulmonary embolism	91	Pleuritic chest pain
PERIPHERAL VASCULAR				
	92	A-V fistula	97	Peripheral edema
	93	Bleeding	98	Peripheral thromboembolic event
	94	Bruising / ecchymosis	99	Pseudoaneurysm
	95	DVT	100	Thromboembolic event
	96	Hematoma	101	Vessel trauma

Appendix B

Approved Ablation Devices for CABANA
IDE: G050233

CATHETER	DESCRIPTION	SIZE	PMA#
Biosense Webster	NAVI-STAR	7F/4mm	P990025
Biosense Webster	NAVI-STAR DS	7F/8mm	P010068
Biosense Webster	CELSIUS Braided Tip	7F/4-5mm	P950005
Biosense Webster	CELSIUS Braided Tip	8F/4-5mm	P950005
Biosense Webster	CELCIUS Long Reach	7F/4-5mm	P950005
Biosense Webster	CELCIUS Long Reach	8F/4-5mm	P950005
Biosense Webster	NAVI-STAR™ and CELSIUS™ Thermo-Cool	7.5F/3.5mm	P030031
Biosense Webster	Navistar® RMT	7F/4mm	P990025
Biosense Webster	Navistar® RMT	7F/8mm	P010068
Biosense Webster	Celsius® RMT	7F/4mm	P950005
Biosense Webster	ThermoCool® SF	8F/3.5mm	P990071
Medtronic Cryocath LP	Freezor®	7F/4mm	P020045
Medtronic Cryocath LP	Freezor® Xtra	7F/6mm	P020045
Medtronic Cryocath LP	Freezor® MAX	9F/8mm	P020045
Medtronic Cryocath LP	Arctic Front®	23mm 28mm	P100010
Medtronic	Cardiac Ablation System		P100008
St. Jude Medical	Livewire TC™ XLS™ Medium Sweep	7F/4mm	P960016
St. Jude Medical	Livewire TC™ XLS™ Large Sweep	7F/4mm	P960016
St. Jude Medical	Livewire TC™ XLS™ Medium Curl	7F/4mm	P960016
St. Jude Medical	Livewire TC™ XLS™ Large Curl	7F/4mm	P960016
St. Jude Medical	Livewire TC™ XLS™ Medium Sweep	7F/5mm	P960016/S006
St. Jude Medical	Livewire TC™ XLS™ Large Sweep	7F/5mm	P960016/S006
St. Jude Medical	Livewire TC™ XLS™ Medium Curl	7F/5mm	P960016/S006
St. Jude Medical	Livewire TC™ XLS™ Large Curl	7F/5mm	P960016/S006
St. Jude Medical	Therapy™ Dual8- small	7F/8mm	P040042
St. Jude Medical	Therapy™ Dual 8- medium	7F/8mm	P040042
St. Jude Medical	Therapy™ Dual 8- large	7F/8mm	P040042
St. Jude Medical	Therapy™ Dual 8- X-large	7F/8mm	P040042
St. Jude Medical	Therapy™ Dual -8 extended	7F/8mm	P040042
St. Jude Medical	Therapy™ Dual -8 far reach	7F/8mm	P040042
St. Jude Medical	Therapy™ Thermocouple small	7F/4mm	P040014
St. Jude Medical	Therapy™ Thermocouple medium	7F/4mm	P040014
St. Jude Medical	Therapy™ Thermocouple large	7F/4mm	P040014
St. Jude Medical	Therapy™ Thermocouple X-large	7F/4mm	P040014
St. Jude Medical	Therapy™ Thermocouple extended	7F/4mm	P040014
St. Jude Medical	Therapy™ Thermocouple far reach	7F/4mm	P040014
St. Jude Medical	Safire™ Sm/Med/Lg Sweep	7F/4mm	P960016/S014
St. Jude Medical	Safire™ Sm/Med/Lg Curl	7F/4mm	P960016/S014
St. Jude Medical	Safire™ Sm/Med/Lg Sweep	7F/5mm	P960016/S014
St. Jude Medical	Safire™ Sm/Med/Lg Curl	7F/5mm	P960016/S014
St. Jude Medical	Therapy Cool Path Med Curve	7F/5mm	P060019
St. Jude Medical	Therapy Cool Path Large Curve	7F/5mm	P060019
St. Jude Medical	Therapy Cool Path X-Large Med Curve	7F/5mm	P060019
St. Jude Medical	Therapy Cool Path Flutter Curve	7F/5mm	P060019
Bard	Stinger	4&5mm	P000020
Boston Scientific	Blazer II RF	7F/4mm	P920047
Boston Scientific	Blazer II XP	8F/8mm	P020025
Boston Scientific	Blazer RPM	8F/5mm	P020047
Boston Scientific	Chilli II Cooled	7F4mm	P980003
Boston Scientific	SteeroCath	7F/4mm	P920047

Appendix C

CABANAgene

A Resource to Evaluate Genetic Predictors of Efficacy and Adverse Reactions During the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) (CABANA sub-study protocol)

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1.0 Background and Significance

CABANA is comparing two major approaches for management of atrial fibrillation (AF): drugs to maintain sinus rhythm and ablation. As in all other large clinical trials, responses to therapy will be variable in both treatment arms. Abundant evidence points to genetic factors as a contributor to such variability in important human phenotypes such as response to treatment,[1] and the goal of CABANAgene is the creation of a large resource linking to test hypotheses that relate genetic variation to disease susceptibility and treatment responses. Collecting DNA from patients in CABANA will address questions such as which patients are most likely to respond to ablation or drug therapy and which patients are most likely to develop complications with ablation or drug therapy.

Approaches to identifying associations between genotypes and phenotypes: Three general approaches have been used in studies addressing the relationship between genotype and phenotype:

1. Family studies: Initial genotype-phenotype relations were identified by studying kindreds with manifest phenotypes like sickle cell disease, long QT syndrome or hypertrophic cardiomyopathy. Indeed, similar approaches have now been used to identify rare but clinically important genetic variants that cause familial AF.[2-7]
2. Candidate gene studies: Here, the biologic basis for the phenotype in question is first intensively studied, and then the role of genes modulating that biology was explored. This approach has been used to identify genetic variants contributing to AF susceptibility in families with more than one affected member. In addition, candidate gene approaches have been remarkably effective in identifying genetic variants that modulate drug action (pharmacogenomics).[1] These can be in the genes involved in drug transport or metabolism (e.g. members of the CYP superfamily), in genes encoding drug targets (e.g. ion channels genes for antiarrhythmics; adrenergic receptor gene variants for beta-blockers; VKORC1 for warfarin), or in other genes that modulate the biologic context in which drugs interact with their target molecules. The traditional approach interrogates a small number of well-characterized variants in a candidate gene, and relates these to the phenotype of interest; in CABANA, such phenotypes may include beneficial drug effect, failure of drug or ablation, or adverse drug effect. Newer “next-generation” sequencing technologies can interrogate whole candidate genes or pathways, and analytical approaches to identifying true positive signals in this work are in development.
3. “Unbiased” approaches: Human genomes contain millions of common polymorphisms, such as single nucleotide polymorphisms (SNPs) or copy number variations (CNVs). The genome-wide association study (GWAS) paradigm[8,9] compares hundreds of thousands of such variants in cases and controls (or across a continuous trait) to identify, in an unbiased fashion, loci modulating the trait. Because GWAS searches for common variants that confer modest odds ratios, large cohorts are required,[10,11] and there is a high risk of false positive associations; thus, the accrual of a very large well-ascertained cohorts (as in this proposal) represents an important enabling tool for these studies. A compromise approach has been to focus not on high priority single genes or single variants, but to cast a somewhat wider net and focus on variation in genes within a “pathway”, e.g. a cholesterol[12] or thrombosis “pathway”. Indeed, this approach has been adopted to interrogate >1500 SNPs in 18 candidate genes in an “arrhythmia drug response pathway” to study determinants of drug-induced arrhythmias, among others.[13]

2.0 Rationale and Specific Aims

The primary goal of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is to establish appropriate roles for medical and ablative intervention by randomizing 2,000 – 2,200 patients. **This protocol will create CABANAgene: a resource that will accumulate DNA samples from CABANA subjects to enable subsequent genotype-phenotype studies, based on the rationales described above.**
Examples of issues that CABANAgene could address include:

- predictors of response to antiarrhythmic or rate control drug therapies
- predictors of response to ablation therapy
- predictors of response to anticoagulation therapy
- genetic factors defining AF subtypes
- predictors of LA morphology size and function
  - Is it primary AF or AF secondary to underlying heart disease
  - Is it early recurrent atrial fibrillation (ERAF)
  - Does it increase the non pulmonary vein foci.
  - Left Atria and Stroke
  - Anticoagulant issues

All projects will require approval of the CABANAgene Principal Investigators and CABANA Executive Committee. The CABANAgene project is included in the Pharmacogenetics of Arrhythmia Therapy (PAT) node of the Pharmacogenomics Research Network (PGRN). CABANAgene's participation under the PGRN umbrella will also provide access to advanced genotyping and genetic statistical methods via this resource.

3.0 Previous Human Studies

PAT investigators, in collaboration with other arrhythmia groups around the country and internationally, have used family studies, candidate gene studies, and unbiased approaches to identify genetic predictors of variability in AF susceptibility and in response to drugs used to treat AF. Examples of these findings are presented here in brief to illustrate the value of a resource such as CABANAgene with well-phenotyped patients and outcomes in advancing AF-related genome science. One important conclusion to draw from the studies presented is that large datasets, such as Framingham, the Vanderbilt AF registry, the German AF network, or CABANAgene are enabling for contemporary unbiased genomic studies.[14-17] In addition, large datasets permit the accrual of subjects with specific intermediate phenotypes that may relate to AF risk. Examples of such phenotypes include prolonged P wave duration,[4] atrial fibrillatory rate derived from frequency-domain analysis of surface ECGs during AF,[18] and right precordial J point elevation, that is reported to be common in lone AF[19] and that we have observed with AF-associated mutations in sodium channel genes.[20] A resource such as CABANAgene will allow much more rigorous exploration of the relationships among these endophenotypes, genetic variants that underlie them, and clinical course in AF.

Family studies

With the support of the NHLBI's Resequencing and Genotyping (RS&G) resource, PAT investigators screened subjects in the Vanderbilt AF Registry for variants in genes encoding ion candidate channel subunits (KCNQ1, KCNE1-5, KCNJ2, KCNA5, sodium channel [α- and β-subunits], L-type Ca^{2+}) and non-ion channel protein candidates (connexin40, PITX2, ANP). Non-synonymous variants in sodium channel α-subunits, β-subunits, and potassium channels have been identified in ~10% of subjects. These cosegregate in extended kindreds (where they are available), and those studied to date show abnormal electrophysiology *in vitro*.[5,20,21] One common feature in these kindreds is that penetrance is variable; that is, each kindred includes multiple mutation

carriers with early onset AF as well as other mutation carriers with no AF by age 50. As described below, GWAS has identified common variants at chromosome 4q25 as risk factors for atrial fibrillation. We studied 12 families in which AF was present in ≥2 individuals who also shared a rare genetic variant in ion channel or related genes thought to cause familial AF. There were a total of 33 subjects with AF before age 40 and 17 mutation carriers who had reached age 50 without AF. We found a very highly statistically significant association between the presence of common 4q25 variants and clinical AF in these families ($P<10^{-9}$): that is, those family members with AF carried both rare mutation as well the common susceptibility allele, while those with only the rare mutation (without the 4q25 susceptibility allele) did not display AF.[22] These data support the overall concept that AF risk includes multiple genomic components; identifying these components requires large datasets. In addition, the rare ion channel and other variants that we and others have identified in patients with AF have obvious (but as yet untested) therapeutic implications. A gain of function potassium channel mutation would be predicted to respond to a potassium blocking drug, while sodium channel blockers would be predicted to be ineffective (and possibly proarrhythmic) in subjects with AF arising from slow conduction or decreased sodium current.

Candidate gene studies

Candidate gene approaches have been especially useful in pharmacogenomics, where single variants in genes responsible for drug disposition or for the interaction of drugs with their pharmacologic targets may produce large and clinically important variability in drug action.[1] This is especially the case for drugs with narrow therapeutic indexes such as antiarrhythmic and anticoagulant agents. We and many others (including the International Warfarin Pharmacogenomic Consortium)[23-27] have shown that ~50% of the variability in warfarin steady state dose is determined by variants in CYP2C9 (responsible for the drug's metabolism) and VKORC1 (encoding the warfarin target). In addition, PAT investigators have shown that the time to initial anticoagulation is determined by VKOC1 variants. The extent to which warfarin use will be supplanted by newer agents in CABANA is uncertain, but the collection of a large set of patients with well-characterized warfarin responses will be of considerable interest to the IWPC and other investigators in the warfarin and anticoagulant areas.

Proarrhythmia is one well-recognized risk during drug therapy for AF. We have used both candidate and unbiased approaches to address risk for drug-induced torsades de pointes (diTdP) in large cohorts generated by collaborations among multiple sites. Screening coding and flanking regions of these has identified potential contributory rare DNA variants, i.e. sub-clinical congenital long QT syndrome, in <10-20% of patients with diTdP. We used a candidate pathway approach to interrogate 1536 common SNPs in 18 candidate genes and identify rs1805128, resulting in *KCNE1* D85N, as a risk allele: the allelic odds ratio for 176 cases versus 530 drug-exposed controls was 9.0 (95% confidence interval: 3.5-22.9), and the variant allele was present in 8.6% of cases, 2.9% of drug-exposed controls, and 1.8% of population controls. Other drug hypothesis: Do drugs create problems due to genetics? Is there a 'hopeless' patient population?

Unbiased approaches

The GWAS paradigm has been successfully applied to identify risk loci for AF at Chromosomes 4q25, 1q21 and 16q22.[14,15,28] Interestingly, these loci not only represent risk factors for the development of AF, but also appear to predict development of AF after cardiac surgery,[29] stroke,[30] and (in smaller studies) the success of ablation therapy[31] and of antiarrhythmic or rate control therapy in AF.[32,33] The biologic underpinnings of this increased risk are now being explored in mouse models and for the 4q25 locus (the one with the largest signal), evidence points to variable expression of a cardiac isoform of the transcription factor PITX2c.[34,35] Consistent with this observation is the finding that multiple SNPs at the 4q25 locus act independently to modulate AF risk;[36] this finding allows the identification of small sets of subjects drawn from larger databases

(such as CABANA) in whom response to ablative or medical therapies may differ on a genetic basis. GWAS has also been applied to study warfarin steady state dose, and has identified variants in CYP2C9, VKORC1, and CYP4F2 (which plays a role in vitamin K metabolism) with major effects, but no other common variants.[25,26]

4.0 Inclusion/Exclusion Criteria

Inclusion/exclusion in this study is dependent only on inclusion/exclusion in the primary study. The CABANA specific criteria can be found in Appendix A.

5.0 Enrollment/Randomization

All enrollment will be performed at CABANA participating centers and subjects enrolled in CABANA are eligible to participate in this ancillary study. There will be no randomization specific to CABANAgene. No subjects will be enrolled at the CABANAgene Coordinating Center.

6.0 Study Procedures

Consent: PGRN has developed standard suggested language for consent to perform genomic analyses of the type proposed here, subject to local IRB revision. We have created a model consent form in which this language was incorporated and this form is provided to each site for local modification if necessary and IRB submission. IRBs at PGRN affiliated centers have adopted this or very similar language in most instances.

Current NIH guidelines require that the results of large genotyping efforts accomplished with NIH funds be deposited in public databases such as the database for Genotypes and Phenotypes (dbGaP). dbGaP submissions include deidentified phenotypic data; thus, current consent forms include consent for such deposits.

Once consent is obtained, a 30 mL blood sample for subsequent DNA extraction will be obtained at any time during the CABANA trial, preferably at the time of a scheduled venipuncture. Each study site will be provided with kits for mailing the samples to the Vanderbilt DNA Resources Core, where DNA extraction and archiving will be performed. Contents of each subject kit and instructions are listed in Appendix B. If it is determined that a sample is damaged/unusable upon arrival, communication with the sender will be made and a replacement sample will be requested.

The Vanderbilt DNA Resources Core has extensive experience in storing and extracting DNA from over 100,000 individuals. 2D bar-coding of samples and aliquots eliminates repetitive paper work, thereby reducing recording errors. All DNA is currently extracted using the automated Autopure system (Gentra systems, Minneapolis). Samples are logged into the system using a study specific code number to match with the assigned DNA Resources Core sample number, and only the sample number is used thereafter. Each sample must be associated with an IRB-approved consent form. The Autopure system generates very high quality, high yield (routinely 20-30 µg/ml), and substantial consistency across samples. All samples are quantitated and stored at 4°C in a locked cold room. An aliquot is also frozen at -20°C to serve as a back-up in case a sample is accidentally contaminated, lost, or depleted. DNA samples for approved CABANA projects can be provided to investigators in a range of formats, most commonly 96-well plates.

Results of the tests run on specific samples will not be shared with or reported to subjects, care providers, or the general public.

Genotyping

CABANA currently anticipates enrolling in 2009-2015, with an average of approximately 5 years follow-up. Thus initial analyses of end-points will not be available until interim analysis early 2018. We anticipate that investigators will develop hypotheses that require accrual of *specific genotypes* (e.g. CYP2D6 and beta-blocker response; 4q25 variants and response to ablation therapy). Further, we anticipate that the size and scope of the CABANA dataset will provide an opportunity for *directed resequencing* to test other hypotheses (e.g. do patients with a specific AF endophenotype have coding region variants in specific candidate genes?). Finally, we anticipate that *unbiased approaches* will be proposed to address other questions (e.g. are there genomic regions that predict response to ablation therapy?); we anticipate that genome-wide analysis will still be the standard for addressing these questions, although whole genome resequencing may be a competing method by 2014.

Funds to support accrual of DNA at participating centers, mailing costs, and DNA extraction at Vanderbilt have been incorporated into the CABANAgene proposal. We anticipate that the process to access CABANAgene samples by CABANA (or other) Investigators will require submission of a specific study plan, including appropriate quality control and statistical analysis, access to clinical variables in the central CABANA dataset, and approval by the CABANA steering committee.

The current PAT budget includes support for genome-wide genotyping and analysis of genotype-drug response phenotype relations and these will be used to develop a separate PAT proposal to access CABANA samples. The specific questions to be addressed and platform to be used will be selected at the time of projected analysis, at the termination of the trial (~3-5 years after study initiation). Technologies available at the Vanderbilt, and at multiple other sites in PGRN, include Affymetrix and Illumina high-throughput systems, as well as robust lower throughput systems for targeted genotyping, such as the Illumina Bead-station, Sequenom, or Taqman. Genotyping laboratories in PGRN adhere to standard practice, including appropriate negative and positive controls, to ensure that the genotyping results are robust. Genotypic and phenotypic data will be combined in an Oracle database to allow biostatistical and genetic epidemiologic analysis. The PAT center has developed expertise in robust quality control and statistical analyses of these large datasets.

7.0 Risks

Minor soreness and/or bruising when blood is taken, feeling lightheaded, or although rare, continued bleeding or infection at the site of the needle stick are risks involved at the participating centers.

The risk of released PHI exists, but this is minimized by the use of code numbers in the DNA Resources Core.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Any adverse events or unanticipated problems occurring at participating centers will be reported to the IRB of record. Any release of information that occurs will be immediately reported to the PI and the Vanderbilt IRB.

9.0 Study Withdrawal/Discontinuation

Participation in this study is voluntary. A patient who has agreed to participate in this study may leave at any time. This will not affect their regular care or cause them to lose any benefits they

would normally have. If a patient wants to withdraw, they must contact the primary study physician. Samples in storage at the Vanderbilt University DNA Resources Core will be destroyed upon notification from the participating centers. Research data that have already been gathered using the withdrawn subject's sample will not be withdrawn.

The investigator or research sponsor (NHLBI) may decide to withdraw a subject if the study is stopped. The sponsor may stop the study at any time.

10.0 Statistical Considerations

Study power will depend on the number of genotypes and other variables being assessed (the problem of multiple comparisons), the effect size, the sample size, and variance of the phenotype under study. For genome-wide experiments, even in a set of this magnitude, any analysis is likely to be underpowered and to require replication by analysis in other populations or by other approaches (e.g. studies of biologic function). We anticipate that use of the CABANAgene resource will be conditioned on a statistical plan appropriate for the study size proposed.

11.0 Privacy/Confidential Issues

Samples will only be labeled with a study identification (ID) number. No other data will be included that would identify a person. Any health information which might identify the patient will not be available to any person or group other than the investigators of this study. The files with the ID numbers that link the sample to the patient will be kept in a locked, secure area accessible only to the study team. The results of any study using the resource may be published for all the subjects as a group but will not identify the patient individually.

12.0 Follow-up and Retention

Samples for DNA extraction will be collected and genotyping will be performed the 4th year of the study. Following completion of the primary study, data analyses will be performed once genotyping is complete. Genotype data may be archived indefinitely for subsequent analyses. The DNA sample will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed. Samples will be used for research only and will not be sold or used to make products that could be sold for money.

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Appendix A: CABANA Inclusion / Exclusion Criteria

Inclusion Criteria
To be eligible for the trial, subjects must meet all of the following criteria:

1. Over the preceding **6** months have:
   a) ≥2 paroxysmal (***electrocardiographic documentation*** of at least 1) AF episodes lasting ≥1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48h of AF onset): or
   b) ***electrocardiographic documentation*** of 1 persistent AF episode: (sustained for ≥7 days or cardioversion is performed more than 48h after AF onset): or
   c) ***electrocardiographic documentation*** of 1 longstanding persistent AF episode: (continuous AF of duration >1 year).
2. Warrant active therapy (within the past 3 months) beyond simple ongoing observation
3. Be eligible for catheter ablation and ≥2 sequential rhythm control and/or ≥2 rate control drugs.
4. Be ≥65 yrs of age, or <65 yrs with **one or more** of the following risk factors for stroke: Hypertension (treated and/or defined as a BP >140/90 mmHg) [90], Diabetes (treated and/or defined as a fasting glucose ≥126 mg/dl) [91], Congestive heart failure (including systolic or diastolic heart failure), Prior stroke, TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size >5.0 cm (or volume index ≥40 cc/m^2), or EF ≤35. Subjects <65 yrs of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify.
5. Have the capacity to understand and sign an informed consent form.
6. Be ≥18 years of age.

NOTE: Subjects may have recent onset AF (in the past 4-6 months), AF present for a longer time period, or may have been treated with a single anti-arrhythmic drug, providing they remain realistically eligible for ≥2 membrane active drugs and/or ≥2 rate control agents. Patients receiving new drug therapy initiated within the previous 3 months may continue that therapy if randomized to the drug therapy arm. Reasonable expectation of a response to therapy must be present. Subjects will not be excluded because of advancing age or underlying heart disease. Subjects with a history of a single episode of paroxysmal AF do not meet the “crossing the threshold/warranting therapy” litmus test. Subjects with persistent or long-standing persistent AF will require at least 1 documented episode, if it is of sufficient clinical importance that drug or ablative therapy is warranted. Subjects can be randomized before cardioversion, even if restoration of sinus rhythm is a desired endpoint of therapy. Patients may have documented atrial flutter in addition to atrial fibrillation and remain eligible for enrollment.

3.2 Exclusion Criteria

If a subject has ***any*** of the following criteria, he or she may not be enrolled in the study:

1. Lone AF in the absence of risk factors for stroke in patients <65 years of age
2. Patients who in the opinion of the managing clinician should not yet receive any therapy for AF
3. Patients who have failed ≥2 *membrane active* anti-arrhythmic drugs at a therapeutic dose due to inefficacy or side effects (Table 5.2.2)
4. An efficacy failure of full dose amiodarone treatment ≥8 weeks duration at any time
5. Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma
6. Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months

7. Hypertrophic obstructive cardiomyopathy (outflow track)
8. Class IV angina or Class IV CHF (including past or planned heart transplantation)
9. Other arrhythmias mandating anti-arrhythmic drug therapy (i.e. VT, VF)
10. Heritable arrhythmias or increased risk for torsade de pointes with class I or III drugs
11. Prior LA catheter ablation with the intention of treating AF
12. Prior surgical interventions for AF such as the MAZE procedure
13. Prior AV nodal ablation
14. Patients with other arrhythmias requiring ablative therapy
15. Contraindication to appropriate anti-coagulation therapy
16. Renal failure requiring dialysis
17. Medical conditions limiting expected survival to <1 year
18. Women of childbearing potential (unless post-menopausal or surgically sterile)
19. Participation in any other clinical mortality trial (Participation in other non-mortality trials should be reviewed with the clinical trial management center)
20. Unable to give informed consent

NOTE: Exclusion Criterion #3 includes failed membrane active antiarrhythmic drugs started within 3 months prior to enrollment. Prior ablation of the cavo-tricuspid isthmus alone is not an exclusion if the patient develops subsequent recurrent AF. Planned atrial flutter ablation in combination with the left atrial ablation is not an exclusion.

Appendix B: CABANAgene Kit Contents and Instructions

Patient Kit Contents

I. Blood Draw supplies

one pair (1 pair) disposable gloves
one (1) tourniquet
two (2) alcohol Swabs
one (1) #23 or 21 G Butterfly with tube holder
three (3) 5cc EDTA purple top Vacutainer tubes
one (1) gauze ball
one (1) band-aid

II. 3-Tube Mailing System

one (1) absorbent square
one (1) styrofoam container
one (1) strip of red sealing tape
one (1) biohazard bag
one (1) cardboard outer shipping container
one (1) UN 3373 Diagnostic Specimen label
one (1) FedEx ClinicalPak
one (1) FedEx Airbill with completed *ship to* information

III. Instructions with contact information

Instructions for Blood Draw and Shipping

Blood draw and shipping supplies included in the patient kit are listed above. Please draw blood Monday-Thursday and ship overnight via FedEx (or UPS) for arrival at Vanderbilt Tuesday-Friday am. Notify receiving lab by submitting subject sample(s) at website address

I. Blood Draw

1. Draw 3 purple top Vacutainer tubes (5cc each).
2. Mix the blood well with the anticoagulant by gently inverting the tube several times.
3. Label the tubes with the Sample ID. Please keep the samples at room temperature.

II. Shipping

1. Package samples by securely placing the blood tubes in the styrofoam container slots.
2. Place the absorbent pad on top of the blood tubes and close the container.
3. Peel off the protective strip from the red tape and seal the styrofoam container with the tape.
4. Place the sealed styrofoam container inside the biohazards bag and seal the bag.
5. Place the sealed biohazards bag inside the cardboard outer shipping container.
6. Affix the UN 3373 Diagnostic Specimen label to the outside of the cardboard shipping container.
7. Place the shipping container inside the FedEx Clinical Pak and seal the pack
8. Complete the FedEx Airbill, including date and sender information.
9. Ship overnight at room temperature via FedEx.
10. Notify receiving lab of shipment:
    Login to the member page at website address and *Submit Subject Sample(s)*

III. Ancillary Study Contact: Kris Norris, RN
Phone: 615-936-1131
Fax: 615-936-2222
E-mail: kris.norris@vanderbilt.edu

IV. Shipping Address: Vanderbilt University Medical Center
1266 MRB IV
Nashville, TN 37232-0575