CABANA TRIAL

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

Protocol
Version 2.*6*
(October 10, 2007)

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Summary

The investigator-initiated, **C**atheter **Ab**lation Versus **A**nti-arrhythmic Drug Therapy for **A**trial Fibrillation (**CABANA**) Trial is designed to test the hypothesis that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of the elimination of atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or anti-arrhythmic drugs for reducing total mortality (primary endpoint) and decreasing the composite endpoint of total mortality, disabling stroke, serious bleeding and cardiac arrest (secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy. The need for this trial arises out of 1) the rapidly increasing number of pts ≥ 60 years of age with AF accompanied by symptoms and morbidity, 2) the failure of anti-arrhythmic drug therapy to maintain sinus rhythm and reduce mortality, 3) the rapidly increasing application of radio-frequency catheter ablation without appropriate evidence-based validation, and 4) the expanding impact of AF on health care costs.

This 125 center mortality study will randomize 3000 pts over 3 years to a strategy of catheter ablation (n=1500) vs. state-of-the-art rate or rhythm control drug therapy (n=1500). Each pt will have 1) characteristics similar to AFFIRM pts (>65 yo or ≤ 65 with ≥1 risk factor for stroke, 2) Documented AF warranting treatment, and 3) Eligibility for both catheter ablation and ≥ 2 anti-arrhythmic or ≥3 rate control drugs. Pts will be followed every 6 months for ≥ 2 yrs and will undergo repeat trans-telephonic monitor, Holter monitor, and CT/MR studies to assess the impact of treatment. The primary and secondary endpoints will be examined in pts with paroxysmal, persistent, or permanent AF, without regard to age or underlying heart disease.

With the anticipated mortality rate of 12% in drug treated patients, 1500 patients in each treatment group should reveal a >30% relative reduction in the primary mortality to ≤9%, at 90% power. Freedom from AF rates of 70% in the ablated pts and 30% in the drug treated pts should detect a >33% reduction in AF, at ≥90% power. The CABANA trial will disclose the role of medical and non-pharmacologic therapies for an ever-escalating national healthcare dilemma, establish the cost and impact of therapy on quality of life and will help determine if AF is a modifiable risk factor for increased mortality. CABANA will be a landmark trial that will shape therapy and health care policy in the AF arena for years to come.

Research Plan

Introduction

This Clinical and Administrative Center R01 Proposal describes the investigator-initiated, 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 a sufficiently broad spectrum of patients, to allow far-reaching applicability to the dramatically increasing numbers of patients with this arrhythmia. This trial arises out of the AFFIRM, RACE, STAF and other investigations of rate versus rhythm control therapy, and the International AF Ablation Registry. Although the development of this trial began several years ago, the CABANA trial is also directly responsive to the preliminary recommendations of the NHLBI-convened "AF Ablation Work Group" that met on September 13, 2005 "to advise the NHLBI on the types of clinical studies the Institute should support or initiate, and to assess the place of catheter ablation for the treatment of AF." This group, which included Dr. Packer, came to a consensus for the need of a large, multi-center clinical trial to examine outcomes of AF ablation in comparison to drug therapy. We believe that a total mortality trial, conducted with a population at increased risk will provide the most compelling endpoint for reaching this goal. The CABANA trial format has been revised based on the Work Group discussions, and on conversations with the NHLBI over the past 12 months. We also met with the FDA on October 7, 2005 to review the trial, and an IDE application was submitted and conditionally approved on June 8, 2006, with full approval on August 18, 2006 (IDE# G050233/S002). In that process, the CABANA Trial was also designated a CMS category B2. The CABANA Pilot Study design was also approved by the Mayo Clinic IRB on September 7, 2006.

This proposal is a collaborative effort between:

- Mayo Clinic (MCAR), Douglas L. Packer MD, Rochester, MN Clinical / Admin Coordinating Center]
- Duke Clinical Research Institute (DCRI), Durham, NC, Kerry L. Lee PhD, [Coordinating Center]
- Duke Clinical Research Institute (DCRI), Durham, NC, Daniel B. Mark MD, [Economics and Quality of Life]
- The Biomedical Imaging Resource Center, Rochester, MN, Richard Robb PhD, [CT / MR Imaging Core]
- Seattle Institute of Cardiovascular Research (SICR), Seattle WA, Jeanne Poole MD, [ECG/TTM Core Lab]
- The National Heart, Lung, and Blood Institute (NHLBI), Bethesda Maryland, and the International CABANA Investigators at 125 enrolling centers.

The application is made as 4 linked R01 proposals from the first four of the component centers. The organization of the trial is as shown in Figure 1.

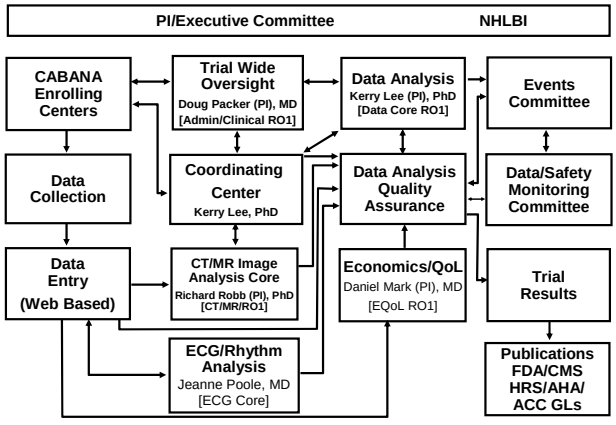

Figure 1

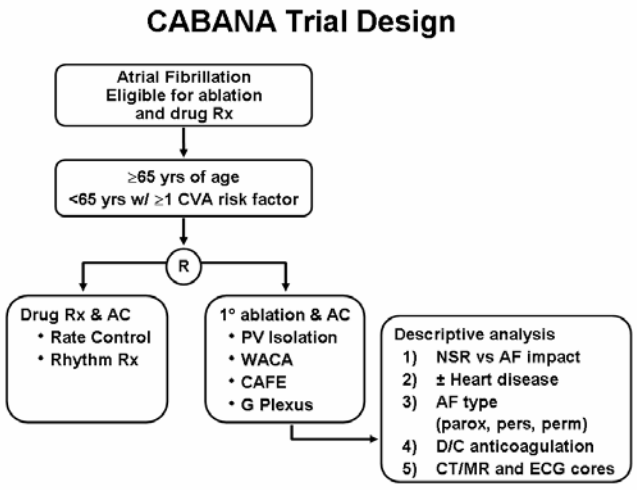

Figure 2

This document is the Administrative/Clinical Coordinating Center proposal, with companion applications including the trial Coordinating Center proposal submitted by Dr. Kerry L. Lee, the CT / MR Imaging Core proposal from Dr. Richard A Robb and the Economics and Quality of Life proposal submitted by Dr. Daniel B. Mark. Additional details related to this proposal, letters, and supportive material is appended to this application.

A. SPECIFIC AIMS

The **Primary Aim** of the CABANA Trial is 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 anti-arrhythmic drugs for reducing total mortality in patients with untreated or incompletely treated AF.

The **Secondary Aims** of CABANA are to compare the following outcomes in patients undergoing Catheter ablation and drug treated patients:

1. A composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest
2. Cardiovascular death
3. Cardiovascular death or Disabling stroke
4. Arrhythmic death or Cardiac arrest
5. Heart failure death
6. Freedom from recurrent AF
7. Medical costs and resource utilization and cost effectiveness
8. Quality of Life
9. Composite adverse events

This trial will also determine the impact of age, AF type, symptom state, and presence of underlying disease on these outcomes, and will establish the importance of AF elimination in this population of patients.

B. BACKGROUND AND SIGNIFICANCE

B.1 Rationale for the Primary Hypothesis

B.1.1 Atrial Fibrillation: The Problem

Atrial Fibrillation is an increasing burden on the US Health Care system because of an increasing incidence, unbridled progression, accompanying mortality, stroke risk and skyrocketing costs.

Increasing 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 in 2001, with a projected increase to 5.6 million by the year 2050 [1,2]. 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 [3-5].

Progression of AF

In addition to validating these numbers, a variety of studies have examined the natural history of AF. While many patients with paroxysmal AF show little propensity for arrhythmia progression, the majority of studies document a transition to more persistent AF in many patients. For, example, the Canadian Registry of AF (CARAF) showed that 63% of 757 patients with paroxysmal AF had recurrent arrhythmia over a 5 year period, and progression to permanent AF was seen in 25% [6]. Similar numbers have been documented by others [7,8], although Olmsted County population based studies suggest a rate of < 25% [9].

AF Mortality and Stroke Risk

There is also reason to anticipate an increasing impact of this arrhythmia on mortality. In the Framingham study [10], 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 is further incremented in those individuals between the ages of 75 and 94 years, in whom the mortality rate increased from around 30% to

nearly 70% in the presence of AF [10]. A relationship between AF and stroke has also been demonstrated in both population-based and cohort studies. Up to 50% of individuals with a new stroke, have underlying (potentially related) AF. This risk increases with age over 50 years [11-13] from an attributable risk of 1.5% in the 6th decade of life to 23.5% in 80-89 year olds [13]. That this problem is increasing is corroborated by another population-based study from Olmsted County demonstrating an increasing prevalence of stroke related to AF over the past 3 decades, which may be due to increasing AF occurrence [14].

Health Care Costs

Furthermore, this illness is a rapidly increasing burden on the health care system due to inpatient hospitalization and outpatient care costs. Data from the National Discharge Survey, 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 [15]. Other studies have shown an increase in hospitalizations, as well as nursing home requirement because of this arrhythmia [15-16]. The cost of this hospitalization and drug therapy is likewise increasing [17]. The projected numbers of patients with this arrhythmia suggest an even greater increase in these costs in the future.

B.1.2 Atrial Fibrillation: Drug Therapy Outcomes

The medical approach to patients with AF by definition requires poly-pharmacy. Specifically, many patients with recurrent AF show inappropriately rapid heart rates, requiring therapy directed at improving rate control. Other patients, 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 drug therapy. Despite years of experience with these membrane-active agents, health care providers remain unenthusiastic about their limited efficacy and increased proarrhythmic risks.

Anti-Thrombotic Therapy

The critical importance of anti-thrombotic therapy in the management of patients with AF has been established in a wide variety of trials. The AFASAK, SPAF, BAATAF, EAFT, and CAFA, trials have all demonstrated a reduction in the risk of stroke with aggressive anticoagulation with warfarin [18]. While several of these trials demonstrate a benefit with aspirin, this has been less impressive than with warfarin anticoagulation alone. In addition, the response to clopidogrel and aspirin has been disappointing as shown in recently reported ACTIVE trial data [19]. Although not an objective of several more recent studies comparing rhythm control versus rate control for the treatment of AF, both the AFFIRM and RACE trials clearly demonstrated excess stroke morbidity in patients in whom warfarin anticoagulation was discontinued [20,21]. Specifically, in the AFFIRM trial, 79(5.9%) patients treated with rate control had a thromboembolic event, while an increased number of 84(7.6%) patients in the anti-arrhythmic drug therapy group had comparable events [20]. In rhythm control patients, events occurred after discontinuation of warfarin or in those with inappropriate levels of anticoagulation (based on INRs). Similar findings have been reported in the RACE trial [21]. Perhaps the most crucial contribution of these trials was the clarion call to maintain anticoagulation, even if sinus rhythm had been restored and maintained. This finding may be related to occurrence of asymptomatic AF, seen in 40-60% of patients, even in the absence of symptomatic arrhythmia [22-24]. In the absence of appropriate validating trials, it remains unclear whether these data apply to post-ablation patients.

Drug Therapy for Rate Control

In many patients with new onset AF, therapy with rate control agents alone can be valuable. Agents such as beta-blockers, calcium channel blockers, or even digitalis may control heart rate in the majority of patients treated aggressively. The AFFIRM trial demonstrated that 65% of patients so treated had appropriate rate control at one year, with 70% at two years, and 75% at three years [20]. Comparable findings were seen in the RACE trial [21]. Combination therapy for rate control is required in many patients [25]. Nevertheless, patients so treated require anticoagulation for their AF and may have a variety of constitutional side effects.

Drug Therapy For Maintaining Sinus Rhythm

A variety of small randomized and non-randomized trials have demonstrated 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 the recent larger comparative clinical trials [Appendix A]. In AFFIRM, 82.4% of patients

treated with membrane active anti-arrhythmic drugs were in sinus rhythm at the end of one year, 73.3% at three years, and 62.6% at five years [20]. This is in comparison with the 43% prevalence of sinus rhythm at one year, which decremented to 34.6% at 5 years in those receiving Nodal blocking agents alone.

It should be noted however, that many more of these patients, in sinus rhythm at the time of each 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 three years. This was significantly better than the 52% recurrence of AF in sotalol-treated patients at one year, and 71% recurrence at 3 years [26]. The findings were similar in RACE, with only 39% remaining in sinus rhythm at the end of the trial [21], and only 38% at two years in STAF Trial patients [27]. While this has translated into an improvement in the quality of life of patients treated with membrane-active drugs, a comparable quality of life was achievable with rate control alone [20,21,28,29]. In addition, an increase in morbidity and mortality risk with membrane-active drug therapy has been suggested. While some of this may be attributable to proarrhythmia, patients in AFFIRM also had excess non-cardiac mortality. Nevertheless, the quest for maintaining sinus rhythm remains viable for patients with highly symptomatic AF, where class III drugs fare better than 1C agents [26].

Mortality Benefit of Drug Therapy in Randomized Trials

The morbidity and mortality response to drug therapy designed to prevent AF has been disappointing. At least 4 studies [Appendix A] have provided outcomes data detailing the impact of rate control vs. rhythm control treatment strategies on a variety of composite endpoints, including mortality and serous adverse event rates [20,21,27,28]. The AFFIRM Trial, conducted in patients who were at increased risk because of underlying age or the presence of risk factors for stroke, demonstrated equivalent mortality outcomes in patients treated with rate control vs. rhythm control strategies [20]. Specifically, there were 310 deaths (21.3% at 5 yrs.) in the rate control group vs. 356 deaths (23.8% at 5 yrs.) in the rhythm control population p=0.08, producing a hazard ratio of 1.15. (0.99-1.34) for anti-arrhythmic drug therapy. Patients treated with rhythm control were also more likely to require rehospitalization (80.1%) compared to rate control patients (73.0%) [p<0.001] and rhythm control therapy was likewise more expensive [30]. Outcomes were also similar in both groups in the secondary endpoint of death, disabling stroke or anoxic encephalopathy, major bleed, or cardiac arrest. Importantly, similar trends of mortality and composite endpoints were seen in the RACE [21], PIAF [29], and STAF [27] trials. This disappointing finding of unclear mortality benefit from rhythm control could indicate that 1) other underlying factors (other than AF) control morbidity and mortality, 2) AF is a risk factor, yet silent AF remains despite anti-arrhythmic drug therapy, or 3) offsetting proarrhythmia or other untoward drug-related adverse events counter any benefit from membrane-active drugs.

These data have been used to suggest a preference for a rate control strategy in these patients, rather then exposing them to the risk of anti-arrhythmic drug therapy. Any recommendation for rhythm control must also be tempered by the pro-arrhythmic risk and occurrence of intolerable side effects from these drugs. In the AFFIRM trial, 5% of patients had a pro-arrhythmic event [31], with drug discontinuation because of side effects in 10% of rate control and 30% of rhythm control patients [20,21]. Because of the specific demographics of the patients studied, these data may be incompletely applicable to younger patients without heart disease. In addition, as suggested by accompanying editorial opinion, it is possible that only 40 to 50% of eligible patients were enrolled in these trials, in part because of bias toward rhythm control in the most symptomatic patients.

B.1.3 Atrial Fibrillation: Un-validated Ablative Therapy

Single Center Ablation Success Rates

The efficacy and safety outcomes of catheter ablation for AF are available in the form of descriptive reports from individual centers [Appendix B]. These clinical studies document AF elimination rates of 55-80% with lasso-guided ablation of paroxysmal AF [32], with an increased success rate to 70-90% using more aggressive wide area circumferential or high frequency, complex electrogram-guided ablative approaches [33,34]. 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 portion of the left atrium, and the disruption of candidate initiation and substrate-mediated maintenance mechanisms of AF [33]. These studies are flawed by the absence of randomized enrollment, variability in techniques, differences in end-points, and the use of blanking periods. Moreover, the 52% ablation success rate seen in the recent International AF Ablation Registry detailing outcome in 8,745

patients from 181 centers ablated between 1995 and 2002, suggests that the efficacy rate of ablation may be appreciably less than seen in earlier observational studies [35].

While the above-mentioned randomized trials disclose the side effects of drug therapy, the complication rates of ablative intervention have been inadequately documented. While recent studies demonstrated a 1% stroke rate with ablative intervention and a reduced PV stenosis rate down to 1-2%, the same International AF Ablation Registry suggested that serious ablation event rates are closer to 6% [34]. Additionally, no study provides documentation of outcomes over follow-up >12 months. The occurrence of strokes, PV stenosis, tamponade and the recently reported lethal atrial-esophageal fistulae [36], suggest that the true complication rates of AF ablation have yet to be established. Although not disqualifying available descriptive reports, the variability of outcomes also identify the need for rigorous clinical trials to establish the merits of ablation and provide data bearing on relative safety and efficacy in comparison to medical treatment.

Comparative Ablation Trials for Atrial Fibrillation

At present, even fewer long-term data detailing the impact of the catheter ablation of AF on mortality or major morbidity are available. An early ablation trial, comparing catheter-based intervention and drug therapy in 1,171 patients, showed that 38 of 589 (6.5%) ablation patients died over a median of 900 days of follow-up, which was significantly less than the 83 of 582 (14%) mortality rate in medically treated patients [34]. Morbidity rates were also reduced from 91 to 81% in ablation treated patients.

Results of a smaller, appropriately randomized study, the CACAF Trial, were also recently reported [37]. In this study, 68 patients, including 25 who had undergone prior ablation were treated with catheter-based radiofrequency ablation, while 69 were treated with anti-arrhythmic drug therapy. One of the ablation patients (1.5%) and one in the control group (1.5%) sustained a stroke, and 2 patients (3%) in the drug control group died over the course of 12-month follow-up. Thirty (44%) of ablated patients and 63 (91%) of drug treated patients developed recurrent AF ($p < 0.001$, hazard ratio of 3.2).

Additionally, the feasibility of PV isolation as first-line therapy for treating patients with symptomatic, and largely paroxysmal AF was considered in 70 patients with AF episodes for at least 3 months in the RAAFT Trial [38]. Recurrent AF, seen in 22 (63%) of 35 drug treated patients, was significantly more common compared to only 4 of 32 (13%) similarly followed patients undergoing ablation ($p < 0.001$). Over one-year of follow-up, hospitalization was required in 19 (54%) of anti-arrhythmic drug treated patients compared with only 3 (9%) of those ablated ($p < 0.001$). While no patients sustained thrombo-embolic events, 2 (6%) of the ablated patients developed mild-moderate PV stenosis. No mortality was seen in either treatment group. Quality of life was substantially better in the ablated group as established by serial SF-36 assessment. Of note, however, 4 patients with recurrent AF in the ablation treated group required a second procedure.

Another recent trial conducted in Milan, Italy likewise showed a higher ablation success rate for eliminating AF than seen in drug treated patients [39]. The Ablation for Paroxysmal Atrial Fibrillation (APAF) trial randomized 198 patients to flecainide, sotalol or amiodarone vs catheter ablation. In a sub-study of 150 patients, these investigators showed a significantly better AF free outcome with ablation than drug therapy (87% vs 29%, $p <0.001$) at one year of follow-up. Five of the ablation patients required drug therapy, and 3 underwent re-ablation. Thirty-eight of 52 drug treated patients (73%) crossed over to ablative therapy. Finally, the results of the Atrial Fibrillation Ablation vs Anti-arrhythmic Drugs (A4) Trial were reported at the recent Heart Rhythm Society Annual Scientific Sessions. Dr Jais and coworkers [40] found that 40 of 53 ablation patients (75%) were free of recurrent AF, which was substantially better that the 7% AF freedom (4 of 59) with drug therapy. In this trial, 63% of drug treated patients crossed over to ablative therapy. Since patients over the age of 75 years and patients with underlying disease were largely excluded, these early trial results may not apply to the increasing elderly population of AF patients at risk for untoward AF related morbidity and mortality. Nevertheless, these data show similar rates of AF elimination, and all favor ablative intervention.

B.1.4 Mortality Rationale For A Randomized Ablation Vs Drug Trial

While highly important, these data do not address the additional far-reaching question of the merit of maintaining sinus rhythm for reducing morbidity and mortality. If AF is a risk factor for excess morbidity or mortality, its elimination should produce a demonstrable impact on event rates. In contrast, if AF is only a

marker of risk due to other underlying pathophysiology, its elimination should not alter long-term outcomes. Recent data from the AFFIRM trial provide a glimpse into this issue. In a post-hoc, time-dependent co-variate assessment of the relationship between cardiac rhythm and survival in the AFFIRM Trial, warfarin therapy and the presence of sinus rhythm were associated with a lower risk of death (HR = 0.53 with 5-99% CI= 0.39-0.72 (p-value < 0.0001) [41]. Similarly, 18 of 19 primary endpoint events in the STAF trial occurred in those patients remaining in AF [27]. Interestingly, 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 myocardial infarction or heart failure [42]. 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. This effect was also seen in the placebo group where survival was 50% in those in sinus rhythm and less than 40% in those without. Pappone et al [33] in his comparative trial noted an excess of adverse events occurring in those patients remaining in AF: 72% percent of all adverse events were observed in patients in AF, including 79% of all ischemic strokes. Obviously these studies are limited by numbers and the post-hoc nature of the analyses.

The only available prospective data bearing on the issue of post-ablation mortality come from Nademanee et al [43], who examined outcomes in AFFIRM-like patients undergoing AF ablation. This study demonstrated a reduction in mortality following LA ablation in patients remaining in sinus rhythm, compared to those with ongoing AF. The death rate was 2.7% in successfully ablated patients vs. 16% in those remaining in AF (p=0.005). While these data have not yet been published, these trials taken together, along with data from population-based studies, provide the theoretical underpinnings for a large, multi-center trial to prospectively examine the impact of sinus rhythm on overall mortality outcomes in patients with AF.

Given the limitations of both drug and ablation therapies, it is difficult to mandate one approach over the other in any given patient population. We nevertheless believe that information from thoughtful randomized mortality trials is critically needed to provide a reasoned basis for the continued application of advanced ablation technology and justify its concomitant cost. Despite limitations, we believe that we have sufficient information to estimate the relative merits of these therapies in terms of elimination of AF and mortality.

B.2 Rationale for ECG / Rhythm Assessment

Most studies examining outcomes of drug and ablative therapy use symptomatic episodes of AF for establishing endpoints. While this gives a clear foundation for assessing AF burden and quality of life, it is an inadequate basis for making critical decisions regarding ongoing anticoagulation. The AFFIRM trial demonstrated excess mortality and morbidity in anti-arrhythmic drug treated patients in whom warfarin had been discontinued [10]. Presumably, these patients were felt to have complete control of their AF by anti-arrhythmic drug therapy. It is unclear whether their subsequent events were due to undetected silent AF, or some other underlying factor responsible for ongoing events. A variety of studies have documented a high prevalence of asymptomatic or “silent” AF in other settings [22-24,44,45]. Several recent ablation studies have also shown that 10-40% of successfully ablated, asymptomatic patients may have silent AF [46,47]. This raises the possibility of continuing stroke risk, even though symptoms are eliminated. Nevertheless, others have reported far lower occurrence rates of asymptomatic AF, questioning the validity of these recent studies [34,48]. These continuing issues provide the clear rationale for careful monitoring of patients in this trial, whether they are treated with medical or catheter-based therapy. A clear delineation of on-treatment rhythm will also be required to make recommendations for discontinuing anti-coagulation.

B.3 Rationale for Cost and Quality of Life Investigations

AF is responsible for almost 500,000 in-patient hospitalizations in the US every year [49-51]. The direct medical costs associated with AF account for several billion dollars of excess health care spending a year in this country. At the individual level, AF increases medical spending from 9 to 22 times that for similar patients without AF. AF also causes significant impairment in quality of life (QOL). Case control studies have suggested this impairment is between that of having 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 with the aging of the US population, more effective therapy offers the potential of relieving suffering in a substantial and 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, currently in use in recent or ongoing trials (OAT, STICH and SCD-

HeFT). This component of CABANA will establish the cost effectiveness of drug and ablative therapies, and clarify quality of life achieved with successful therapy, and its dependence on the elimination of AF.

B.4 Rationale for Non-Invasive Cardiac Imaging Studies

Atrial remodeling, occurring with AF has been well documented [52-58]. In other cases, however, it is difficult to know whether changes in atrial structure were due to AF, or were triggered by underlying disease. Follow-up studies suggest a reversal in anatomic remodeling with drug therapy. Nevertheless, it remains uncertain whether a similar reversal of underlying atrial dysfunction or enlargement occurs following ablation. In theory, elimination of AF should produce both electrical and anatomic remodeling, regardless of the therapy used to accomplish that goal. It is possible, however, that ablation may produce scarring or other changes that counter any beneficial effect from elimination of AF. At present, post-ablation studies describing LA size and function outcomes are contradictory. In an early effort, Pappone et al [52] showed a 10% improvement in LA function after ablation. Beukema et al [53], also found a 3-4mm decrease in LA size following successful ablation in patients with either paroxysmal or persistent AF. In contrast, LA size actually increased by a comparable amount in patients with recurrent arrhythmias. Similar findings were observed by Tops and coworkers [54], with a reduction in atrial dimensions in those in whom AF was eliminated versus LA enlargement in those with continued AF. An 18% reduction of LA size in patients with paroxysmal AF, a 23% reduction in those with permanent AF, along with an improvement in echocardiographically assessed LV EF following segmental PV isolation has also been reported by others [55,56]. In contrast, Lemola et al, [57], showed a decline in LA EF as measured by serial CT studies in patients with paroxysmal AF undergoing more extensive left atrial circumferential ablation. A partial return of LA function was seen in patients undergoing ablation for permanent AF, although this remained below the post-ablation LA function level seen in individuals without AF. We have preliminary data suggesting that the LA dysfunction remains beyond the traditionally applied 3-month time frame for stopping anti-coagulation [58]. These data suggests an improvement in LA size and function may be seen following more limited PV ablation, although this might be offset by more aggressive intervention. Additional studies will be required to more specifically document the occurrence of remodeling and assess whether this in turn has an impact on stroke risk and the use of post-ablation anti-coagulation.

An Image Analysis core will be required to provide morphological data critical in understanding the roles of such remodeling and more directly, reverse remodeling following therapy for AF. We will thereby assess differences between drug and ablative therapy, and expand the understanding of AF phenotypes, thromboembolic risk, and its elimination with therapy. The infrequent but potentially catastrophic adverse impact of ablation on structures adjacent to the LA will also be carefully examined with emphasis on the AVs and the esophagus. Ongoing imaging studies should also establish the true occurrence risk of PV stenosis.

B.5 Potential Impact of the Trial on Clinical Practice

This trial is of substantial importance at multiple levels. Clinically, the trial is of considerable importance in establishing or rejecting the role of aggressive catheter ablation in the treatment of AF. 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 or 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 and quality of life outcomes.

Scientifically, the trial will determine whether the attainment of normal sinus rhythm is of mortality or morbidity advantage. No trial to date has prospectively addressed this issue, nor will any currently envisioned 1-2 year study be powered to look at mortality. The trial should also provide outcomes-based support for the role of AF as a modifiable risk factor for increased morbidity and mortality. In addition, the trial will establish the impact of age, AF type, or underlying disease on the outcome of ablation, and whether these factors are more problematic than with drug therapies.

From a health care policy standpoint, this trial will disclose the place for medical and non-pharmacologic therapies for an ever-escalating national healthcare dilemma. Aggressive intervention on an increasing number of patients, resulting in a mushrooming burden to society in general and limited health care resources

in specific, may or may not be justified. The Quality of Life and cost components of the trial will firmly establish whether ablation therapy represents good value for the money and is therefore 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 diffusion of this technology on the overall health care system. These unresolved issues strongly favor proceeding with this study. We believe that a critical window of opportunity for a randomized trial is now present, and that the outcome of this landmark trial will shape therapy decisions and health care policy in the AF arena for years to come.

C. PRELIMINARY STUDIES AND CABANA TEAM EXPERIENCE

C.1 CABANA Trial Investigator Experience

General Trial Management and Oversight: Douglas L. Packer, MD, will serve as the overall PI of the trial. Dr. Packer is an internationally respected cardiac electrophysiologist with extensive expertise in the ablation of cardiac arrhythmias in general, and AF treatment in specific. He is a Professor of Medicine at the Mayo Clinic School of Medicine, the Director of the Applied EP Translational Laboratory, and is also the Director of the Mayo Clinic Cardiac Electrophysiology / Heart Rhythm Service. He is the Treasurer and a member of the Executive Committee of the Heart Rhythm Society (HRS) and has been involved extensively in NIH-sponsored clinical trials. He was on the executive/ steering committees of the MUSTT and SCD-HeFT trials, and the ongoing HAT trial. He designed the end-points adjudication methods and is the chair of the Events Committee for both the SCD-HeFT and HAT trials, and was a site PI in the AFFIRM trial. Dr. Packer was also a member of the recent NHLBI-convened AF Ablation Work Group, and is part of the ongoing "FDA / Heart Rhythm Society Task Force on AF Ablation" impaneled to recommend new clinical trial strategies in the ablation device approval process. He is also a member of the executive committee of the International Ablation Registry and is co-editor of the HRS-initiated AF Ablation Consensus Document writing group.

Data Coordinating Center: Kerry L. Lee, PhD, will serve as the PI of the Coordinating Center at the Duke Clinical Research Institute (DCRI). Dr. Lee has been the faculty leader of all clinical trial statistics at the DCRI since 1985. He is a senior clinical trial bio-statistician with extensive expertise in the conduct of large NIH-funded clinical trials such as the MUSTT, MOST, SCD-HeFT, and currently the HAT and STICH trials, as well as numerous industry-sponsored studies including the large GUSTO trials. He is an Associate Professor of Bio-statistics and Bio-informatics at Duke University, has authored over 200 peer-reviewed articles and is widely considered to be the preeminent cardiac arrhythmia trial statistician in the US. He has also chaired the American Statistical Association's Biometrics Section and has been a past member of the NHLBI's Clinical Trials Review Committee.

Economics and Quality of Life: Daniel B. Mark, MD, MPH, will serve as PI of the Economics and Quality of Life Core, which will be submitted as a linked RO1 application. Dr. Mark is a Professor of Medicine at Duke University Medical Center and a clinical cardiologist who directs the 70 member Outcomes Research Group in the DCRI. This team is considered one of the best in the world at performing outcomes research, economic impact evaluation, and QOL studies for large NHLBI sponsored studies. Dr. Mark has authored over 170 peer-reviewed publications. These have included the recently completed SCD-HeFT trial, as well as the ongoing OAT, STICH, TACT, and HAT trials. He was responsible for the economic and quality of life sub-study for the 41,000-patient GUSTO-I mega-trial and sub-studies in the ESSENCE, EPISTENT, and PURSUIT trials, among many others. He is also the current Editor of the American Heart Journal.

CT/MR Imaging and Analysis Core: Dr. Richard Robb, PhD, has directed the Biomedical Imaging Resource Center at Mayo Clinic for 25 years, and is a world-renowned expert in multi-dimensional, multi-modality biomedical imaging. He is the author of several books, and several hundred articles on biomedical imaging, visualization, and analysis. He has had NIH funding for 30 years and is currently the PI of a NIBIB research grant examining the development and validation of methods and systems for incorporation of 4/5-D imaging in cardiac arrhythmia ablation. He will lead the imaging core as described in the CT/MR Imaging RO1.

ECG / Trans-telephonic Monitoring Core: Jeanne Poole, MD will serve as the Director of the ECG / TTM core, which will be responsible for rhythm assessment and AF recurrence determination. Dr Poole is an Associate Professor of Medicine and Director of the Arrhythmia Service and Electrophysiology Lab at the

University of Washington in Seattle. She was a co-Investigator for the recent NIH-funded SCD-HeFT Trial and the ongoing Home Automatic External Defibrillator Trial (HAT) and is the director of the ECG Core Labs of both of those studies. She has had substantial experience in receiving, reviewing, adjudicating and synthesizing large numbers of rhythm strips from over 100 centers as will be required by this trial. The Seattle Institute of Cardiac Research, where she is active, is the clinical coordinating center for the SCD-Heft and HAT Trials.

C.2 Studies Bearing on the Design and Conduct of the Trial

Recently, several preliminary studies with mortality data have been compiled by members of the CABANA team [59-61]. We now have preliminary data bearing on mortality in the Mayo Clinic AF ablation patients. Outcomes in 731 patients undergoing circumferential PV ablation for AF were compared with a 4609 AF patient, age and gender-matched control population from Olmsted County, Minnesota [59]. Twenty one percent of the ablated patients had underlying heart disease. Over an average follow-up of 18$\pm$16 months, 10 patients died, including 5 of cardiac causes. The projected 5-year survival was 94% (CI 87-100) after AF ablation vs. 52% (CI 51-54) in controls, p<0.001. In patients with paroxysmal AF, the 5-year survival was 98% (CI 96-100) after ablation vs. 53% (CI 51-55) in controls, p<0.001. In patients with persistent/permanent AF, the 5-year survival was 85% (CI 65-100) after RF ablation vs. 50% (47-53%) in controls, p<0.001. After adjustment for age and gender, ablation remained associated with significantly improved survival [HR 0.16 (CI 0.09-0.30), p<0.001]. If the control group was restricted to patients <65 years of age, the survival benefit after RF ablation persisted [HR 0.10 (0.05-0.19) p<0.001]. Within 3 months, all 8 Quality of Life scores established from SF-36 assessment normalized to those of the healthy population. These data demonstrate low long-term mortality in ablation patients, which is significantly better than in gender, and arrhythmia-matched patients in the community. This reduction in mortality is also greater than seen in patients undergoing AV node ablation and pacemaker implantation [60]. Taken together, this information supports the feasibility of a prospective clinical trial showing a difference in mortality in successfully ablated patients versus those with ongoing AF.

The data from Nademanee and coworkers [43] 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$75 years of age, and 124 with an EF<40%. 40% had paroxysmal, 26% had persistent, and 34% had permanent AF. Each patient underwent ablation (374 only 1 session, 121 underwent 2 sessions, 43 underwent 3 sessions and 2 patients 4 sessions), and 492 were followed for 4.2$\pm$1.1 years. The 2.7% long term mortality rate in the 431 (86%) patients remaining in normal sinus rhythm was substantially better than the 16% death rate in the 63 (14%) who remained in AF (p<0.0001). Warfarin was discontinued in 392 (80%) patients, whose stroke rate was only 1% compared to 2.7% in those with continued warfarin treatment. Using a Cox-proportional hazards model, sinus rhythm was the most important independent predictor of favorable survival outcome (p=0.002), whereas EF and warfarin therapy had little prognostic value in this patient population. While very preliminary, these data provide early support for a mortality benefit conveyed by sinus rhythm following successful ablation of AF. This is particularly critical in that this occurred in the very population to be studied in CABANA.

C.3 CABANA Trial Survey Results

The likelihood of successfully completing the CABANA Trial was also examined via a detailed survey sent to 79 potential North American investigators [61]. Fifty-five (70%) see >10, and 18 (23%) see 5-10 new AF patients each week. Sixty-three (69%) see >7 new untreated or minimally treated patients. Forty-two (53%) of these investigators see >6 new patients with underlying disease. Seventy four (95%) were comfortable using membrane active drug therapy without a prior trial of rate control agents alone. Sixty-five investigators (83%) believed AF ablation to be an established therapy in large medical centers only, 9 (12%) felt that it was established everywhere, and 3(4%) felt that it was still investigational. Of these centers, 39 (51%) perform 5-10 AF ablations each month, 20(16%) do 10-20 cases, and 10(13%) perform 20-30 ablations each month. Over 90% use PV isolation as an acute endpoint for ablation. Forty-three (85%) said that the PV stenosis rate was 1% and 20 (27%) said it was 2-3%.

More importantly, 33(43%) reported that their comfort zone for ablating AF as first-line therapy was high, and 35 (45%) said that it was medium, indicating the need for a trial to more definitively establish ablation as

first line therapy. Fifty-nine (76%) were comfortable in ablating patients with LV dysfunction. Fifty (65%) were comfortable in ablating patients over the age of 70 years. Fifty six (72%) of investigators were comfortable with implanting a Reveal type loop recorder in their ablative patients. When asked whether this trial could be done now, 40 (52%) responded absolutely, and an additional 29(38%) said yes. Level of enthusiasm for CABANA was high or very high in 74 (95%). Only 4 centers were involved in 2 other AF ablation trials. In establishing the number of available centers and level of enthusiasm of the investigators, these data support the feasibility of CABANA, the level of comfort each center has in enrolling a broad spectrum of patients, yet the need for outcomes based data to guide treatment decisions.

C.4 CABANA Pilot Study

In anticipation of the pivotal CABANA Trial, we have initiated the CABANA Pilot Study, funded by a grant from an industry partner. Up to 15 centers will be enrolling patients meeting the CABANA inclusion and exclusion criteria. Obviously, we will not be able to test our primary mortality hypothesis in the pilot study, although it will 1) assess the 12-month efficacy of left atrial ablation for AF, 2) compare the 12-month efficacy outcomes of ablation and drug treatment, 3) establish preliminary medical costs and resource utilization, 4) establish our analytical instruments for assessing quality of life and describe their data, and 5) demonstrate the feasibility of recruiting, enrolling and conducting the trial. In so doing, this pilot study will gather preliminary data to optimize the study design of the Pivotal Trial. We believe that we will have sufficient information demonstrating feasibility, and our ability to successfully conduct this extremely important clinical trial.

D. EXPERIMENTAL DESIGN AND METHODS

D.1 Detailed Clinical Protocol

D.1.1 Primary Hypothesis and Objectives

We hypothesize 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 anti-arrhythmic drugs for reducing total mortality (primary endpoint) and decreasing the composite endpoint of total mortality, disabling stroke, serious bleeding and cardiac arrest (secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy.

D.1.2 Primary Endpoint and Objective

It is unclear if there is a mortality advantage to either drug or ablative therapy. Furthermore, it is unknown whether elimination of AF will result in mortality reduction. If AF is a risk factor for untoward morbidity and mortality, elimination of the arrhythmia should be followed by a reduction in mortality. Alternatively, no benefit would be expected if AF were simply a “risk marker” for the presence of some other underlying factor. Differences in total mortality alone as the primary endpoint must therefore be examined.

Hypothesis: Treatment with percutaneous left atrial catheter ablation for the purpose of eliminating AF will reduce mortality at least 30% compared to state-of-the art drug therapy for rate or rhythm control.

D.1.3 Secondary Endpoints and Objectives

Secondary Endpoints include:

1. A composite endpoint consisting of total mortality, disabling stroke, serious bleeding, or cardiac arrest
2. Cardiovascular death
3. Cardiovascular death or Disabling stroke
4. Arrhythmic death or Cardiac arrest
5. Heart failure death
6. Freedom from recurrent AF
7. Medical costs and resource utilization and cost effectiveness
8. Quality of Life
9. Composite adverse events

Composite Morbidity / Mortality

This trial will compare whether catheter ablation for the elimination of AF has an impact on the composite end-point of total mortality, disabling stroke, cardiac arrest or serious bleeding, when compared with drug therapy, as analyzed on an intention to treat basis. To detect the relative contribution of each of these factors, outcomes will also be considered independently, again on an intention-to-treat basis. Because of a mechanistic concordance of events, arrhythmic death and cardiac arrest will be considered together. Cardiovascular death and disabling stroke will be similarly grouped.

Hypothesis: Catheter ablation for AF will result in a significant (>25%) reduction in the composite end-point of total mortality, disabling stroke, serious bleeding, or cardiac arrest.

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 outcomes in the form of death should be less likely with elimination of AF through ablation than with ongoing pharmacologic treatment.

Hypothesis: The occurrence of heart failure death should be 30% lower in ablation than drug patients.

Freedom from Recurrent Atrial Fibrillation

The purpose of therapy is largely to eliminate accompanying symptoms in affected individuals. This should be of particular importance in the most symptomatic patients. 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.

Hypothesis: Catheter ablation for AF will be significantly (>30%) more effective in eliminating AF than membrane-active drug therapy, when considered as freedom from recurrent AF.

Cost / Economic Impact of AF

AF is responsible for almost 500,000 in-patient hospitalization episodes in the US every year. In this country, the direct medical costs associated with AF account for several billion dollars of excess health care spending a year. At the individual level, AF increases medical spending from 9 to 22 times that for similar patients without AF, with increasing costs and numbers of patients and increasingly complicated therapies. As part of the CABANA trial, we plan to comprehensively examine the economic impact of AF using state-of-the-art tools and techniques, currently used in the OAT, STICH and SCD-HeFT trials.

Quality of Life

AF also causes significant impairment in quality of life (QOL). Case control studies have suggested this impairment is between that of having an MI or 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, Cost and QOL are critical factors for consideration.

Adverse Events

Of specific note: while both drug and ablative therapies have known complications and side effects, those accompanying catheter-based interventions have been less thoroughly characterized. This trial must provide a more clear delineation of the "down side" to both therapies. This study will track serious untoward events that may be unique to each therapy. Although strict comparisons will be difficult because of therapy-specific differences in adverse events, additional analyses will look at each adverse event type descriptively. Nevertheless, a composite Serious Life Threatening "Event Triad" will be compared. Although the component events are also different, this will allow a comparison of the occurrence of the most serious events in each group. For drug therapy, this "Event Triad" will include unanticipated heart failure hospitalization, pro-arrhythmia or pulmonary toxicity from amiodarone. For ablative intervention, this "Event Triad" will include intervention for symptomatic PV stenosis, esophageal-atrial fistula formation, and myocardial perforation with tamponade requiring emergent intervention. Analysis of both complication Event Triads will be critical to the comparison of these two approaches. Of note, we will also track and descriptively address other complications or adverse events of either therapy, as outlined in Appendix C. Again, while adverse events will be carefully

scrutinized in the trial, differences in specific events in both treatment groups will preclude addressing them as a secondary endpoint. Nevertheless, we anticipate that morbidity, in terms of the composite adverse Event Triads will be equivalent in both treatment arms, although the specific complications vary in type and extent.

D.1.4 Descriptive Objectives / Additional Specific Aims

The above-mentioned endpoints will be carefully established, characterized, and reported on an intention to treat basis. Nevertheless, the CABANA Trial will seek to answer other questions. Pre-established sub-group analyses, informative in the interpretation of the outcome of the study, will include evaluation of specific mode of death, heart failure hospitalization for more than simple diuresis, the occurrence of pro-arrhythmic events, syncope, cross-overs, discontinuation of therapy, and withdrawal from treatment. "On treatment" analyses for the primary and major secondary end-points will also be performed. Analysis of outcome based on presence of sinus rhythm vs AF will be undertaken. These analyses will be used to:

1. Determine whether these interventions have an impact on the occurrence of stroke or peripheral thromboembolic events.
2. Assess whether symptom state at enrollment plays a role in trial outcomes.
3. Assess the impact of AF type: paroxysmal, persistent, or permanent on outcomes.
4. Determine the impact of underlying disease on outcomes.
5. Determine the prevalence of heart failure hospitalization for active intervention beyond diuresis.
6. Determine whether post-ablation asymptomatic AF carries continued stroke risk.
7. Establish the effect of age on the results of treatment.
8. Acertain whether full-disclosure monitor-established complete AF freedom identifies a group of patients in whom anti-coagulation can be safely discontinued.

D.1.5 Trial Time Line, Design, and Implementation

This multi-center study will enroll and randomize 3000 patients in a 1:1 fashion to a strategy of catheter ablation (n=1500) vs. that of state-of-the-art drug therapy for either rate or rhythm control (n=1500), as seen in Figure 2. Each will have untreated or incompletely treated AF, which in the opinion of the investigator warrants therapy. The time line of the trial will include a 6 month start up beginning July 1, 2007, with 3 yrs of enrollment from January 1, 2008 to December 31, 2010, a minimum of 2 yrs of follow-up through December 31, 2012 and 6 months for close out and data analysis ending in June 2013. The Trial will be reported at a major cardiology meeting in 2113. The flow of the study will be as follows:

D.1.6 Patient Selection

Those enrolled in CABANA will include symptomatic or asymptomatic patients with paroxysmal, persistent, or permanent AF. Each patient will be screened for the presence of the following inclusion/exclusion criteria, which are similar to those of the AFFIRM trial [19].

Inclusion Criteria

Patients must:

1) Have documented AF, which warrants active drug or ablative treatment,

2) Be eligible for both catheter ablation and at least 2 sequential anti-arrhythmic drugs and/or 3 sequential rate control drugs.

3) Be $\geq$ 65 yrs of age, or <65 yrs with one or more of the following risk factors for stroke:
Hypertension, Diabetes, Congestive heart failure (including systolic or diastolic heart failure), Prior stroke or TIA, Left atrium >4.5 cm, EF $\leq$35% by echocardiogram, radionuclide evaluation or contrast ventriculography.

The spirit of the trial is to enroll patients who have untreated or incompletely treated AF. Patients may have recent onset AF (in the past 3-6 months) or AF may have been present for a longer period of time, providing the patient warrants ongoing therapy. Patients may have been treated with a single anti-arrhythmic drug in the past, but must remain realistically eligible for at least 2 membrane active drugs or 3 rate control agents. Reasonable expectations of a response to such membrane-active therapy must be present. Patients

will not be excluded because of advancing age or underlying heart disease. Of note, 58% of the 1000 patients in the Mayo Clinic AF ablation database meet these criteria.

At a minimum, paroxysmal AF episodes must be ≥ 1 hour in duration, with 2 episodes occurring in the past 3 months. At least one qualifying episode must be documented by ECG or rhythm strip recordings. Patients with a history of only one episode of paroxysmal AF do not meet the "warranting therapy" litmus test. Patients with persistent or permanent AF will require at least one documented episode, which is of sufficient clinical importance that drug or ablative therapy is warranted, as determined by the treating physician. Patients can be randomized before any attempt at cardioversion, even if restoration of sinus rhythm is a desired endpoint of therapy.

Exclusion Criteria

1. Previously failed 2 or more membrane active anti-arrhythmic drugs
2. Efficacy failure of a full dose Amiodarone trial of ≥ 12 weeks duration
3. Any amiodarone therapy in the past three months
4. Reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures, or trauma
5. Lone atrial fibrillation in the absence of risk factors for stroke in patients <65 years of age
6. Recent cardiac events including MI, PCI, or valve or coronary bypass surgery in the preceding 3 months
7. Hypertrophic obstructive cardiomyopathy
8. Class IV angina or congestive heart failure
9. Planned heart transplantation
10. Other mandated anti-arrhythmic drug therapy
11. Heritable arrhythmias or increased risk for torsade de pointes with class I or III drugs
12. Prior LA catheter ablation with the intention to treat AF.
13. Patients with other arrhythmias requiring ablative therapy
14. Prior surgical interventions for AF such as the MAZE procedure
15. Prior AV nodal ablation
16. Medical conditions limiting expected survival to <1 year
17. Contraindication to warfarin anti-coagulation
18. Renal failure requiring dialysis
19. Women of childbearing potential
20. Participation in any other clinical mortality trial or
21. Unable to give informed consent

Prior ablation of the cavo-tricuspid isthmus is not an exclusion, if the patient later has recurrent AF.

D.1.7.1 Informed Consent

The principal investigator, coworkers, or IRB-documented members of the research team will approach the patient to obtain written informed consent [Appendix D]. The underlying rationale for the study, the procedures to be followed, the potential benefits and risks, as well as those factors common to the consent process will be fully disclosed. The consent form must be signed before any intervention is made. An Enrollment Screening Log of patients who are eligible, but decline enrollment or those eligible for enrollment, who are not offered enrollment because of physician preference will be kept. A manageable data collection identifying key demographics is included in the CRFs. This will allow determination of the denominator for patients enrolled and will track sufficient information to characterize those who make it into the trial, versus those who refuse. Thereby, enrollment bias, if present, will be established.

D.1.7.2 Randomization Approach

After informed consent is obtained, randomization will be supervised by the trial's biostatistician with centralized, IRVS-based randomization for each site as established prior to the beginning of enrollment. All patients will be randomized in the order that they qualify, although randomization will be stratified by site.

D.1.7.3 General Trial Flow

Patients meeting inclusion criteria, with no exclusions, will be randomized in a 1:1 fashion in an unblinded, parallel arm treatment format to either drug therapy directed at rate or rhythm control or catheter ablation. All therapies will be established and optimized in a 3-month treatment initiation period. During this time, patients may receive alternative drugs or undergo repeat ablation if AF recurs. For all morbidity and mortality end-points, intention-to-treat analysis will begin at randomization. Thereafter, therapy will be administered and patients followed without interruption for a minimum of 2 years. Efficacy with respect to AF treatment will be established from long-term follow-up beginning after the 3-month initiation phase. Any AF occurring after the 3 month blanking period will be considered a treatment failure for the purposes of the AF recurrence secondary endpoint. Patients will be monitored during follow-up with trans-telephonic monitoring alone, a full-disclosure implanted loop recorder, and / or Holter monitoring. Information from the resulting recordings may be used to guide therapy as they disclose recurrent symptomatic or asymptomatic AF. Because of cost, implanted loop recorders will not be mandated for this trial. Nevertheless, we anticipate that investigators may implant devices in up to 375 patients in each treatment arm. These may therefore be used in the follow-up process.

D.1.8 Baseline Testing

It is anticipated that each patient, regardless of randomization to drug versus ablative intervention, will undergo standard baseline evaluation to establish the presence and extent of their AF, allow its classification, and determine whether underlying disease is present. This assessment should include:

1. Historical examination
2. Drug History assessment
3. Physical examination
4. ECG
5. 24-hour Holter monitoring
6. Trans-thoracic 2-D echocardiography
7. Trans-esophageal echocardiogram
8. CT / MR examination

The trans-thoracic echocardiographic (TTE) studies are designed to characterize the substrate underlying the patient's AF. Specifically, TTE studies will establish LV ejection fraction, presence or absence of LV dysfunction, regional wall motion abnormalities, hypertrophy, diastolic dysfunction, and other structural abnormalities. The TTE will also establish LA size and volume, as well as mitral valve inflow and LA appendage inflow and outflow patterns and velocities. RA size will also be assessed qualitatively. Trans-esophageal echocardiographic (TEE) studies are designed to exclude the presence of intra-atrial thrombus as required prior to chemical or direct current cardioversion or ablative therapy. TEE data may also be used to confirm atrial size and morphology data. The information from all baseline testing will be entered into the Electronic Data Collection (EDC) system in specified eCRF fields. CT / MR studies will be undertaken in all ablation patients to serve as a baseline for LA size, morphology, and function studies, as well as PV and esophageal investigations as summarized in D.4.4 and described in detail in the CT / MR Imaging proposal from Dr. Richard Robb.

D.2 Treatment Strategies

Rather than comparing a specific drug therapy against any specific ablative intervention, CABANA examines 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.

D.2.1 Pharmacologic Approach to AF

In this trial, the choice of rate vs. rhythm control will not be constrained in those randomized to drug therapy. Nevertheless, medication use will conform to the Practice Guidelines for Management of Subjects with AF published in 2006 by the ACC/AHA/ESC [62] regardless of whether a rate or rhythm control strategy is selected. Approved drugs and minimum dosing guidelines are as specified below.

Table I Drugs Approved for Rate control

Drug	Administration	Minimum recommended daily dosage
Beta Blockers		
Metoprolol (Toprol)	Oral	50-100 mg
Atenolol (Tenormin)	Oral	50-100 mg
Propranolol (Inderal)	Oral	40-80 mg
Acebutolol (Sectral)	Oral	200 mg
Carvedilol (Coreg)	Oral	6.25 mg
Calcium Channel Blockers		
Diltiazem (Cardizem)	Oral	180-240 mg
Verapamil (Calan)	Oral	180-240 mg
Digoxin (Lanoxin)	Oral	0.125 mg

It is anticipated that patients without other heart disease will receive beta or calcium channel blockers as first line rate control therapy. Patients with underlying coronary artery disease will receive beta-blockers, patients with limited ventricular hypertrophy not warranting exclusion would receive either beta- or calcium channel blockers, while patients with heart failure would be expected to receive carvedilol or metoprolol. Rate control medications may be used in combination and doses adjusted so as to achieve appropriate rate control with exercise heart rates <110 bpm and resting values <90 bpm. These will be insured by clinical activity assessment in patients capable of exercising, as monitored by the patient's clinical cardiologist.

Table II. Drugs Approved for Maintenance of Sinus Rhythm

Drug	Administration	Minimum recommended daily dosage	Type/Level
Propafenone (Rhythmol)	Oral	450 mg	1C/B
Flecainide (Tambacor)	Oral	200 mg	1C/B
Sotalol (Betapace)	Oral	240 mg	Class III/ A
Dofetilide (Tykosin)	Oral	500 mcg	Class III/A
Amiodarone (Cordarone)	Oral	200 mg	Class III/B
Quinidine (Quini-glute / dex)	Oral	600-900 mcg	Class I, III/B

Patients randomized to drug therapy may be started on a membrane active drug, in an approach consistent with the recommended Guidelines for Management of Subjects With AF [62]. Each patient will be placed on an anti-arrhythmic drug for an appropriate period and the patient cardioverted to sinus rhythm if necessary. Patients will then be followed for a period of up to 3 months, during which dosage adjustment can be made or the drug replaced with a different anti-arrhythmic drug. In general, patients with no other heart disease may be treated with propafenone, flecainide, sotalol or dofetilide. Patients with underlying ischemic heart disease may be treated with sotalol, dofetilide, or amiodarone. Patients with underlying heart failure can be treated with dofetilide or amiodarone.

Drugs for Future Consideration

A chief goal of the trial is to provide relevant up-to-date information for guiding drug and ablative therapy for AF. It is therefore anticipated that other clinically beneficial rate control agents and membrane-active anti-arrhythmic drugs will become available over the course of the trial. These will be included in CABANA drug treatment strategies, once approved by the CABANA Innovative Drug Therapy and Executive Committees.

AV Nodal Ablation

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

Changing Drug Therapy

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

Cross-Over to Ablative Therapy

During follow-up, drug arm patients with recurrences may be treated with additional anti-arrhythmic drugs or the alternative rate controlling drug-treatment strategy. This will be continued throughout follow-up, with ablative intervention strongly discouraged, cross-overs must be approved by the CABANA Trial Administrative Center. Most patients in single center trials to date were treated for over one year before undergoing ablation. It follows that it should not be difficult to continue drug therapy over that time frame in these patients randomized to drug therapy since they have untreated or incompletely treated AF upon enrollment. Patients will be fully informed of this at the time of the consenting process.

D.2.2 Primary Catheter Ablation for AF

Pre-ablation Assessment

Pre-ablation assessment will follow standard practice patterns, and will provide baseline data against which to compare safety and efficacy outcomes of the intervention. In addition to the above-mentioned testing, patients who are randomized to ablative intervention will also undergo baseline CT or MR scanning and TEE evaluation. These specific studies will form the basis of comparisons of PV and LA and function. These screening methods may also be used in selection of specific catheter types or sizes for intervention.

Approved Methodologies

A potential limitation of any trial examining ablative intervention for AF is the number of different methodologies used for the primary curative ablation. The most commonly used approaches are:

1. Primary PV isolation using a circular mapping catheter as described by Haissaguerre, et al. [63,64]
2. Antral, lasso-guided approach as described by Natale, et al. [65,66]
3. Wide area circumferential ablative approach as pioneered by Pappone, et al, [34,67,68].
4. Ablation specifically targeting complex, fractionated electrograms as described by Nademanee et al [33].
5. Targeting the location of anticipated ganglion plexes as described by Jackman et al [69].

At the Boston AF Symposium in January 2006, a panel was convened to consider ablative approaches and whether there was any agreement on specific methods to be recommended. This group agreed that the starting point for ablation trials should be PV isolation. The same conclusion was reached by the NHLBI Work Group on AF Ablation in September of 2005. In this trial, it will be strongly recommended that each patient undergo PV isolation using approaches 1,2 or 3. Catheterization will follow standard procedures as described in the above references. Single or double trans-septal catheterization will be permitted. The selection of an ablation guidance system (i.e. lasso, Carto, NavX, fluoroscopy, intracardiac ultrasound) will be left to the discretion of the site PI, providing that site has performed at least 100 AF ablation cases.

The acute endpoint of ablation will be the creation of entrance block in each of the four (or five) PVs. The specifics of the approach to be used for isolation will otherwise be chosen by the primary investigator, who will have already ablated 100 patients with AF using that approach. This will establish an adequate level of expertise for participation in the trial. The creation of linear lesions, or the targeting of complex fractionated atrial electrograms or site of apparent parasympathetic ganglia will also be left to the investigator, but will only be undertaken as a secondary ablative approach. An additional end-point of “non-inducibility”, and programmed stimulation paradigm used in that assessment will be tracked, but not required, under those circumstances where the last two procedures (4 and 5) are used. The ablation approach used will be tracked, with no attempt made to stratify outcomes by specific ablation paradigm. Of note: ablation of the AV conduction system will not be considered an alternative for primary ablative intervention.

Approved Ablation Devices

The specific choice of ablation catheters will be left to the investigator. Nevertheless, standardization will be achieved by requiring the use of one of the catheters listed in Appendix E, as referenced in the CABANA IDE #G050233 approved on August 18, 2006.

Table III Ablation Devices

Manufacturer	Catheter	Reference#
St. Jude Medical	Livewire TC™ XLS™	P960016
St. Jude Medical	Therapy™ Dual / Thermocouple	P040014
St. Jude Medical	Safire™	P960016/S014
Biosense Webster	NAVI-STAR / NAVI-STAR DS	P990025 / P010068
Biosense Webster	Celsius Braided Tip / Long Reach	P950005
Biosense Webster	NAVI-STAR Thermo-Cool	P030031
Biosense Webster	Navistar® RMT	P990025
Biosense Webster	Celsius® RMT	P950005
CryoCath	Freezor® / FreezorMax	P020045
Bard	Stinger	P000020
Boston Scientific	Blazer II RF / RPM / SteeroCath /XP	P920047 / P020025
Boston Scientific	Chilli Cooled	P980003

Approaches for Future Consideration

Undoubtedly, primary ablative intervention for AF will also evolve with 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 will be permitted, as approved by the Innovative Ablation Therapies / Executive Committees.

Cross-over to Drug Therapy

Patients with recurrent AF during the blanking period can be maintained on anti-arrhythmic drug therapy, although this must 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 receive anti-arrhythmic drug therapy, but will continue to be followed on an intention-to-treat basis as part of the ablation study group. Nevertheless, the re-initiation of anti-arrhythmic drug therapy will serve as an endpoint for the arrhythmia-free interval following ablation and blanking period, but will not close out the trial for the primary and secondary endpoints for that patient.

D.2.3 Guidelines for Anti-thrombotic Therapy

Guidelines For Anti-Coagulation in Drug Treated Patients

Given the data generated in the AFFIRM and RACE trials, patients undergoing rate control therapy alone will remain on active anticoagulation therapy with warfarin throughout the duration of the trial. This is because of the presence of risk factors for stroke or peripheral thromboembolic events established at the time of enrollment. Unlike the AFFIRM trial, patients receiving rhythm control therapy will also be required to remain on warfarin anticoagulation throughout the trial. In both cases, target INRs of 2 to 3 will be required, unless higher INRs are required because of underlying disease.

Guidelines For Anti-thrombotic Therapy in Ablation Patients

The following guidelines for anti-coagulation in ablation patients are strongly recommended. Prior to the ablative intervention, patients with persistent and permanent AF will require at least one month of warfarin anticoagulation with INRs between 2 and 3, or undergo trans-esophageal echocardiographic evaluation to exclude intra-atrial thrombus at the time of intervention. It is recommended that those patients with paroxysmal AF will also be anti-coagulated during this time period. Prior to the ablation, warfarin may be discontinued for a period of 3 to 4 days, with appropriate bridging low molecular weight heparin. During the ablative intervention, maintaining an ACT between 300 and 400 seconds is strongly recommended. Following the ablative intervention, each individual center will follow their standard anticoagulation regimen. It is recommended, however, that patients be placed back on IV heparin or subcutaneous injections of low molecular weight

heparin beginning 4 to 6 hours after all sheaths are removed, and warfarin anti-coagulation reinstituted the evening of the intervention. Thereafter, low molecular weight heparin is to be maintained until standard dose warfarin achieves a target INR of 2 to 3. Warfarin anticoagulation is to be continued for at least 6 months in all patients.

In those patients with a prior history of stroke, TIA, or peripheral thromboembolic event, warfarin is to be continued throughout the duration of the trial. In those patients with hypertension with modest or no hypertrophy, or those <65 years of age, anticoagulation can be discontinued, providing 1) atrial size and function are normal (as established echocardiographically through the examination of LA appendage inflow and outflow velocities, as well as mitral valve inflow patterns), and 2) there is no symptomatic or asymptomatic AF by standard or implanted full-disclosure monitoring. Those patients will be converted to standard adult dose aspirin therapy. This approach to this subpopulation of patients, as guided by aggressive TTM or Full Disclosure monitoring will facilitate determination of the propriety of discontinuation of anticoagulation, and the role of monitoring for selecting those in whom it is safe to stop coumadin. Events rates are of insufficient magnitude to allow randomized testing of warfarin anti-coagulation withdrawl.

D.2.4 Items Left to the Discretion of the Physician

1. The specific choice of rate control or active drug therapy to be used
2. The specific drug in each category to be used
3. Hospitalization to begin the study or initiate anti-arrhythmic drug therapy
4. Choice of TEE guided DCCV vs. DCCV after 4 weeks of warfarin to an INR of 2-3.
5. Pre-ablation TEE assessment in patients with simple paroxysmal AF and Hypertension without hypertrophy
6. Exact ACT level maintenance during the ablation
7. The specific approach of adjunctive ablation to be used

D.2.5 Patient Follow Up

Follow-up in both drug treated and ablated patients will occur at 3, 6 and 12 months during the first year, following the date of therapy initiation and every 6 months thereafter. Either a standard surface event recorder or implanted full disclosure monitor will be used to document the rhythm underlying any recurrent symptoms during the 3 month therapy initiation period. Patient follow-up data will then be collected at 6-month intervals. To screen for asymptomatic AF, rhythm strips will be obtained once daily from one week before to one week after the 6-month follow-up intervals. Patients will also undergo 24-hour Holter monitoring at 3, 6, and 12 months, respectively. In addition to these preset evaluation intervals, patients with symptoms must undergo investigation to establish the ECG correlate to those symptoms. A detailed plan for seamless rhythm monitoring and analysis is provided in Appendix F. Complete follow-up data will also be obtained at the time of the institution of "innovative" therapy, at the time of drug discontinuation, with crossover in treatment strategy, and at the emergence of any primary or secondary endpoints. Functional status and quality of life questionnaires will be obtained at baseline, at the 3 and 12 month follow-ups, and every year thereafter throughout the course of the trial.

Schedule of Activities

Activity/ Time Frame	**Baseline**	***3 month -7day + 30d***	**6 month ± 30 d**	**12 month ± 30 d**	**6 month Interval ± 30 d**
Informed Consent	x				
Medical history/Interval history	x	x	x	x	x
Patient status (alive or dead)		x	x	x	x
Concomitant meds	x	x	x	x	x
Interim Adverse Events		x	x	x	x
Expedited Events		x	x	x	x
QOL	x	x		x	annual
Physical Exam	x	x	x	x	x
NYHA Class	x	x	x	x	x

12 Lead ECG / 24hr Holter	x	x	x	x	x
Echocardiogram (TTE)	x				
Echocardiogram (TEE) (1)	x				
VQ scan (2)	x				
CT/MRI (2), (3)	x	x	x	x	x
Event recorder (4)		.	x	x	x

1: If warranted prior to any cardioversion and at any time throughout the trial; 2: If randomized to ablation therapy; 3: If medically indicated due to Pulmonary Vein stenosis; 4: To be used after therapy initiation to document symptomatic episodes during the 3 month blanking period as well as for both groups for 1 week prior and 1 week after each follow-up visit (total of 14 consecutive days).

Additional Post-Ablation Assessments

Patients undergoing ablative intervention will undergo CT or MR scanning at baseline and after three months. Patients with >50%-75% narrowing of any PV will be re-scanned 3-6 months later, as necessary for clinical follow-up. Patients with >75% stenosis of a PV in the absence of any prior intervention will undergo repeat scanning in 3 months or as dictated by interventional requirements.

D.2.5.1 Management Of Arrhythmia Recurrences During Follow-Up

During the first three months following either drug or ablative intervention, patients will be considered to be in the "therapy initiation stage." During this time interval, a replacement drug may be substituted for that initially chosen in patients randomized to drug therapy. Changes in drug therapy will be tracked. 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 anti-arrhythmic drug therapy, providing it is discontinued by the end of the blanking or "therapy initiation phase". Any event occurring during this period will be considered as an "Early Event" and will be tracked, and included in Primary and Secondary Composite Endpoints. Long-term follow-up with respect to recurrence of AF will begin at three months after the initiation of drug therapy or ablation. Thereafter, AF recurrences in both groups will be tracked. These 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.

D.2.5.2 Establishing Endpoints

Primary Endpoint

Primary endpoint data will be submitted to the Coordinating Center, and forwarded to the Events Committee for detailed review. Specifically, the "Death" form will be filled out at the time of a patient death. All EMT/paramedic/medic notes, emergency room notes, hospital notes, admission and discharge summaries, operative notes, pathology reports, lab tests, ECGs, autopsy reports needed to characterize the mode of death, along with a detailed narrative from the principal investigator describing the setting and occurrence of this event will be required. The occurrence of death will be confirmed by the Events Committee using this information. This committee will also be charged with adjudicating the mode of death, whether it is witnessed versus un-witnessed, sudden versus non-sudden, or cardiac versus non-cardiac in origin. Cardiac mortality will be further categorized into arrhythmic, bradyarrhythmic, heart failure, or other cardiac causes using the events adjudication form seen in Appendix G. These details will be sought to provide descriptive information, useful in reporting and understanding the outcomes of the trial.

Secondary Endpoints

Secondary endpoint events, including disabling stroke, cardiac arrest or serious bleeding, chronicled in the composite endpoint will be handled in a similar manner. Appropriate data will be entered into the eCRF, and the presence of a secondary composite event confirmed by the Events Committee. Sufficient data, as described above, will also be required from the individual site to make this determination. A **Disabling Stroke** will be considered to be present if the stroke is readily documented by neurologic evaluation or brain CT / MR studies and a major disabling, irreversible physical limitation occurs. This will be scaled using the Rankin Stroke scoring approach [70]. **Serious (or Life-threatening) Bleeding** will be considered to be present if any intracranial bleeding or other bleeding occurs that is accompanied by hemodynamic compromise, and requires surgical intervention or transfusion of ≥2 units PRBC, but will not include bleeding occurring with cardiac

perforation and tamponade. This is a modification of the GUSTO bleeding Scale as adapted for use in catheter ablation [71]. These events will be tracked regardless of treatment randomization.

Although strict comparisons of adverse events between treatment arms will be difficult because of therapy-specific differences in event type, additional analyses will look descriptively at each adverse event classification. Nevertheless, a composite **Serious Life Threatening Event Triad** will be compared. Even though the component events in ablative and drug therapies are different, this analysis will allow a comparison of the occurrence of the overall "most serious events" in each group. In drug treated patients, **Unplanned Heart Failure Hospitalization {1}** will be considered to be present if the patient has signs of either systolic or diastolic dysfunction, evidence of pulmonary edema and aggressive therapy is required. Hospitalization for simple diuresis will not be considered an endpoint in this regard. Hospitalization for advanced heart failure requiring other drug interventions such as inotropic support (not routinely scheduled), blood pressure support, continuous IV diuretics, Nasiritide or other third line agents, ultra filtration, or intubation and ventilation will be appropriate indicators for this endpoint. This will be determined at each individual site using the related check boxes on the Events Form. A potentially life-threatening, drug-related **Proarrhythmic Event {2}** will be considered to be present in the presence of a resuscitated cardiac arrest due to ventricular fibrillation, ventricular tachycardia, or torsade de pointes, or marked prolongation of the QT interval accompanied by a non-sustained polymorphic ventricular tachycardia meeting criteria for torsade de pointes occurring in relationship to drug therapy. **Pulmonary Toxicity {3}** from amiodarone will be considered to be present in the setting of clear-cut interstitial changes on chest x-ray, with changes on pulmonary function testing, or other clear indicators for pulmonary toxicity, and where heart failure with interstitial edema or pneumonia as alternative explanations are excluded. Components of the Event Triad are as indicated **{1-3}**.

For patients undergoing ablative intervention, the definition of Disabling Stroke will be the same. **PV Stenosis {1}** as a secondary complication endpoint will require the presence of PV stenosis (>75%) on at least two orthogonal views of CT or MR scans, with symptoms requiring percutaneous catheter-based intervention. Complete occlusion of a PV in the absence of symptoms will likewise be considered an endpoint of sufficient severity to be used in the establishment of the "Event Triad". Any **Esophageal-Atrial Fistula {2}** formation documented pre- or postmortem will be included in the establishment of this endpoint. The presence of esophageal pathology, along with endocarditis, with or without esophageal bleeding or air embolus will also be considered as sufficient information to establish the presence of an atrial-esophageal fistula. **Perforation with tamponade {3}** requiring emergent intervention such as pericardiocentesis or operative intervention will also be considered to be an adverse event.

The presence of PV stenosis, atrial esophageal fistula formation, and other structural complications will be established by CT /MR imaging. All images will be archived, processed, and reviewed, by the CT/MR core lab, which has the primary aim to support the main CABANA Trial by providing the expertise and imaging systems to examine the impact of therapy on the morphology and remodeling of the left atrium and neighboring structures including the pulmonary veins and esophagus occurring with Ablative therapy. The aims, hypotheses, and operation of this imaging core are completely described in the linked Imaging RO1. The flow of data from the individual enrolling site and the Imaging / Coordinating Centers is as shown in Appendix H.

Other Adverse Events

While the above-mentioned "Serious Event Triad" events will be considered in addition to the establishment of the other secondary endpoints, this trial will more closely track the occurrence of other adverse events from either drug or ablative therapy. In so doing, the endpoint definitions, classifications, reporting and analysis listed in Appendix C will be utilized. Primary, Secondary, and Serious Event Triad events will be confirmed and adjudicated by the events committee and the most proximate cause of that event established. Any other adverse events will be tracked, reported and addressed descriptively, but will not be used in the composite secondary end-point. Of special consideration: in CABANA, hospitalization for AF treatment will not be considered, in and of itself, an adverse event. This approach arises out of the trial's intention to specifically address both efficacy and safety issues arising out of therapy for AF. While hospitalization for AF in both treatment arms will be carefully tracked and compared, it will typically be considered for "*AF recurrence"* and therefore counted against efficacy, not safety. If hospitalization is for

treatment of a stroke, heart failure, lightheadedness or any other anticipated or unanticipated adverse event listed in Appendix C, that precipitating symptom, sign, or finding will be viewed as *"the adverse event"*, and the *hospitalization* will be considered to be due to the precipitating adverse event, and will not constitute an adverse event, in and of itself.

Recurrence of Atrial Fibrillation

Recurrent AF as a secondary endpoint, (or conversely continuing sinus rhythm), will be documented by ECGs, Holter Monitoring, Implanted Loop Recorders, and/or Trans-telephonic Monitors. The process to be followed along every step of the process is as diagramed in Appendix F. Holter and Implanted loop recorder rhythm strips will be obtained from those patients with such a device, and will be reviewed at each site. Recordings will be forwarded to the ECG Core Lab electronically. Event recorder acquisitions will also be made and rhythm strips transmitted at the time of any symptomatic recurrence. These strips will be transmitted and reviewed by the Agility Inc. Monitoring service with processes as outlined in Appendix F. Patients will be instructed to go to their primary care provider to obtain an ECG for more detailed characterization of the arrhythmia. We anticipate that at least 30% of the 1500 ablated patients and at least 70% of the anti-arrhythmic drug treated patients (~70% of 1500=1050 patients) will have a recurrence during follow-up. Some of these patients will have been randomized to drug therapy and treated with rate control agents.

In addition, we will screen for the presence of asymptomatic AF in both groups. At least 25-30% of ablated patients will have recurrent asymptomatic atrial arrhythmia. The prevalence of asymptomatic AF in drug treated patients is less clear. Continuous monitoring or implanting loop recorders in all patients for this purpose is not feasible due to cost. Nevertheless, periodic Holter monitoring, implanted loop recorder rhythm sampling (in those with these devices) and trans-telephonic monitoring will be employed. Holter monitors will be obtained every 6 months during follow-up. In addition, daily loop recorder and TTM strips will be obtained for fourteen consecutive days every six months. The details of the seamless data management of ECG rhythm documentation are outlined in Appendix F.

D.3 Patient Recruitment: Feasibility / Management

Forty-two centers enrolling 2 patients/month over the course of 3 years would be sufficient for reaching the 3000 patient goal. If each center only enrolled 1 patient / month (a more reasonable estimate), 84 centers would be required. To provide greater certainty of reaching enrollment targets, we intend to enroll and treat patients at 100 centers in the US and Canada. Their willingness to participate in the trial is reflected by their answers to the survey noted in the preliminary results section, and the 94 letters of commitment reproduced in Section L of the grant. To further increase enrollment, 10 centers in Australia and New Zealand, 5 from the United Kingdom, and 10 from Continental Europe will be added within the first year of the trial. Their addition will also ensure a broader applicability of the results of this trial to patients around the world. The Economics and Quality of Life Studies will focus on the 100 US and Canadian centers. We anticipate enrolling 3000 over the course of 3 years, with a minimum of 2 years of follow-up on each patient (median of 3.5 years).

D.3.1 Selection Of Investigative Sites

To qualify as an investigative site, each group will be required to have done 100 prior ablations for the primary elimination for AF, and be committed to enrollment and randomization without prejudice toward early cross-over from drug to ablative therapy. Each site will also be required to demonstrate the skill and expertise for participating in clinical trials as judged from their past trial performance. A team approach to the enrollment and treatment of patients will be required at each enrolling center. Specifically, 2 PIs from each site will be chosen. The first, a cardiac electrophysiologist skilled in the art of AF ablation will work closely with a non-interventionalist clinical cardiologist or internist as co-PIs at each site. The latter individual will interact closely with the patients for enrollment and for managing their treatment. This will parallel the approach taken in SCD-HeFT in which electrophysiologists worked closely with a co-PI from the heart failure community. The focus or recruitment will be 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 treatment to <2 weeks. This will require "holding" open CABANA ablation slots in busy clinical schedules.

D.3.2 Initiating A Site

Sites will come on-line for active participation once all regulatory requirements established by both the trial and individual IRBs have been met. Unconditional IRB approval will be required at each site, along with any general division or institutional approval of the trial design required at that location. Training for data collection and reporting must be completed. Thereafter, that site may actively enroll patients.

D.3.3 Terminating A Site

Any site may be terminated from the trial if it fails to comply with the requirements listed above. Specifically, any site consistently failing to provide timely reports of patient enrollment or events, or inadequate data quality will be withdrawn from active enrollment. A cross-over rate $\geq$33% over any enrolling year will result in a warning to that site. A 3-month period for resolving any operational difficulties will be required prior to reinstating or permanently terminating a specific site.

D.3.4 Conflicts Of Interest

The two principal investigators from each trial site, along with data coordinators (if relevant) will be required to sign a document affirming the absence of any significant conflicts of interest. These would include, but not be limited to, financial connections with any of the ancillary industry study partners, following guidelines established by the ACC.

D.4 Data Management, Quality Control, and Data Analysis

D.4.1 Data Collection All Patients

All data collected at any point in the trial will be entered into the electronic data capture (EDC) system established by the Coordinating Center and more completely described in the Coordinating Center Proposal, and displayed in Appendix I. Fields in the electronic case report forms (eCRFs) will facilitate collecting and archiving data from the Enrollment/Randomization process, Baseline Data, Ablation Therapy, Drug Therapy, EQOL, Euroqol, and all Interval Follow-up events. Additional forms to capture End Point events (Death/Cardiac Arrest, CVA, Bleeding, Death Notification and any AF Recurrence, or Adverse Event) will also be included in the CABANA EDC system. A complete description of the EDC and data management system to be employed in the trial is provided in the Coordinating Canter application (Dr. Lee's proposal).

D.4.2 Data Quality Assurance

Data Entry and Transmission

The successful completion of this study obviously requires that data for this trial be monitored for quality assurance at several levels. 1) Data entered using the *Inform*-based approach will be validated through review of source documents for a representative selection of patients. 2) The quality of the clinical laboratory studies will be reviewed in each individual Core lab for each test. The core labs will determine whether the studies are of sufficient quality to allow quantitative assessment, as well as make comparisons of baseline and follow-up data from the individual contributing centers. Details of the data flow and quality assurance measures are contained in Appendix F for the ECG core lab and in the linked RO1 for the CT / MR imaging core. 3) The Coordinating Center will present a summary of findings to the executive committee on a semi-annual basis, including enrollment progress, promptness of follow-up data submission promptness, and site performance.

Source Documentation

Each clinical trial center will be required to maintain copies of all source documents utilized in filling out the web-based report forms. The Clinical Trial Coordinating Center will be responsible for oversight of the data acquisition process. The Coordinating Center will be responsible for compiling twice-yearly reports, which will be submitted to the Data and Safety Monitoring Board and the NHLBI. Recommendations regarding continuing or stopping the trial will be made by the DSMB to the NHLBI and information conveyed to the site principal investigators. The security of all data will be insured at multiple levels using DCRI security protocols.

Training

Individual sites will be trained at the time of the first general investigator meeting held at the beginning of the trial. The specific site's arrhythmologist investigator, the clinical study coordinator, and the principal investigator from the primary care group will be required to attend these meetings. A second meeting will occur at the end of the first and second years of the trial.

D.4.3 Statistical Analysis

Sample Size And Power Calculations

The AFFIRM, RACE, STAF, and PIAF studies provide information regarding the event rates that would be expected in the CABANA population. The 5-year actuarial mortality rate in AFFIRM was 22%. The crude death rate based on a mean follow-up at 3.5 years was 16.4%, yielding an annual mortality rate of approximately 4.7% /year. Available mortality or cardiovascular mortality rates in RACE and STAF were 3-3.5% /year. Since our primary endpoint of CABANA is total mortality and the CABANA study population is most like AFFIRM's, we have used a conservative mortality estimate of 4%/year. Our patients will be followed for a minimum of 2 years, with a median follow-up of 3.5 years. The CABANA death rate in drug treated patients should therefore be approximately 12% at 3 years and 14-15% at 3.5 years, but could be higher.

In the comparative ablation study of Pappone et al [34], the total mortality rate in ablation patients at 900 days (2.5 years) was 38/ 589 (6.5%) or 2.6% /year. These results suggest that at 3 years, the mortality rate in ablation patients may be as high as 8% or 10% at 3.5 years. This rate is actually quite high compared to the 0-1% / year rates seen in ablation patients in 10 other trials, including two recent ablation studies of patients with substantial LV dysfunction [72-74]. The mortality rate in ablation patients at Mayo is 1.5% /year. Even if we presume a 10% mortality rate in ablation patients over the average 3.5 years of follow-up, 3000 patients will provide high power ($\geq$90%) for detecting a 30% reduction in total mortality in ablation patients compared to drug treated patients. Since the event rates for the key composite secondary endpoint will be even higher, 3000 patients will provide excellent power for addressing our composite secondary endpoint (total mortality, disabling stroke, serious bleeding, and cardiac arrest) in addition to the primary mortality question. A detailed description of the sample size / power calculations are continued in the Coordinating Center application.

Statistical Analysis

Statistical analysis will be performed by the Coordinating Center as described in Dr. Lee's Coordinating Center proposal. Although the methods and operational details of the data analysis will be organized and coordinated by the study biostatisticians, the approach to analyses of study data will emphasize collaborative interactions between the statisticians and physicians to insure that interpretation of the data appropriately addresses important clinical questions. 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 crossover or post-randomization medical care. Statistical comparisons will be performed using two-sided significance tests. The log-rank test will be the primary analytic tool for statistically assessing mortality differences between the two randomized arms. Kaplan-Meier estimates of cumulative mortality rates as a function of follow-up time will be calculated and graphically displayed. Relative risks will be expressed as hazard ratios with 95% confidence intervals generated using the Cox proportional hazards model. Many of the secondary endpoints will be similarly analyzed using the log-rank and Cox model time-to-event methodology. Interim analyses of the data will be performed and reviewed by an independent Data and Safety Monitoring Board appointed by the NHLBI. Interim treatment comparisons will be monitored using 2-sided O'Brien-Fleming type boundaries generated with the Lan-DeMets spending function approach to group-sequential testing. Full details of the data analysis are contained in the CC application.

D.4.4 Sub studies/Ancillary Studies

The CABANA Trial is sufficiently powered to test the primary mortality and secondary endpoint hypotheses. Other pre-specified, sub-group analyses, as described in the Coordinating Center Proposal by Dr. Kerry Lee, will be preformed to identify contributors to the outcomes of the trial,. We fully appreciate the issues involved with further analyses beyond the scope and power of the proposal. Nevertheless, the CABANA Trial

does offer the unique opportunity to at least descriptively consider other issues such as the impact of sinus rhythm on mortality and the comparative impact of therapy on LA size, morphology and function.

Sinus Rhythm Sub-Study

The first of these is the Sinus Rhythm Sub-Study, which will descriptively examine the mortality rate in patients remaining in continuous sinus rhythm versus in those with persistent AF. This question arises out of the Post-Hoc analysis of the AFFIRM Trial which showed sinus rhythm to be a strong predictor of survival(40). This will be considered by analysis of outcomes in 4 groups of patients [Appendix J]:

1. Ablation patients in whom AF is successfully eliminated (70%): [1500 patients x .70 success rate = 1050 patients].
2. Patients on membrane active anti-arrhythmic drug therapy (70% of all drug treated patients), in whom AF is controlled, who remain in sinus rhythm (50%): [1500 patients x .70 on AA Rx x .50 with AF controlled = 525 patients) plus Ablation patients remaining in sinus rhythm (12.5%) in whom AF is controlled because of additional anti-arrhythmic drug therapy [1500 x .125 = 185 patients]: [total = 710 patients].
3. Patients on membrane active anti-arrhythmic drug therapy (70% of all drug treated patients), in whom AF is not controlled, who do not remain in sinus rhythm (50%): [1500 patients x .70 on AA Rx x .50 with AF not controlled = 525 patients]
4. Patients treated with rate control alone (30% of all drug treated patients) in persistent or permanent AF (85%). [1500 x .30 x .85% on rate control = 385 patients].

The most compelling evidence for the benefit of sinus rhythm in this trial would be disclosed by the demonstration of a mortality advantage in patients randomized to ablation and a large difference or gradient in AF prevalence between drug and ablation treated patients. This would in turn support a role for AF as a modifiable risk factor for morbidity and mortality. No effect would be expected if AF were simply a marker of risk from other underlying factors. Still, this sub-study may supplement the primary end-point analysis and further clarity a role for sinus rhythm, and thereby extend the observations made in the AFFIRM [41] and DIAMOND [42] trials.

LA Size, Morphology, and Function Studies

The repeat CT / MR scans will allow an examination of the impact of ablative therapy on PVs and the esophagus, as described in greater detail in the CT / MR Imaging Studies proposal submitted simultaneously by Dr. Richard Robb. These scans will also allow additional studies determining the impact of therapy on LA size, morphology (remodeling), and function, which will also be approached descriptively. The specific aims for these studies include:

1. Determine the impact of ablative therapy on LA size and morphology (remodeling)
2. Establish the impact of ablation therapy on return of LA function
3. Assess the relationship between LA size/morphology and function before and after therapy
4. Determine the contribution of underlying anatomy to ablation success or failure
5 Assess the impact of paroxysmal, permanent, or permanent AF on LA size morphology and function
6 Identify the impact of disease on underlying LA size / morphology and function before and after treatment
7. Establish the beneficial and detrimental changes in LA size occurring with ablation

Quantitative information for all anatomic imaging studies will be obtained from 64 row helical CT scans, which will be available in most enrolling centers during the course of this trial. LA size and morphology information will be available from 16 row studies, even if formal LA EF assessment is limited by technique. The reproducibility of CT / MR scanning methods across all trial centers should allow consistent data acquisition for quantitative analysis.

D.5.0 CABANA Trial Organization and Administration

D.5.1 CABANA Organization

Clinical and Administrative Center

Overall trial clinical direction, leadership and administration [Figure 1] will be the responsibility of the Principal Investigator and the Mayo Clinic Arrhythmia Research group. Responsibilities will include oversight of the Clinical aspects of the trial, as well as coordination of the DCRI Coordinating Center, Economic and Quality of Life Center, and CT/MR and ECG core laboratory efforts. The Mayo center will also manage general trial finances, including contractual and consortium arrangements. All communications to the NIH, industry sponsors, and outside entities will be the responsibility of the PI.

Coordinating Center

The Coordinating Center will be based at the Duke Clinical Research Institute (DCRI) at Duke University, under the direction of Dr. Kerry Lee PhD, Co-PI. It will be responsible for all clinical site training, site initiation, ongoing monitoring, site termination, and closeout management at individual clinical centers and for receiving eCRF transmitted data from the clinical sites, storing all primary data, cataloging all of the patient care information, and for the creation of a SAS database. They will also be responsible for assurance of data quality, and deal with ongoing day-to-day organizational issues. Web site security and patient privacy protection will comply with all regulations as established by the FDA. Finally, this Coordinating Center will be responsible for SAS-based analysis of all data from contributing sites and the Core Labs. The Center will also be responsible for the operation of the Events Committee and interaction with the DSMB. The Coordinating Center R01 is being simultaneously submitted by Kerry L. Lee, Ph.D.

Economics and Quality of Life Coordinating Center

The Economics and Quality of Life (EQOL) Coordinating Center will be based at the Duke Clinical Research Institute (DCRI) at Duke University, under the direction of Daniel Mark MD, MPH, Co-PI. The main responsibilities of this core will include: 1) training of all sites and EQOL Coordination Center personnel to collect follow-up quality of life data 2) oversee and facilitate collection of all hospital billing data; 3) database development, entry, quality control, management and closeout; 4) assurance of seamless interface with the Clinical and Coordinating Centers, to provide updates on study progress; and 5) analysis of the EQOL and health care economics data. The Economics and Quality of Life proposal is being submitted simultaneously by Dr. Daniel B. Mark.

Data and Safety Monitoring Board

An independent outside review body will be appointed by the NHLBI. We recommend that this committee include three senior cardiac electrophysiologists (not involved in the study), a statistician, an ethicist, and a clinical trial expert. The DSMB will be responsible for reviewing data from the Data Coordinating Center to insure the well being of enrolled patients. This committee will function independently and will be empowered to recommend stopping the trial if appropriate.

National Heart, Lung, and Blood Institute

The NHLBI will monitor the progress of the study and provide organizational and scientific guidance. A CABANA Investigational Device Exemption (IDE) will be held by the NHLBI and the Principal Investigator.

D.5.2 Standing CABANA Committees

Executive Committee

This committee, including the principal investigators, NHLBI representative, Events committee chair, and at large members will provide scientific direction to the project, and deal with any organizational matters encountered during the study. Emphasis will be placed on insuring prompt communication of deliberations from this committee to each investigator.

Endpoint / Events Committee

Under the direction of the Principal Investigator and the Coordinating Center, an Events Committee will be impaneled to review endpoint occurrences. Data from the contributing centers will be prospectively reviewed at meetings occurring twice yearly to insure that primary or secondary endpoints have in fact occurred, as coordinated by the Data-Coordinating Center. Three clinicians from the ECG / TMM core lab will internally adjudicate all arrhythmia events, with support from the Clinical Events Committee in the occurrence of disputed end-point specifying arrhythmic recordings.

Other Committees

Other committees to be formed at the beginning of the trial will include the Steering, Publication, Recruitment, Innovative Medical Therapy, Innovative Ablative Therapy, Sub and Ancillary Studies, Quality of Life, and Cost of Living Endpoint Committees.

D.5.3 Core Laboratories

ECG / Monitoring Core

The ECG /Monitoring core will be responsible for processing observed ECGs, Holter Monitors, rhythm strips, and full disclosure strips forwarded or transmitted by each patient at the time of symptomatic episodes or the routine follow-up periods described above. They will characterize the rhythm as AF, atrial flutter, atrial tachycardia or normal sinus rhythm. Any other abnormalities of rhythm or QRS or QT duration will be determined. While the PI and Mayo administrative Team will be responsible for Agility administrative and operational matters, Dr. Jeanne Poole of the ECG Core Lab, will be responsible for oversight of the Agility rhythm strip acquisition and processing [Appendix F]. The ECG Core Lab will also be responsible for all quality assurance issues involving the recording, transmission, processing, and final analysis of ECG, Holter, Implanted Loop Recorder, and TTM strips.

CT/ MR Image Analysis Core

The image analysis core will provide morphological data critical in understanding the roles of remodeling and more directly, reverse remodeling following therapy for AF. This will include detailed analysis of LA function. We will thereby assess the impact of ablative therapy, and expand the understanding of AF phenotypes, thromboembolic risk, and its elimination with therapy. The infrequent but potentially catastrophic adverse impact of ablation therapy on structure adjacent to the left atrium will also be carefully examined, with particular emphasis on the PVs and the esophagus. [Appendix H and Linked Imaging RO1]

D.5.4 Publication Policy / Dissemination Plan

A major objective of this study will be to disseminate to the medical community new information learned through the CABANA trial so that evidence-based treatment strategies can be advanced more quickly to the clinical realm. We propose to fulfill this aim using traditional methods such as publishing the results in the medical literature and presenting results at national and international meetings. However, we will also work with the NHLBI, ACC, AHA, and heart.org to ensure the results are communicated to clinicians at major medical universities as well as private practices and public health departments.

DCRI has extensive experience in the dissemination of trial results. As the CC, we will organize writing committees and provide editorial assistance by the DCRI Editorial Team. DCRI has been able to publish findings quickly in leading peer-reviewed journals. The GUSTO trials (GUSTO I, II, III, and IV) alone have resulted in more than 85 published manuscripts to date. Following is a summary of DCRI's publication record: *Circ* – 411; *JACC* – 243; *AHJ*- 323; *AJC* – 402; *NEJM* – 71; *EHJ* – 54; *JAMA* – 61; *Lancet* – 31.

Both the national meetings of the AHA and ACC will be excellent venues to present the CABANA results. The turn-around time for abstracts is six months or less so that new information can be brought before a national and international audience in a short time. We will also work with these associations to ensure we are part of their "late breaking trials" sessions. We have already established a history of presenting at these venues as DCRI recently reported the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial at the late breaking clinical trials session of the ACC in March 2004.

The SCRI will further accelerate the dissemination of the CABANA findings through a web site, web casts, additional regional and national meetings, and conventional presentations and publications. The DCRI had also provided in this application a Resource Sharing Plan (section K) that will further foster the dissemination of results and allow other investigators to use the data to further their research.

In the final year of our application, we have included effort (~$11,000 direct cost) for any editorial assistance required to ensure the CABANA results quickly go to publication. We have also included approximately 50% effort of a statistician (~ $50,000 direct cost) to help analyze and summarize the data for the Investigators for main manuscript publication as well as secondary publications. We expect the first publication and public presentation to be available by November 2013, in time for the AHA Scientific Session.

The data will be presented, without delay to the relevant HRS/ACC/AHA abodies responsible for the development of clinical practice guidelines. We will assist them in the generation of new guidelines and policy statements regarding the treatment of AF. The data will be presented to CMS to form the basis for the revision of reimbursement policy for the ablation procedure and post-procedure monitoring, and we will meet with the FDA to provide recommendations for appropriate revisions of their guidance document for AF ablation trials.

D.5.5 Data Analysis and Results Release

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 any 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.

We believe that we will successfully recruit, enroll, randomize, treat, and follow the 3000 patients necessary to address these sub-study issues. Much more importantly, we believe that the CABANA trial will disclose the role of medical and non-pharmacologic therapies for an ever-escalating national healthcare dilemma, establish the cost and impact of therapy on quality of life and will help determine if AF is a modifiable risk factor for increased mortality. CABANA will be a landmark trial that will shape therapy and health care policy in the AF arena for years to come.

E. HUMAN SUBJECTS

E.1. Human Subjects Research

E.1.1. CABANA - Protection of Human Subjects

E.1.1.1. CABANA - Risk to the subjects

Human Subjects Involvement and Characteristics: Patients enrolled in the CABANA study will have documented AF (atrial fibrillation), which warrants active drug or ablative treatment, will be eligible for both catheter ablation and at least 2 sequential anti-arrhythmic drugs and/or 3 sequential rate control drugs, and will be ≥65 years of age, or <65 years with one or more of the following risk factors for stroke: hypertension, diabetes, congestive heart failure (including systolic or diastolic heart failure), prior stroke or TIA, left atrium >4.5 cm, or an ejection fraction ≤35% by echocardiogram, radionuclide evaluation, or contrast ventriculography. The intent of the trial is to enroll patients who have untreated or incompletely treated AF. The catheters to be used in the ablation arm have been approved for treatment of other abnormal heart rhythms; however, none have been approved by the FDA for ablating atrial fibrillation. We are conducting this study specifically to compare drug therapy and catheter ablation for atrial fibrillation. This trial will help decide which treatment approach is best or when one or the other therapy is preferred. The CABANA trial will also compare the cost of care for the two approaches and determine the effect these therapies have on quality of

life. This trial will represent both women and minorities. It is expected that 30% of the study population will be women. AF in women under the age of 50 is very uncommon. Furthermore women of child bearing potential will be excluded from the trial because of risk from the ablation and ongoing drug therapy that cannot be consistently avoided.

Sources of Material: All patient data will be entered into case report forms (eCRFs) in the Phase Forward InForm™ system. Data will be archived and analyzed by the Coordinating Center. The Inform EDC System is fully 21 CFR Part 11 compliant and has been validated and tested within the DCRI environment by the DCRI IT Group. Data that to be captured on the eCRF will include demographics, past medical history, current hospitalization data (vital signs, procedures, medications, clinical status), laboratory data, and follow-up clinical events. Some of these data would have been obtained in the usual care of the patient, and some of the data are recorded specifically for analysis of this study. The CC is committed to maintaining patient confidentiality. Access to eCRF forms will be controlled by the CC and maintained within a secure firewall protected environment. This protects forms from unauthorized viewing or modification, as well as inadvertent loss or damage. Patients will be identified by unique patient number on eCRFs collected in the InForm™ system. Patients will not be identified by name on the eCRF. All information received by the CC (eCRFs, patient records for data verification purposes) will have all patient identifiers removed.

Potential Risks: Both treatment pathways of the study apply doses and methods of administration typically used in routine clinical practice for the treatment of atrial fibrillation. Participation in this research study will not result in any additional risks to the patient compared to the risks of the same routine therapy outside of this research study. The possible side effects of drug treatment depend on the specific drug used and the presence and type of any underlying heart disease. In the ablation arm of the trial, there are a variety of risks or complications that can occur with during the interventional procedure. These may be related to the insertion or placement of catheters, the use of medications, moving the catheters in the heart, or delivery of energy inside of the heart.

A Data and Safety and Monitoring committee will be established to monitor the conduct of the study, assure patient safety, and stop the study if deemed necessary due to safety concerns. Each individual site IRB will also review the CABANA protocol and receive information regarding patient safety from the local investigators, as well as adverse events notification from the CC.

E.1.1.2. Adequacy of protection against risks

Recruitment and Informed Consent: All research proposed in this application will be performed with stringent attention to the protection of the rights of human subjects. The study will be reviewed and approved by the Mayo Clinic and Duke University Medical Center Institutional Review Board (IRB) prior to beginning patient enrollment. Each participating site must have approval from their institution before enrolling any patients. All patients will be fully informed regarding the nature of the study and the risks and benefits of their participation. All patients will provide signed informed consent prior to study enrollment. All concerns/risks will be specifically addressed in the patient consent form following the guidelines set forth by the Mayo Clinic and DUMC IRBs and the IRBs at each center. Patients will also be notified in the consent form that they may withdraw their consent for participation at any time without influencing the medical care that they receive. The proposed study will not include children. Consent will be sought and obtained by the principal investigator and study coordinator at each center. Patients will have received initial stabilizing therapies prior to being approached for consent. Patients must be able to understand the information provided to them and provide written informed consent prior to enrollment.

Protection Against Risks: To protect against the risk of loss of confidentiality, the study will follow the procedures specified by the Mayo and DUMC IRBs and IRBs of the other centers. Data will be stored in a locked, secure location. Computerized data is accessible only by password, and a centralized monitoring system records and reports all access to data. The computer network is protected by a firewall. CRFs will be identified by study number only to insure patient anonymity. No patient identifiers will be used in the presentation of data. Study records that might identify patients will be kept confidential as required by law. Except when required by law, patients will not be identified by name, social security number, address,

telephone number, or any other direct personal identifier in study records. This information will be retained by each individual center and will not be disclosed to the coordinating center. Patients will be informed that the study physician and his/her study team will report the results of study related tests to the data coordinating center and to the NIH. Subjects will be informed that their records may be reviewed in order to meet federal or state regulations. Reviewers may include the FDA, IRBs, or the NIH. Subjects will be informed that if their research record is reviewed, their entire medical record may also need to be reviewed. If an adverse event occurs, drug or ablation therapy will be treated according to appropriate care practices which will be implemented under the direction of the treating physician. The therapies used in this study are current standard of care; thus, no special education for the physician regarding any investigational therapy is needed. A Data and Safety Monitoring Board (DSMB) is being used in this study, as previously described.

E.1.1.3. Potential benefits of the proposed research

Patients will directly benefit from participating in the study if either treatment results in elimination of / or fewer episodes of atrial fibrillation. This research will allow a conclusion to be drawn regarding the safety and efficacy of these therapies in the AF population.

E.1.1.4. Importance of Knowledge to be Gained

The information learned from this study will advance medical understanding of the treatment of AF. Furthermore, since recurrent AF is common, many patients will sustain such an episode in the future, and the knowledge gained from this study will be used to better direct their future treatment and determine differences between AF therapies. Successful completion of this study will result in significant advances in the field of AF.

E.1.2. Data and Safety Monitoring Plan

The Data and Safety Monitoring Board (DSMB) will be comprised of at least five members. Three members will be senior cardiac electrophysiologists (who are not involved in the study) with expertise in both clinical research and clinical care of AF, an ethicist, and a statistician with expertise in large outcomes trials. During the planning phase, the DSMB will meet to develop the specific monitoring plan, including the monitoring frequency, data to be reviewed, and statistical boundaries. The final plan must be approved by all members of the DSMB. The final data and safety monitoring plan will be submitted to the Mayo and DUMC IRB as well as the IRB of each participating site and the NHLBI prior to the initiation of patient accrual. Because this is a randomized trial, it is anticipated that the DSMB will review grouped data at regular intervals during the study. The stopping rules developed with the DSMB will take the multiple testing into account. DSMB meetings will take place at least every six months during enrollment and the follow-up phase. At the conclusion of each meeting, the DSMB will submit recommendations regarding trial continuation to the NHLBI. Any changes in study conduct recommended by the DSMB will be submitted to each participating site's IRB. The DSMB will review all expedited event data in accordance with the protocol. Unexpected Adverse Device Effects (UADEs) will be handled by the CC. All serious, treatment related, and unexpected events will be reported to the NIH in an expedited fashion. Real time reporting by the sites to the CC will be required on all unexpected deaths related to therapy, events of interest, and SAEs not specified in the grant (per NHLBI requirements.) These events will be forwarded to the NHLBI and DSMB chair within 1-2 business days of receipt. Reports will also be sent to each participating site for the site to report the serious adverse event to the local IRB.

E.1.3.2. Subject selection criteria/population characteristics

The proposed study will recruit and enroll patients across all ethnic groups. The diversity seen within typical AF populations should allow for NIH mandated recruitment. This has already been considered in site selection. As shown in the table below, the majority of committed(in yellow) and pre-committed/survey responder sites(in white) are in regions with considerable ethnic diversity. The top portion of the table shows diversity by state, and the second shows diversity within the specific communities of enrolling centers. These centers should allow us to reach 20% enrollment from non-Caucasian / non-Hispanic populations. We will also work closely with ethnic associations to provide education programs about AF and its treatment in their communities.

2005 Population by State and Ethnicity					
State	Population	White	Black	Hispanic	other
Alabama	4,557,808	70	**26**	1	4
Alaska	663,661	65	3	6	**25**
Arizona	5,939,292	61	3	**30**	6
Arkansas	2,779,154	78	**16**	3	3
California	36,132,147	45	6	**34**	**14**
Colorado	4,665,177	71	4	**21**	5
Connecticut	3,510,297	77	9	**10**	4
Delaware	843,524	71	**19**	6	4
DC	550,521	30	**57**	9	4
Florida	17,789,864	63	15	**19**	3
Georgia	9,072,576	61	**29**	7	4
Hawaii	1,275,194	17	2	7	**74**
Idaho	1,429,096	85	0	**10**	4
Illinois	12,763,371	68	**15**	**12**	5
Indiana	6,271,973	85	8	4	3
Iowa	2,966,334	90	2	5	3
Kansas	2,744,687	82	6	6	6
Kentucky	4,173,405	88	7	2	2
Louisiana	4,523,628	63	**32**	2	2
Maine	1,321,505	95	1	1	4
Maryland	5,600,388	59	**27**	7	6
Massachusetts	6,398,743	81	6	8	5
Michigan	10,120,860	78	**14**	3	4
Minnesota	5,132,799	87	4	3	6
Mississippi	2,921,088	59	**37**	2	2
Missouri	5,800,310	82	**11**	3	4
Montana	935,670	90	0	3	7
Nebraska	1,758,787	84	4	8	4
Nevada	2,414,807	63	7	**21**	9
New Hampshire	1,309,940	94	1	2	3
New Jersey	8,717,925	65	**13**	**14**	7
New Mexico	1,928,384	43	2	**45**	**11**
New York	19,254,630	62	**15**	**15**	7
North Carolina	8,683,242	66	**21**	7	5
North Dakota	636,677	90	1	2	7
Ohio	11,464,042	83	**12**	3	3
Oklahoma	3,547,884	73	7	5	**15**
Oregon	3,641,056	81	2	**10**	8
Pennsylvania	12,429,616	83	**10**	4	2
Rhode Island	1,076,189	82	5	**10**	3
South Carolina	4,255,083	66	**29**	2	2
South Dakota	775,933	87	1	2	**11**
Tennessee	5,962,959	78	**16**	4	2
Texas	22,859,968	47	**11**	**38**	4
Utah	2,469,585	86	1	**10**	4

2005 Population by State and Ethnicity					
State	Population	White	Black	Hispanic	other
Vermont	623,050	96	1	1	3
Virginia	7,567,465	69	**19**	6	6
Washington	6,287,759	78	3	8	**11**
West Virginia	1,816,856	95	3	0	2
Wisconsin	5,536,201	85	6	5	4
Wyoming	509,294	89	1	7	3
Total U.S.	**296,410,404**	67	**12**	**14**	6

2005 Population by Major City and Ethnicity									
Per City	population	White	Black	Hispanic	Other	Asian	Am. Indian	Males	Females
Washington DC	550,521	28	**60**	8	4	1	1	47	53
New York City	8,008,278	35	**26**	**27**	**13**	**10**	1	47	52
Dallas	1,188,580	34	**25**	**35**	**17**	2	1	50	50
Houston	1,953,631	30.8	**25**	**37**	**16**	5	1	50	50
Atlanta	416,474	31	**61**	5	2	1	1	50	50
Miami	362,470	12	**22**	**65**	5	0	1	50	50
Raleigh	276,093	60	**28**	7	3	3	1	50	50
Boston	589,141	50	**25**	**14**	8	6	1	48	51
Los Angeles	3,694,820	30	**11**	**47**	**26**	**12**	1	50	50
Chicago	2,896,016	31	**37**	**26**	**14**	4	1	49	52
Salt Lake City	181,743	71	2	**19**	9	3	2	51	49
San Francisco	776,733	44	8	**14**	7	8	1	51	49
Seattle	563,374	68	8	5	2	**14**	2	50	50
Portland	529,121	76	7	7	4	6	2	49	51
Boise	185,787	90	1	5	2	0	1	50	50
Denver	554,636	52	**11**	**32**	**16**	1	2	50	50
Kansas City	441,545	58	**31**	7	3	1	1	48	52
St. Louis	348,189	43	**51**	2	1	1	1	47	53
New Orleans	484,674	27	**67**	3	1	2	1	47	53
Phoenix	1,321,045	56	5	**34**	**16**	0	3	51	49
Charlotte	540,828	55	**33**	7	4	3	1	49	51
Miami Beach	87,933	41	4	**53**	4	0	1	51	49
Provo, Utah	105,166	84	0	**11**	5	2	1	48	52
Park City, Utah	7,371	77	0	**20**	**16**	1	1	54	46
Maywood, IL	26,987	6	**83**	**11**	6	0	1	47	53
Hartford, CT	121,578	18	**39**	**41**	**27**	1	1	48	52
Tampa	303,447	51	**26**	**19**	4	1	1	49	51
Scottsdale	202,705	88	1	7	2	1	1	48	52
Milwaukee	596,974	45	**37**	**12**	6	2	2	48	52
Baltimore	651,154	31	**64**	2	1	0	1	47	53
Jacksonville	735,617	62	**29**	4	1	1	1	48	52
Colorado Springs	360,890	75	7	**12**	5	1	2	50	50
Palo Alto, CA	58,598	73	2	5	2	**16**	1	49	51
Cleveland	478,403	39	**51**	7	4	0	1	47	53
Minneapolis	382,618	63	**18**	8	4	6	3	50	50
Brentwood, TN	23,445	94	2	1	0	2	0	49	51

2005 Population by Major City and Ethnicity									
Per City	population	White	Black	Hispanic	Other	Asian	Am. Indian	Males	Females
Birmingham	242,820	24	**74**	2	1	0	0	46	54
Des Moines	198,682	80	8	7	4	3	1	48	52
Philadelphia	1,157,150	43	**43**	9	5	4	1	47	53
Richmond, VA	197,790	38	**57**	3	2	0	1	47	54
Evanston, IL	74,239	63	**23**	6	3	7	1	47	53
Little Rock, AR	183,133	54	**40**	3	1	0	1	47	53
Santa Barbara	92,325	58	2	**35**	**16**	2	2	49	51
Ann Arbor	114,024	73	9	3	1	**11**	1	49	51
Wynnewood, PA									
Pittsburgh	334,563	67	**27**	1	1	2	1	48	52
St. Louis Park	44,126	88	4	3	1	2	1	48	52
Marshfield, WI	18,800	97	0	1	0	0	0	47	53
Hershey	12,771	90	2	2	0	4	0	46	54
Providence	173,618	46	**15**	**30**	**18**	6	2	48	52
Stanford	13,315	56	5	9	4	**13**	1	54	46
Indianapolis	781,870	68	**26**	4	2	0	1	48	52
Charlottesville, VA	45,049	68	**22**	2	1	4	1	47	53
Iowa City	62,220	86	4	3	1	5	1	49	51

CABANA sites	**Above 10%**

If under representation of minority groups are observed during the course of the trial, additional efforts will be discussed and implemented.

A wide rage of investigative sites across the United States, Canada, Australia, and Europe have been selected to optimize the opportunity for the CABANA to adequately recruit and represent women. Between 20 and 40% of patients in prior AF ablation studies were women, including 35% of the International AF Ablation Registry of over 8000 patients. As such, we believe it realistic to expect that 30% of our study population will be women. This population will be older, however, since AF occurs at a significantly later age in women. The CABANA Trial will also implement a four-fold plan to enhance recruitment of women in the study. First, this issue will be discussed at all investigators meetings. Second, at site initiation, all investigators will be required to sign a document confirming their willingness to ensure an appropriate level of focus on recruiting women and minorities. Third, the CABANA trial coordinating centers will develop an education / CME program presenting Women's Health Issues in general, with specific information regarding AF in women (and the increased complication rates that go with it). This education piece will be distributed for use by primary care physicians in each catchment area of that institution. Fourth, the importance of the participation of women in clinical trials will be extended to a Grand Rounds program for each recruiting center. This will include a section on AF in women. These approaches should increase the number of women with AF who make their way to cardiologists and treating or referral centers. We will report the data as a function of gender in the primary report, in addition to a more specific sub study. In so doing, we hope to narrow the gender gap that has been present in other clinical trials. We will carefully track the number of women enrolled at each center and provide a feedback report card to each site, the DSMB, and NHLBI. Inadequate enrollment level in any site will be considered in removing ineffective sites from the trial.

E.1.3.3. Rationale for exclusion of gender or racial/ethnic groups

Women of childbearing potential are excluded because of concern about the possible effects of the drugs used in the trial on a developing fetus. Otherwise women may be enrolled. There are no exclusion criteria based on gender or on racial/ethnic groups.

E.1.3.4. Proposed outreach programs for recruiting minority group members as subjects

As described in Section E.1.3.2., demographic data will be monitored throughout the trial to ensure adequate enrollment and representation of all gender and racial/ethnic groups. If any group enrollment falls under targets, efforts will be implemented to boost enrollment of these groups. There are medical practices that we have worked with previously with a high likelihood of being able to contribute minority patients (primarily African American, Hispanic, and Native American) to this study. Some of these centers are in central city and rural locations with a large minority population. Duke University Medical Center is also located in Durham, NC an area with a large minority population. Other centers with adequate representation of minorities will be part of the network and hence, expect that these measures will ensure all gender and racial/ethnic groups are represented.

E.1.3.5. Expected response differences based on gender or race/ethnicity

We do not anticipate that significant differences in response to treatment will be observed among gender or race/ethnic groups, as these have not been observed in prior studies of atrial fibrillation.

E.1.4. Inclusion of Children

The occurrence of atrial fibrillation in patients under the age of 18 is very unlikely. The research topic to be studied in this application is therefore not relevant to children. For this reason, children will be excluded from this study.

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Appendix A

Event Rates in Drug Therapy Trials

		n	Follow-up	Death	%	Cardiac	Arrhy death	Non-arrhy	Vasc death	CNS death	Non-CV death	Cardiac arrest
AFFIRM	Rate	2,017	3.5 yr	*310	21.3 @ 5 yr	130 (10%)	79 (3.9%)	43 (2.1%)	37 (3%)	28 (1.4%)	113 (36.5%)	10 (0.7%)
	Rhythm	2,033	3.5 yr	*356	23.8 @ 5 yr	129 (9%)	77 (3.8%)	46 (2.2%)	35 (3%)	28 (14%)	169 (47.5%)	9 (0.5%)
RACE	Rate	256	2.3 yr	CV 18	7.0	CV 18 (7.0%)	8 (3.1%)	4 (1.5%)	6 (2.3%)	0 (0%)	–	–
	Rhythm	266	2.3 yr	18	6.8	18 (6.8%)	8 (3.0%)	1 (1%)	9 (3.4%)	6 (2.3%)	–	–
STAF	Rate	100	20 mo	8	8 4.5/yr	Vasc 8 (8%)	4 (4%)	–	–	–	0 (0%)	0
	Rhythm	100	20 mo	4	4 2.9/yr	3 (3%)	2 (2%)	–	–	–	1 (1%)	0
PIAF	Rate	125	12 mo	2	1.6	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	–
	Rhythm	127	12 mo	2	1.6	2 (1.6%)	2 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
HOT CAFE	Rate	101	20.4 mo (1.7 yr)	1	–	–	–	–	–	–	–	–
	Rhythm	104	20.4 mo	3	–	–	–	–	–	–	–	–
META ANALYSIS	Rate	2,609	–	339	13.0	–	–	–	–	–	–	–
	Rhythm	2,630	–	383	14.6	–	–	–	–	–	–	–
Pappone	Abl	589	900 days 2.5 yr	38	6.5	16 (2.7%)	0 (0%)	16 (2.7%)	–	2 (0.3%)	20 (3.4%)	0 (0)
	Drug	582	900 days 2.5 yr	83	14	45 (7.7%)	12 (2.1%)	33 (5.7%)	–	14 (14%)	24 (4.0%)	12 (2.0%)
CACAF	Abl	68	–	0	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Drug	69	–	2	2.9	2 (2.9%)	1 (1.5%)	–	–	–	–	1 (1.5%)

Appendix A (cont)

Event Rates in Drug Therapy Trials

									Complications					
		n	Any CVA	Distable stroke total	Thromb embol event	Anoxic enceph	Major bleed (not cas)	CNS hemor	CHF	Pulm event	Tdp	Other	Hosp	Endpoint comp
AFFIRM	Rate	2,017	105 (7.4%)	77 (3.8%)	86 (6.0%)	4 (0.2%)	107 (7.7%)	29 (1.9%)	37 (2.1%)	24 (2.1%)	2 (0.2%)	–	1,220 (73%)	416[1] (32.7)
	Rhythm	2,033	106 (8.9%)	80 (3.9%)	87 (7.5%)	5 (4.0%)	96 (6.9%)	29 (2.1%)	42 (2.7%)	108 (7.3%)	12 (0.8%)	–	1,374 (80%)	445[1] (32%)
RACE	Rate	256	–	–	14 (5.5%)	–	12 (4.7%)	–	9 (3.5%)	0	0	2 (0.8%)	–	44[2] (17.2%)
	Rhythm	266	–	–	21 (7.9%)	–	9 (3.4%)	–	12 (4.5%)	0	3 (1.1%)	12 4.5%)	–	60[2]** (22.6%)
STAF	Rate	100	–	1:0.6%/yr (1%)	2 (2%)	–	8 (8%)	–	–	–	–	–	26 (26%)	10[3] (10%)
	Rhythm	100	–	5:3/yr (5%)	5 (5%)	–	11 (11%)	–	–	–	–	–	54 (54%)	9[3] (9%)
PIAF	Rate	125	–	–	–	–	–	–	17++ (14%)	–	–	–	30 (24%)	–
	Rhythm	127	–	–	–	–	–	–	31++ (25%)	–	–	–	87+ (69%)	–
HOT CAFE	Rate	101	–	0 (0%)	–	–	–	–	–	–	–	–	–	–
	Rhythm	104	–	3 (2.9%)	–	–	–	–	–	–	–	–	–	–
META ANALYSIS	Rate	2,609	–	78 (3.5%)	–	–	–	–	–	–	–	–	–	–
	Rhythm	2,630	–	88 (3.9%)	–	–	–	–	–	–	–	–	–	–
Pappone	Abl	589	4 (0.6%)	6 (1%)	5 (10.8%)	–	2 (0.3%)	2 (0.3%)	33 (5.6%)	1 (0.2%)	–	–	–	–
	Drug	582	15 (2.3%)	22 (3.8%)	18 (3.1%)	–	7 (1%)	7 (1%)	57 (9.8%)	3 (0.5%)	–	–	–	–
CACAF	Abl	68	1 (1.5%)	1 (1.5%)	1 (1.5%)	–	–	–	–	–	–	–	–	–
	Drug	69	1 (1.5%)	1 (1.5%)	1 (1.5%)	–	–	–	–	–	–	–	–	–

+2/3 DCCV;**AR -5.4% (-111.0 to 0.4%) HR 0.73% (0.52 to -1.01); 1) Death, disabl CVA, anox enceph, major bleed, CA; 2) CV death, CHF, TE events, bleeding, PM, severe AE; 3) Death, CPR [like CA], CVA, periph TE

Appendix B

Outcome of Ablation for Atrial Fibrillation

	Pt	Veins	AF Type		Success Off Drug		Controlled on Drug*		F-U (mo)	Redo		
					No.	%	No.	%		No.	%	
Haissaguerre	45	69	Parox		28	62	na	na	8±6	na	na	NEJM 339:659, 1998
Chen	79	103	Parox		68	86	10	13	6±2	7	9	Circ 100:1879, 1999
Haissaguerre	90	197	Parox		64	71	12	13	8±5	49	54	Circ 101:1409, 2000
Haissaguerre	15	32	Perm		9	60	na	na	11±8	8	53	JCE 11:2, 2000
Pappone	251	956	Parox	(179)	148	83	4	2	10±5	na	na	Circ 104:2539, 2001
			Perm	(72)	40	56	9	13				
Gerstenfeld	41	95	Parox		29	70	6	15	9±2	0	0	JCE 13:971, 2002 Macle/
	136	544	Parox		90	66	20	15	9±5	67	49	JCE 13:1067, 2002
Haissaguerre												
Oral/Morady	40	125	Parox		26	81	0	0	n/a	0	0	Circ 106:1256, 2002
Marrouche	190				176	93	11	6	4±2	na	na	JACC 40:464, 2002
			Parox	(102)	96	94	4	4	9±3	na	na	
	29		Persist	(29)	26	90	3	10	8±4	na	na	
	59		Perm	(59)	54	89	4	7	8±2	na	na	
Oral	70	230	Parox	(58)	41	70	na	na	5±3	6	9	Circ 105:1077, 2002
			Persist	(12)	3	22	na	na				
Sanders/	51				15	30	na	na	11±8	2	4	Int Med J 32:202, 2002
Kalman												
Magrum/	64	82	Parox		42	66	na	na	13±7	7	27	JACC 39:1964, 2002
Haines												
Deisenhofer	75	226	Parox		38	51	na	na	230 ±133	30	40	AJC 91:159, 2003
Packer	203		Parox		104	70	15	10	15±5	32	16	PACE 26:962, 2003
			Persist		25	56	7	15		na	na	

*Data for AF on drug separated out from total data

Appendix B (cont)

Outcome of Ablation for Atrial Fibrillation

	Pt	Veins	AF Type	Success Off Drug		Controlled on Drug*		F-U (mo)	Redo		No AF*	
				No.	%	No.	%		No.	%		
Takahashi	49	112	Parox	39	80	na	na	7±4	13	27	39(80%)	Circ 105:2998, 2002
Mansour	80	na	Par/Pers	47	59	7	9	≥11±3	10	13	54(68%)	JCE 15:532, 2004
Pappone	297	na	Parox	267	90*	na	na	12	na	na	267(90%)	Circ 109:327, 2004
Oral PVI/WACA	80	na	Parox	62	78*	na	na	6	7	9	62(78%)	Circ 108:2355, 2003
Pappone	589	na	Parox (69%) Perm (31%)	469	80*	na	na	30 2.5 yr	na	na	469(80%)	JACC 42:185, 2003
Chen/Lin	240	na	NonPV	53	73	na	na	22±11	na	na	53(73%)	Circ 107:3176, 2003
Marchlinski	107	293	Parox Persist	65	61	9	8	12	na	na	74(69%)	JCE 14:358, 2003
Marrouche	315	1202	Parox (51%) Persist (13%) Perm (36%)	271	86*	na	na	14	na	na	271(86)	Circ 107:2710, 2003
Nademanee	121	-	Parox (47%) Perm (53%)	100	83	10	8	12	18	15	110(91%)	JACC 43:2044, 2004
Cappato	8745	na	na	4550	52	2094	24	12±8	2389	27	6644(75%)	Circ 111:1100, 2005
Haissaguerre	70	na	Prolonged	55	79	na	na	7 ±3	9	13	55(79%)	Circ 109:3007, 2004

Pt = patient; AF=atrial fibrillation; F-U=follow up; PVI=pulmonary veins; Parox/Par=paroxysmal; Pers/Persist=persistent; Perm=permanent; na=not applicable; Circ=Circulation; JCE=Journal of Cardiovascular Electrophysiology; JACC=Journal of the American College of Cardiology

Appendix C

CABANA ADVERSE EVENTS PROTOCOL

The purpose of this section is to clearly establish the methods to be used in the CABANA Trial to identify, categorize, report, and address adverse events that occur in the course of the trial. The definitions and approaches to be followed in this process are as outlined:

ADVERSE EVENTS

Adverse events, defined as any undesirable medical occurrence in a clinical study patient that 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) if they are clinically relevant and if they are clinically related to the study. Adverse events will be recorded on the case report forms by the study site team. Event, severity, and relationship to the study will also be recorded on the appropriate eCRF form. This data collection will be guided by the following definitions:

ADVERSE EVENT DEFINITIONS

Anticipated Adverse Event

An event that has been previously identified to be related to the disease state or therapies in previous studies, published literature, or product labeling.

Unanticipated Adverse Event

An event that is a new symptom or illness, or worsening of a pre-existing symptom or illness, that is not expected. If deemed serious and related to therapy by the site investigators, this event should be reported to the coordinating center within 24 hours. This includes any other serious problem that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event

An adverse event that warrants additional action, including any untoward event that:

- Is fatal
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization >48 hours with the following exceptions:
    - Preplanned (prior to the study) hospital admissions unless the hospitalization is prolonged >48 hours.
    - Planned admissions (as part of a study – e.g. routine biopsies).
    - 23 hour hospitalizations.
    - Hospitalization for elective procedure.
    - Emergency room visits.
- Results in persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- 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.

Unavoidable Adverse Event

An event inherent to an intervention/medication that is expected to occur for a projected duration in some or all subjects. Unavoidable adverse events will not be tracked during the trial.

Adverse Event Intensity or Severity Classification

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

- Mild: Any event that results in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
- Moderate: Any event which results in moderate transient impairment of a body function or damage to a body structure, or which requires intervention.
- Severe: Any event which is life threatening, results in permanent impairment of a body function or damage to a body structure, requires significant 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.

DEVICE RELATED ADVERSE EVENTS

Device-related adverse event is defined as any adverse event for which a causal relationship between the device and the event is a reasonable possibility. These will be categorized as 1) Definitely, 2) probably, 3) Possibly, and 4) Unrelated.

Device Failure: A device has failed if it is used in accordance with the Instructions for Use, but does not perform according to Instructions for Use and negatively impacts the treatment.

Device Malfunction: A device malfunction is an unexpected change to the device that is contrary to the Instructions for Use and may or may not affect device performance.

User Error: A device that is used by the Investigator in a manner that is contrary to the Instructions for Use. Such an event will not be considered a malfunction.

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 reported to the coordinating center within 24 hours.

The following events have been identified as "Anticipated Events" for this study:

Ablation Therapy events

- Related to catheter insertion:
  - Infection
  - Sepsis
  - Bleeding
  - Bruising / ecchymosis
  - Pain
  - Hematoma
  - Pseudoaneurysm
  - A-V fistula
  - Vessel trauma
  - DVT
  - Urinary tract infection
- Pulmonary embolism
- Pneumothorax
- Hemothorax
- Pleural effusion
- Pneumonia
- Related to medications:
  - Allergic reaction (skin rash, SOB)
  - Hypotension
  - Kidney damage
  - Respiratory depression
  - Left ventricular dysfunction
  - Headache / nausea
  - Bleeding from heparin
  - Visual migraine
  - Complete AV block
  - Transient AV block
  - Permanent AV block
  - Volume overload
- Related to catheter manipulation:
  - Myocardial perforation
  - Pericardial effusion
  - Tamponade

    - Myocardial infarction
    - Other ischemic event
    - Coronary artery spasm
    - Coronary artery occlusion
    - Coronary artery dissection
    - Stroke
    - TIA
    - Peripheral thromboembolic event
    - Cardiac thromboembolic event
    - Air embolism
    - Heart valve damage
    - Clinically relevant sinus node block
    - Clinically relevant AV node dysfunction
    - Pacemaker damage
- Related to ablation:
    - Chest pain during energy delivery
    - Pericarditis
    - Radiation skin burn
    - Radiation related cancers
    - Phrenic nerve damage
    - Pulmonary vein stenosis
    - Pulmonary vein damage/dissection
    - Pulmonary vein thrombus
    - Pulmonary edema
    - Pulmonary hypertension
    - Esophageal atrial fistula
    - Elevated creatinine phosphokinase (CPK)
    - Temperature elevation
    - Vasovagal reaction
    - Esophagus or stomach erosion disorder, esophageal achalasia, esophageal ulcers, or stomach emptying disorder

DRUG RELATED ADVERSE EVENTS

Each of the previously listed definitions will also be used to characterize drug related adverse events, with appropriate change of labeling from Device to Drug related event.

The following events have been identified as "Anticipated Events" for this study:

Drug Therapy events

- Bradycardia
- Hypotension
- Dizziness / light headedness
- Syncope
- Shortness of breath
- Fatigue
- Wheezing
- Asthma exacerbation
- Nausea/vomiting
- Depression
- Impotence
- Peripheral edema
- Heart failure
- Skin rashes
- Diarrhea
- Constipation
- Poor appetite
- Alteration of color vision
- Blurred / double vision
- Deteriorating vision
- Blindness
- Unusual metallic taste
- Hyperthyroidism
- Hypothyroidism
- Abnormal liver functions
- Photosensitivity
- Bluish / gray skin tone
- Unsteady gait / imbalance
- Lung toxicity
- Drug related nonsustained VT
- Sustained VT
- Prolonged QT/Torsade des pointes
- Proarrhythmia; new or worsened arrhythmia
- Ventricular fibrillation
- Stroke / thromboembolic event
- Renal failure
- Seizure

ADVERSE EVENT MONITORING/ DOCUMENTATION/ REPORTING

Expedited Events

There are certain events (specified below), if occurring between randomization through completion of follow-up, require *expedited* (within 24 hours of knowledge) reporting. Expedited events include:

- Unanticipated (i.e., not included in the list of anticipated events) Procedure or
- Therapy Related Serious Adverse Events

- Device Failures or Malfunctions
- User Errors

Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

Documentation

All relevant AEs must be documented on the appropriate eCRF. The outcome of each AE 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 eCRFs.

Expedited Events must be reported on an *Expedited Event Form* and faxed to DCRI Safety Surveillance.

DCRI Safety Surveillance
Telephone: 919-668-8624
Fax: 919-668-7138

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 drug 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 30 days after the last patient enrolled has completed the trial, whichever occurs first.

Regulatory Reporting

There are situations that may necessitate rapid communication to the regulatory authorities. The DCRI Medical Monitor will determine which device-related expedited events meet “unanticipated” criteria (not labeled in the literature). Unanticipated adverse device effects (UADEs) will be reported to the NIH within 1-2 business days, and to the FDA and all participating investigators within 10 working days of the sponsor or DCRI Safety Surveillance’s initial notification of the event. Investigators are responsible for reporting UADEs to their reviewing IRB within 10 working days of first learning of the effect.

Since the CABANA trial is not under an Investigational New Drug Application, sites will be responsible for reporting serious adverse events (SAEs) that are drug related and unexpected to the FDA's MedWatch Adverse Event Reporting program. The site principal investigator is responsible for reviewing the drug labeling and determining if the event is unexpected. Events may be reported online at www.fda.gov/MedWatch/report.htm , by phone 1-800-FDA-1088, or by returning the postage-paid FDA form 3500 which may be downloaded from www.fda.gov/MedWatch/getforms.htm by mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787 or fax 1-800-FDA-0178. In addition, the site will be responsible for notifying DCRI Safety Surveillance of any serious, drug related, unexpected adverse event that requires reporting through the FDA’s MedWatch Adverse Event Reporting program. Sites should fax a copy of the completed MedWatch form and a cover sheet documenting the date and time the MedWatch form was submitted.

Appendix D

Consent Form for Participation in a Research Study

TITLE: Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial

IRB #:

RESEARCHER: **Dr. _____ and colleagues**

PROTOCOL LAST APPROVED BY INSTITUTIONAL REVIEW BOARD:

THIS FORM APPROVED:

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why is this research study being done?

Atrial fibrillation (an abnormal, rapid heart rhythm coming from the upper chambers of the heart [atria]) is the most common arrhythmia. Atrial fibrillation may be treated with drug therapy designed to either prevent the heart rate from going too fast during atrial fibrillation (rate control therapy) or with drug therapy designed to stop the abnormal rhythm and maintain normal heart beating (rhythm control therapy). In many centers, atrial fibrillation is also treated with catheters inserted into blood vessels that can be placed in the heart (left upper chambers) to eliminate the hot spots or triggers that start atrial fibrillation or stop those conditions that keep it going (catheter ablation). It is not known if drug therapy or catheter ablation is better.

You are being asked to participate in the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial which is being done to compare drug therapy and catheter ablation for atrial fibrillation. This trial will help decide which treatment approach is best or when one or the other therapy is preferred. The CABANA trial will also compare the cost of care for the two approaches and determine the effect these therapies have on quality of life.

The sponsor of this study, MAYO Clinic Arrhythmia Research (MCAR) is providing funds to [Institution/health care provider] {and Dr. [PI] if relevant} to perform this research. The National Institute of Health (NIH), St. Jude Foundation, and Biosense Webster, Inc., are funding the research.

How many people will take part in this research study?

The plan is to have 3000 people take part in this study at 125 medical centers located around the world. Up to _____ people will take part at **{INSERT NAME OF YOUR MEDICAL FACILITY}**.

What will happen in this research study?

You will be assigned to one of two treatment groups by chance (as with a flip of a coin), with 1500 participants receiving medication to control heart rate or the heart rhythm and 1500 participants receiving left atrial catheter ablation. All patients, regardless of the assigned group, will undergo a standard evaluation for the treatment of atrial fibrillation which will include a physical examination, chest x-ray, electrocardiogram (ECG), 24 hour heart monitor recording (holter), blood tests, and echocardiogram (sound wave examination of the heart). In some cases, a transesophageal echocardiogram will be performed by passing the echo probe from your mouth into your esophagus (swallowing tube), to look for blood clots in your heart and any other heart abnormalities or problems. The risks specific to a transesophageal echocardiogram will be discussed with you by your physician.

Drug Therapy

If you are assigned to the medication group, your specific medication will be determined by your doctor, based on your medical condition. In this study, your physician may recommend heart rate controlling drugs to slow down or decrease the number of heart beats traveling from the upper to the lower chambers through the

normal electrical conduction system of the heart (AV Node). Drugs such as digitalis (Lanoxin, Digoxin), beta-blockers [atenolol (Tenormin); metoprolol, (Lopressor, Toprol); propranolol (Inderal); acebutolol (Sectral); carvedilol (Coreg);] or calcium channel blockers [diltazem (Cardizem), or verapamil, (Calan, or Isoptin)] are examples of these drugs that may be prescribed. In many patients, combinations of these drugs are required.

You may also be given a drug to restore and maintain normal rhythm, such as: propafenone (Rhythmol); flecainide (Tambocor); sotalol (Betapace AF); dofetilide (Tikosyn); amiodarone (Cordarone, Pacerone); quinadine (Quinadex, Quinaglute). Hospitalization is required to start certain types of these medications. Your doctor will decide if hospitalization is required to monitor your heart rhythm at the time you start your new medication.

Ablation procedures

If you are randomized to the ablation group, in addition to the standard baseline evaluation, you will have additional routine tests. An echocardiogram to look for blood clots in your atria will be completed, by placing the echo probe into the esophagus. A lung scan called a ventilation-perfusion scan (V/Q scan) will measure how well air and blood move through your lungs and MRI (Magnetic Resonance Image) or a CT chest scan (CAT Scan) of the heart will be obtained prior to your ablation.

During the actual ablation procedure, 4 to 8 catheters (long, narrow tubes) will be passed under x-ray guidance through veins in the right and left legs and via a blood vessel in your neck into your heart. These catheters will be used to record the electrical activity occurring during atrial fibrillation and normal rhythm. In some cases, medications such as isoproterenol or epinephrine (adrenaline) will be given to start or "stir up" your atrial fibrillation. These areas may then be mapped (looked at or studied) to identify the tissue that is the source of your atrial fibrillation. This procedure may be performed under local anesthesia, or under general anesthesia. During the ablation, the muscle tissue outside the junction between the veins and the left atrium will be burned using radio waves or other forms of energy. This energy is intended to burn a small amount of tissue to destroy the tissue that causes irregular beats or allows the irregular beats to travel into the upper chambers of the heart. Testing to determine the adequacy of the burn formation will be performed, as necessary. The procedure can take anywhere from 2-12 hours. Every patient is different and the length of the procedure depends on whether other abnormal electrical sites need treatment. The specific ablation approach to treat your atrial fibrillation will be chosen by your physician. After the ablation, you will be monitored in the hospital over night. The catheters to be used in the ablation have been approved for other abnormal heart rhythms; however, none have been approved by the FDA for ablating atrial fibrillation.

Regardless of which therapy is chosen, you will be asked to see your doctor at 3, 6, and 12 months during the first year and then every 6 months for 2-5 years. After enrollment you will have a 24-hour heart monitor recording during your follow-up visits. You will also be expected to use a hand-held transtelephonic monitor to document your heart rhythm seven days before and seven days after each of your 6 month follow-up visits. Throughout the trial, if you feel symptoms from your heart rhythm, you will also be asked to record a heart tracing.

It could take at least one year to fully test the effectiveness of different drug or ablation therapies.

Economics and Quality of Life Assessment

The staff of **{INSERT NAME OF YOUR MEDICAL FACILITY}** and/or representatives of the Economic and Quality of Life (EQOL) Coordinating Center at the Duke Clinical Research Institute will also contact your doctor(s) or hospital(s) to obtain copies of your hospital and doctor bills for up to 5 years after treatment is started (the length of the study). This study is being done so we can understand the cost effects of drug and ablation therapies. You will be asked about any hospitalizations, heart procedures, or doctor visits that you may have had between study visits to provide information about the costs of your illness.

At the time you are enrolled, the staff of **{INSERT NAME OF YOUR MEDICAL FACILITY}** will ask you questions about how you rate your health, about activities, how you are feeling emotionally, and some questions about your work status, education and income. These questions will take about 20 minutes to answer. You may refuse to answer any of the questions. The staff of **{INSERT NAME OF YOUR MEDICAL FACILITY}** and/or representatives of the EQOL Coordinating Center will contact you by telephone at 3, 12, 24,

36, and 48 months to ask similar questions about how you are doing, if there are any changes in how you feel, in your ability to perform your daily activities, or in your working status. This information will allow us to understand the effects of treatment in CABANA on the quality and economics of patients' lives. Also, when you are seen or contacted by the (**INSERT NAME OF YOUR MEDICAL FACILITY**) staff at enrollment, 3, 6, and 12 months during the first year and every 6 months thereafter, you will be asked to rate your health using a scale of 0-100 and answer 5 brief questions about the state of your health. All of these data will be analyzed using coded information without your name or other identifiable information publicized.

Schedule of Activities

Activity/ Time Frame	**Baseline**	***3 month - 7d + 30d***	**6 month ± 30 d**	**12 month ± 30 d**	**6 month Interval ± 30 d**
Informed Consent	x				
Medical history/Interval history	x	x	x	x	x
Patient status (alive or dead)		x	x	x	x
Concomitant meds	x	x	x	x	x
Interim Adverse Events		x	x	x	x
Expedited Events		x	x	x	x
AF burden assessment	x	x	x	x	x
QOL	x	x		x	annual
Physical Exam	x	x	x	x	x
NYHA	x	x	x	x	x
12 Lead ECG	x	x	x	x	x
24 hour Holter	x	x	x	x	x
Echocardiogram (TTE)	x				
Echocardiogram (TEE) (1)	x				
VQ scan (2)	x				
CT/MRI (2, 3)	x	x	x	x	x
Event recorder (4)		.	x	x	x

1: If warranted prior to any cardioversion and at any time throughout the trial
2: If randomized to ablation therapy
3: If medically indicated due to Pulmonary Vein stenosis
4: To be used after therapy initiation to document symptomatic episodes during the 3 month blanking period as well as for both groups for 1 week prior and 1 week after each follow-up visit (total of 14 consecutive days).

How long will I be in this research study?
You will be in the study for 2 to 5 years.

Are there reasons I might leave this research study early?
Taking part in this research study is your decision. You may decide to stop at any time. You should tell your study doctor if you decide to stop and you will be told whether any additional tests may need to be done for your safety. In addition, your study doctor may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What are the risks of this research study?
This trial compares two different routine treatments for atrial fibrillation. These two therapy options, namely drug or catheter ablation, are not experimental or investigational. As such, participation in this research study will not result in any additional risks compared to the risks you would have if you received the same routine therapy outside of this research study.

[Risks of drug therapy]
If you are randomized to the medication group, the drugs used to control your heart rate or rhythm have possible side effects. The possible side effects of drug treatment depend on the specific drug used and the presence and type of any underlying heart disease.

With **rate control medications**, general side effects may include but not be limited to…

- slowing of the heart rate
- dizziness, light headedness
- low blood pressure
- fainting
- shortness of breath, fatigue
- wheezing, worsening of asthma
- nausea/vomiting
- fluid accumulation
- heart failure
- skin rashes
- diarrhea, constipation
- poor appetite
- alteration of color vision
- depression
- impotence

Other side effects may occur, but these are the most common. All of these side effects disappear when the drug dose is lowered or if the drug is stopped.

With **rhythm control medications**, such as propafenone or flecainide, patients may experience…

- blurred vision, double vision
- light-headedness
- an unusual metallic taste
- an excessive decrease in the heart rate or blood pressure

A drug like sotalol may…

- slow the heart rate
- decrease the blood pressure or
- produce a tired feeling

Dofetilide can cause headaches or diarrhea.

Each of these usually resolves when the drug is stopped.

Amiodarone has a number of additional side effects. This agent may rarely affect:

- vision - leading to blurred or severely deteriorating vision or blindness
- the thyroid gland - leading to a sense of feeling too hot and shaky (hyperthyroidism) or too cold and fatigued (hypothyroidism)
- the liver - leading to abnormalities of liver function or enzyme elevation
- the skin - causing increased sensitivity to the sun or development of a bluish or grayish skin tone
- the nervous system - leading to some unsteadiness or imbalance
- the intestinal tract - leading to nausea or constipation and
- the lungs - causing inflammation or scarring.

While most of these side effects are mild and resolve over 4-16 weeks with discontinuation of the drug, amiodarone lung toxicity can be life threatening. However, it does not occur in very many patients. Amiodarone may need to be stopped in one-third of patients over 3-4 years of therapy because of one or more of the listed side effects.

In some people, drug treatment can aggravate the atrial fibrillation, causing it to occur more frequently, last longer, or be more regular but at a faster rate, a proarrhythmic event; new or worsened arrhythmia. The heart rate may even become faster. In addition, a life threatening heart rhythm can occur with any drug in 0.5 - 4% of patients. This is more likely in a patient who has had a prior heart attack, or has other heart disease. In some people, any of these drugs can affect the heart's pumping function, leading to heart failure, or can decrease blood pressure or heart rate. In some patients, these side effects can lead to death. Sometimes patients need a pacemaker to maintain an appropriate heart rate.

Despite side effects, drug therapy can be a very good way of treating atrial fibrillation in a significant number of patients. The risks specific to the drug chosen for you will be discussed with you by your physician. As with any medication, allergic reactions are a possibility. It is possible that your atrial fibrillation may return while taking the medication or that you may develop other heart rhythms that are not treatable with the medication to prevent atrial fibrillation. Overall, with drug therapy, the risk of a serious complication is between 1-4 %. The risk of a minor problem is 5-20 %.

[Ablation Procedure Risks]

If you are randomized to the ablation group; there are a variety of risks or complications that can occur with the ablation procedure. These may be related to the insertion or placement of catheters, the use of medications, moving the catheters in the heart, or delivery of energy inside of the heart.

The **insertion of the catheters** into your neck or leg veins or arteries can be accompanied by the following:

- The possibility of infection, bleeding, bruising, pain or blood clot formation under the skin. A blood clot can develop in one of your veins in the leg or even in the lungs. A vein or artery could be injured and may require surgery for repair.
- Since the neck vein catheter travels close to the lung, it is possible for the lung to be punctured causing it to collapse. If this occurs, a hollow tube may be required. It would be inserted between the ribs to remove the air around the lung and help it re-expand.
- You could also develop a bladder or kidney infection, infection elsewhere in the blood, pneumonia or fluid in the lung.
- The possibility of air entering the blood stream.

Medications given during the procedure could also have side effects.

- X-ray "contrast dye," used to visualize your heart and veins, may cause an allergic reaction resulting in a skin rash, difficulty breathing, or even cause lowering of blood pressure. This dye can also damage the kidneys. Although rare, the pumping ability of your heart may decrease or lung failure could occur.
- You may have an abnormal reaction to any anesthetic used during the procedure.
- The dye and anesthetic may produce an allergic response leading to a skin rash, a drop in blood pressure, or difficulty breathing. If this occurs, breathing can be supported by placement of a tube from the mouth into the upper airways of your lungs. A ventilator, or breathing machine, then assists with the work of breathing and the procedure can be continued. In rare cases, pneumonia could develop.
- The blood thinner, heparin, which is used to prevent blood clot formation during the procedure, could cause bleeding anywhere in the body. While this is rare, such bleeding can be serious.
- There is a chance you may experience nausea or a visual migraine-like headache or see wavy lines in one or both eyes following the procedure.

Other procedure risks are related to **positioning catheters** within your heart.

- The most serious of these is heart muscle perforation by a catheter. In many cases this is resolved, as the hole created by the catheter seals when the catheter is removed.
- In some cases, bleeding into the sac surrounding the heart could result in a pressure build up in the heart producing a drop in blood pressure. In such cases, a needle and catheter tube may be inserted from a position underneath the breastbone or between the ribs to drain this blood. In extreme cases, open-heart surgery may be required.
- Moving the catheters within the heart could damage a heart valve, which could require surgical repair or replacement.
- A heart attack or stroke could also occur.
- The coronary artery may spasm, develop a blood clot, or develop a tear.
- There is also a possibility that the normal electrical system could be damaged, making pacemaker implantation necessary**.**
- The X-rays used to guide catheter placement could cause skin burns, or in the long run result in some form of cancer, or damage to your heart or lungs.
- If you already have a pacemaker, the wires positioned in the heart could be disturbed or the pacemaker damaged, making repair or replacement necessary.

The final group of risks has to do with the actual **ablation**.

- In some cases, you may experience chest pain when the energy is delivered or inflammation around the heart may cause chest pain after the procedure.
- In addition, energy delivery on the left side of the heart could lead to blood clot formation, cause a stroke, or other organ damage.
- With energy delivery, there is also a slight increase in the chance of a heart attack, or the development of an esophageal atrial fistula, where the heart and esophagus are damaged, leading to the formation of a connection between the two structures. This can produce severe infection or a severe stroke which may lead to death.
- Ablation in or near a vein can also damage the vein itself.
- In a low percentage of cases, a pulmonary vein can be narrowed or significant scarring may occur, which can cause permanent lung damage. If this happens in only one vein, you may not experience symptoms. On the other hand, if more veins are affected, the scarring can cause shortness of breath, cough, chest pain, a decrease in exercise capability, elevated lung pressure, fluid in the lungs, or lung damage. In some cases, an angioplasty type of procedure may be required to open up this narrowing or scarring with a balloon catheter. In other cases, a coil or "stent" may be required to keep the vessel open. If the vessel re-narrows after the stent is placed, a repeat catheter procedure on more than one occasion could be required. Under rare circumstances open-heart or lung surgery could be required to correct the narrowing or scarring. In most cases, this can be dealt with successfully, although the consequences can be serious.
- There is a possibility of damage to one of the nerves around your heart. In rare cases, a nerve supplying the diaphragm (the muscle that helps with breathing) may become sufficiently damaged to cause the diaphragm to be paralyzed (unable to move). This is unlikely to be serious, and the muscle function usually returns over the course of 4 to 16 months, although sufficient damage could lead to permanent diaphragm paralysis.
- There may be elevated temperatures or elevated blood tests.
- Your body may retain extra fluid.
- You may experience vagal responses such as decreased heart rate, decreased blood pressure, or near fainting.
- There is possibility of developing esophagus or stomach erosion disorder, esophageal achalasia, esophageal ulcers, or stomach emptying disorder.

It is possible that your atrial fibrillation may return following the catheter ablation procedure. You could require medication therapy, another ablation, or your rhythm may become worse. Overall, from the clinical portion of the ablation procedure, the risk of a serious complication is between 1-4%. The risk of a minor problem is 5-15%.

While you are taking part in this study, you are at risk for these side effects related to drug or ablation therapy. You should talk to your study doctor about these side effects. There also may be other side effects that are not known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Most side effects go away shortly after the treatments are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There is a risk of death with any complication related to either medication or ablation therapy that is serious and does not respond to emergency treatment.

Women of Childbearing Potential

Ablation or drug therapy may be harmful to an unborn child carried by a woman who is taking part in this study. There is not enough medical information to know what the risks might be to an unborn child. Therefore, women who can still become pregnant will be excluded from the trial because of risk from the ablation and ongoing drug therapy that cannot be consistently avoided.

Are there benefits to taking part in this research study?

Either treatment may result in fewer or no more episodes of atrial fibrillation. You may be able to reduce or eliminate some medication you take for your abnormal heart rhythm. In some cases participation in this study may not make your health better. Nevertheless, the information that is learned from this study may benefit

other people with the same condition as yours and may advance medical understanding of abnormal heart rhythms.

What other choices do I have if I don't take part in this research study?
You do not have to be in this study to receive treatment for your condition. Your alternative choices may include further drug therapy to treat atrial fibrillation, a catheter ablation procedure, an ablation of the AV node (cluster of cells between the atria and ventricles that slows the electrical current as it passes to the ventricles – also called the atrio-ventricular node) followed by implantation of a permanent pacemaker, or an open heart operation. Your abnormal heart rhythm may also be treated with a pacemaker or other device that can activate when your abnormal heart rhythm occurs. Each of these treatments has its own risks and benefits. You should think about all of your choices and talk with your doctor about them before you decide if you will take part in this study.

Will I need to pay for the tests and procedures?
Each of the tests and procedures are part of regular medical care for atrial fibrillation. These tests and procedures are the standard baseline evaluation for the drug treatment of atrial fibrillation or are those required prior to a catheter ablation procedure. You or your insurance company will need to pay for these routine tests and procedures as part of your regular medical care.

If you have questions while at the **{INSERT NAME OF YOUR MEDICAL FACILITY}**, please go to the **{INSERT CONTACT AND PHONE NUMBER}**.

What happens if I am injured because I took part in this research study?
If you have side effects from the treatment of your atrial fibrillation, you need to report them to your regular physician and you will be treated as needed. **{INSERT NAME OF YOUR MEDICAL FACILITY}** will bill you or your insurer for these services at the usual charge. **{INSERT NAME OF YOUR MEDICAL FACILITY}** will not offer free medical care or payment for any bad side effects or complications from taking part in this study. In case of injury: contact Dr. _____ (or an associate) by calling the **{INSERT NAME OF YOUR MEDICAL FACILITY AND PHONE NUMBER HERE}**.

What are my rights if I take part in this research study?

Taking part in this research study is voluntary and does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care from **{INSERT NAME OF YOUR MEDICAL FACILITY}**.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

Who can answer my questions?
You may talk to Dr. _____ at any time about any questions or concerns you have with this study. You may contact Dr. _____ (or an associate) by calling the **{INSERT CONTACT AND PHONE NUMBER HERE}**.

You can get more information about **{INSERT NAME OF YOUR MEDICAL FACILITY}** policies, the conduct of this study, or the rights of research participants from **{INSERT CONTACT AND PHONE NUMBER HERE}**.

Authorization To Use And Disclose Protected Health Information

Your privacy is important to us, and we want to protect it as much as possible. By signing this form, you authorize **{INSERT NAME OF YOUR MEDICAL FACILITY}** and the investigators to use and disclose any information created or collected in the course of your participation in this research protocol. This information

might come from different places, including your original medical record or doctor's office, but we will only disclose information that is related to this research protocol for the purposes listed below.

This information will be given out for the proper monitoring of the study, checking the accuracy of study data, analyzing the study data, and other purposes necessary for the proper conduct and reporting of this study. You will not be identified in releasing this information. If some of the information is reported in published medical journals or scientific discussions, it will be done in a way that does not directly identify you.

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by the study protocol, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of (INSERT NAME OF YOUR MEDICAL FACILITY). For records disclosed outside of (INSERT NAME OF YOUR MEDICAL FACILITY), you will be assigned a unique code number. The key to the code will be kept in a locked file in (INSERT NAME OF PRINCIPAL INVESTIGATOR)'s office.

This information may be given to others involved with this study (including MCAR, Duke Clinical Research Institute, St. Jude Foundation, Biosense Webster, Inc., National Institute of Health, and those at other institutions) or private, state or federal government parties or regulatory authorities (U.S. and other countries) responsible for overseeing this research. These may include the Office for Human Research Protections, or other offices within the Department of Health and Human Services, and the **{INSERT NAME OF YOUR MEDICAL FACILITY}** Office for Human Research Protections or other **{INSERT NAME OF YOUR MEDICAL FACILITY}** groups involved in protecting research subjects.

If this information is given out to anyone outside of **{INSERT NAME OF YOUR MEDICAL FACILITY}** the information may no longer be protected by federal privacy regulations and may be given out by the person or entity that receives the information. However **{INSERT NAME OF YOUR MEDICAL FACILITY}** will take steps to help other parties understand the need to keep this information confidential.

This consent/authorization and study results will be retained for at least six years from the date the study is terminated.

You may stop this authorization at any time by writing to the following address:

{INSERT NAME OF YOUR MEDICAL FACILITY}
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
{INSERT NAME OF YOUR MEDICAL FACILITY}

If you stop authorization, **{INSERT NAME OF YOUR MEDICAL FACILITY}** may continue to use your information already collected as part of this study, but will not collect any new information.

A signed and dated copy of this form will be provided to you as well as placed in your medical record.

Participant Statement:
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. "

I have been given a copy of this form.

_____	_____	_____
(Date / Time)	(Printed Name of Participant)	(Clinic Number)

_____

(Signature of Participant)

_____ _____

(Date / Time) (Printed Name of Individual Obtaining Consent)

_____

(Signature of Individual Obtaining Consent

Appendix E

Approved Ablation Devices

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	P95005
Biosense Webster	CELSIUS Braided Tip	8F/4-5mm	P95005
Biosense Webster	CELCIUS Long Reach	7F/4-5mm	P95005
Biosense Webster	CELCIUS Long Reach	8F/4-5mm	P95005
Biosense Webster	NAVI-STAR Thermo-Cool	7.5F/3.5mm	P030031
CryoCath	Freezor®	7F/4mm	P020045
CryoCath	Freezor® Xtra	7F/6mm	P020045
CryoCath	Freezor® MAX	9F/8mm	P020045
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
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
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
Biosense Webster	Navistar® RMT	7F/4mm	P990025
Biosense Webster	Navistar® RMT	7F/8mm	P010068
Biosense Webster	Celsius® RMT	7F/4mm	P950005

Appendix F

ECG Monitoring Core Lab Protocol

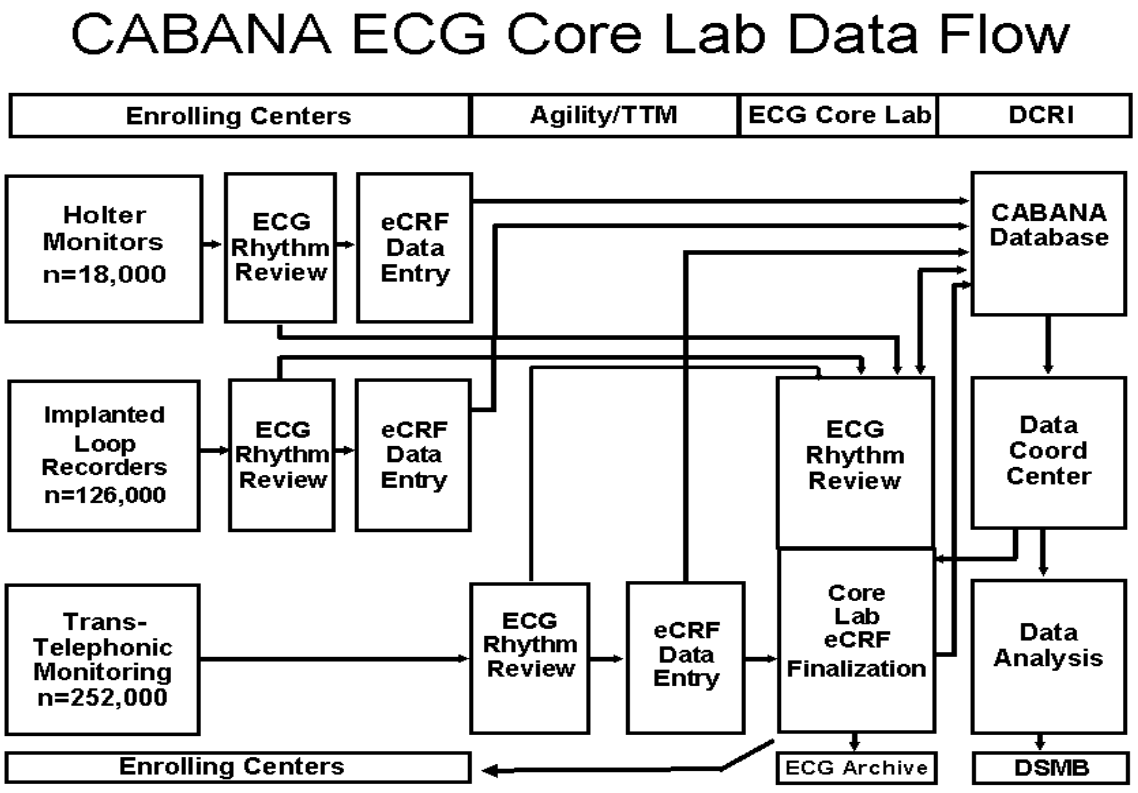
ECG Core Lab Specific Aims

The primary aim of the ECG core lab is to support the main CABANA Trial by providing the expertise and systems to examine the impact of therapy on the occurrence of atrial fibrillation. The CABANA intensity of surveillance will also be mandatory in making decisions about treatment of these patients, regardless of treatment arm. While establishment of the secondary endpoint of recurrent AF will be of paramount importance, the data so acquired will also allow us to descriptively address the following specific aims:

1) Establish and compare AF recurrence in drug and ablation treated patients
2) Characterize the degree of recurrent arrhythmia organization
3) Establish the rate of recurrence of typical and atypical atrial flutter in each group
4) Determine the changes in sinus rhythm occurring immediately before the documented recurrence
5) Assess the impact of treatment on ventricular response rates with recurrence
6) Document the recurrence rate for symptomatic AF
7) Determine and compare the occurrence of post-treatment asymptomatic AF
8) Establish the sensitivity and specificity of patient symptoms for identifying recurrent AF
9) Aid in characterizing and understanding the placebo effect of ablation
10) Compare the sensitivity of surface vs implanted loop recorders for detecting AF
11) Compare the utility of surface and implanted recorders for guiding therapy
12) Determine the advisability of discontinuing anticoagulation following ablation

ECG Monitoring Structure and Processes

The following diagram describes the organization of the ECG core lab for the rhythm monitoring process.



General Rhythm Assessment Procedures

The process of ECG rhythm strip acquisition, transmission, archiving, review, interpretation, and certification will require the interaction of several key organizations. As noted in the above core lab data flow diagram, each investigative site will obtain ECG rhythm information from ECGs, Holter monitors, implanted loop recorders, and/or transtelephonic monitoring. As described in the body of the grant, each patient will undergo Holter monitoring at 3, 6, and 12 months in the first year and at 6 and 12 months of each subsequent follow-up year. Although not mandated, some patients will have an implanted loop recorder. It is anticipated that no more than one-quarter of patients will have such devices. The majority of rhythm information will be obtained via trans-telephonic monitoring.

Each site will be responsible for reviewing each rhythm recording from their own patients and acting on the resulting clinical information. In addition, each site will obtain qualitative and quantitative information from the recordings and enter it into the EDC system maintained on the DCRI web site. In the case of Holter monitors and loop recorders, relevant data will be entered into the respective eCRF forms. The sites will also transmit to the ECG Core Lab, 1) any recording documenting the presence of recurrent atrial fibrillation occurring as a secondary endpoint (true positive recordings), 2) any patient triggered recording acquired during symptoms, even though normal sinus rhythm was present (false positive recordings), 3) routine follow-up tracing showing atrial fibrillation in the absence of symptoms, and 4) Core Lab dictated random recordings necessary internal auditing and quality assurance.

In contrast, all trans-telephonic monitor strips will be called into the CABANA monitoring center at Agility Centralized Research Services, Inc (ACRS). There, the TTM rhythm strips will be reviewed and eCRF data entry made. Agility will communicate with the core lab via email when transmissions requiring clinical action have been posted. Agility will transmit the same 4 categories of recordings to the ECG Core Lab. The Core Lab is then responsible for final adjudication of rhythm present, and completion of the CABANA eCRF forms as outlined below. All data analysis will be undertaken at Duke.

Detailed Holter Monitoring Procedures

Patients will undergo Holter monitoring at each 6-month follow-up, with a median of 3.5 years of follow-up anticipated. For this, the Holter will be applied, retrieved, and interpreted at the individual enrolling center. The coordinator at that site will enter data into the eCRF from the clinically generated report. Digital Holter strips will only be sent to the Core Lab if there is a secondary endpoint triggering AF recurrence, if there is asymptomatic AF, or if the patient claims a recurrence of symptomatic AF (even if strip is normal). For Auditing purposes, the Core Lab will also review a random portion of the 18,000 Holter recordings produced during the trial. These qualifying strips and the site-entered eCRF will be reviewed for accuracy and correlation of symptoms and rhythm. Confirmatory and supplemental data obtained by the ECG Core Lab will be entered into the EDC system. The eCRF pages for site and Core Lab over-read information are constructed to capture basic intervals, rhythm, AF rate, AF organization, AFL occurrence, AF duration, % time spent in AF, and heart rate occurring prior to the AF episode (if captured). Note: the ECG Core Lab will have a computer-based review capability for nearly all commercially available Holter systems. If an unusual Holter recording system is employed, all relevant rhythm strips will be sent to the ECG Core Lab via fax.

Implanted Loop Monitoring

In addition to this above monitoring, up to 375 patients in the drug treated arm, and 375 patients from the ablation treatment arm may have implanted loop recorders. Patient-activated rhythm sampling will occur on a daily basis over the course of the 14-day surveillance period scheduled for every 6 months. As with the Holter recordings, eCRF data will be entered by the individual enrolling site. In addition, the individual enrolling center will send an optical disc with the interrogated tracings to the ECG Core lab; again if there is an endpoint event, any randomly obtained recording showing atrial fibrillation in the absence of AF, or a NSR recording captured because of a patient-presumed AF recurrence. As with the Holter recordings, the eCRF page will be constructed to capture basic intervals, rhythm, AF rate, AF organization, AFL occurrence, AF duration, % time spent in AF, and heart rate occurring prior to the AF episode (if captured).

Trans-telephonic Monitoring

The majority of rhythm surveillance will be done with TTMs, as follows: First, the patient will transmit a rhythm recording at the time of symptoms. They will also be required to transmit a recording each day over the

14 days surrounding each of the 6 month Holter monitoring follow-up, or 28 separate transmissions each year (total 3000 x 28 x the median follow-up time of 3 years = 252,000 transmissions).

Dealing with that many strips, especially if faxed and of poor quality, would be prohibitive. Therefore, all TTM transmissions will go directly to ACRS, a well-established provider of clinical research technologies and rhythm monitoring. They will be responsible for 1) sending out the TTM recording systems, 2) receiving and processing every transmission from each patient, 3) reviewing each strip to establish what rhythm is present, 4) calling the patients every day of the 14 day monitoring period (around every follow-up) if necessary to facilitate all transmissions, 5) verify patient compliance by performing random audits to determine the number of call-ins that are actually made, 6) contacting the patient with important information detected from the recordings, 7) notifying the site of each transmission via email, 8) contacting the site if there are important findings on the recordings, 9) calculating the basic intervals, 10) entering the eCRF data for every single transmission, 11) sending any endpoint or questionable transmission to the core lab 12) forwarding any NSR strip obtained at the time of patient-presumed AF, 13) transmitting any tracing showing AF in the absence of symptoms, 14) forwarding random normal TTM tracings to the Core lab for blinded review, 15) interacting with the sites to improve TTM monitoring yield, and 16) participating in any audits occurring during the trial.

Core Lab Responsibilities

The Core Lab would be responsible for:

1. Receive and archive all Holter recordings transmitted to the ECG Core Lab
2. Receive, archive, review, and adjudicate positive Holter recordings showing end-point AF and correlate with Sx (if any)
3. Receive, archive, review, and adjudicate negative Holter recordings showing sinus rhythm and correlate with the presence of Sx
4. Schedule with sites and then receive, archive, review and adjudicate randomly sampled Holter recordings to assure accuracy of site data entry (5% of AF, and 1% of non-AF strips)
5. Certify the true and false positive rates of Holter recordings
6. Establish the presence of a CABANA AF recurrence endpoint
7. Qualitatively (morphology) and quantitatively (intervals) review Holter transmissions.
8. Validate the rate, organization, % time, and heart rate in NSR prior to an AF episode
9. Review and certify all site entered eCRF data for those strips
10. Enter all related quantitative and qualitative data into the ECG Core Lab portion of the eCRF maintained at DCRI
11. Receive and archive all Implanted Loop recordings transmitted to the ECG Core Lab
12. Receive, archive, review, and adjudicate positive Implanted Loop recordings showing end-point AF and correlate with Sx (if any)
13. Receive, archive, review, and adjudicate negative Implanted Loop recordings showing sinus rhythm and correlate with the presence of Sx
14. Schedule with sites and then receive, archive, review and adjudicate randomly sampled Implanted Loop recordings to assure accuracy of site data entry (5% of AF, and 1% of non-AF strips)
15. Certify the true and false positive rates of Implanted Loop recordings
16. Establish the presence of a CABANA AF recurrence endpoint
17. Qualitatively (morphology) and quantitatively (intervals) review Implanted Loop transmissions.
18. Validate the rate, organization, % time, and sinus rhythm heart rate prior to an AF episode
19. Review and certify all site entered eCRF data for those strips
20. Enter all related quantitative and qualitative data into the ECG Core Lab portion of the eCRF maintained at DCRI
21. Receive and archive all TTM recordings transmitted to the ECG Core Lab by Agility
22. Receive, archive, review, and adjudicate positive TTM recordings showing end-point AF and correlate with Sx (if any)
23. Receive, archive, review, and adjudicate negative TTM recordings forwarded by Agility showing sinus rhythm and correlate with the presence of Sx
24. Schedule with Agility and then receive, archive, review and adjudicate randomly sampled TTM recordings to assure accuracy of Agility data entry (5% of AF, and 1% of non-AF strips)
25. Certify the true and false positive rates of TTM recordings

26. Establish the presence of a CABANA AF recurrence endpoint
27. Qualitatively (morphology) and quantitatively (intervals) review all TTM transmissions from Agility.
28. validate the rate, organization, and sinus rhythm heart rate prior to an AF episode
29. Review and certify all Agility entered eCRF data for those strips
30. Enter all related quantitative and qualitative data into the ECG Core Lab portion of the eCRF maintained at DCRI

This process will provide the data needed for secondary endpoint verification, and that needed for assessing the specific ECG Core Lab aims noted above.

Core Lab Rhythm Strip Calculations

The number of transmissions to actually be processed is as follows: 1) Holters obtained twice each year in 3000 patients, each of the median of 3 years of follow-up, will generate 18,000 reports. 2) Loop recorders implanted in 750 patients (375 in each treatment arm), will generate one capture each day over 14 days, twice each year, for the median of 3 years. This is equal to 126,000 strips over the course of the trial. 3) The 3,000 patients will generate 14 TTM transmissions, twice each year, for each of 3 years, or 252,000 TTM strips.

Based on available single site and recent comparative drug vs ablation studies, at least 30% of the 1500 ablated patients (n=450 patients) will have symptomatic recurrences that are clinically detected. Based on the recent Hopkins and Leipzig experience, as many as 25% (n=375 patients) could have asymptomatic AF detected on screening. Thus 450+375=825 will have first time AF recurrences. An additional 40% (n=560 patients) could have symptoms thought to be due to AF, occurring at the time of sinus rhythm false positive symptoms, as shown in then Hopkins experience. [Total=1325].

We assume that 30% of drug treated patients (n=450 patients) will be treated with rate control agents. Based on AFFIRM and RACE, as many as 65% (~300) may be in symptomatic or asymptomatic AF at the time of 1-3 year follow-up. Conversely, 70% of patients will be treated with an anti-arrhythmic drug (n=1050 patients), of which 80% (n=840 patients) will have a detected AF recurrence. This anticipated prevalence comes from the recent ablation vs drug treatment studies. Taken together, 1350 patients in the overall drug-treatment arm could generate at least one positive AF recording to be forwarded to the ECG Core Lab. In addition, we assume that 40% of drug treated patients will have symptoms attributed to AF (n=600 patients) in the presence of normal sinus rhythm. This number is likewise taken from the recent Hopkins report. Therefore, 1350 + 600= 1950 transmissions in drug treated patients will be processed by the Core Lab.

Randomly, 10% of the Holter and implanted loop recorder strips (1800+1260=2060) and 1% of 252,000 TTM strips (2520) will be reviewed for quality control purposes. [4580 strips] These along with the 1325 ablation and 1950 drug-treatment arm strips will total 7855 ECG Core Lab processed recordings. Note: These calculations assume that any given rhythm event will be transmitted once, by a single recording type. The Core Lab will have the capability of dealing with twice this number of recordings (~15,000), should the event be transmitted from several recording systems.

Appendix G

CABANA TRIAL CLINICAL EVENTS CLASSIFICATION

Death/Cardiac Arrest Event Review Form **

Event to be adjudicated: **I.** ☐ **Cardiac Arrest**

II. ☐ **Death**

W ☐ **Witnessed** (includes any event that is actually seen or heard)
☐ Bystander ☐ EMS

UW ☐ **Un-witnessed** (includes patients where event is not seen, heard, or monitored)

S ☐ **Sudden**

NS ☐ **Non-Sudden**

***Note:** Cardiac arrest: sudden loss of consciousness necessitating CPR and/or transthoracic defibrillation to stabilize BP and rhythm.
*** Note:** Sudden death = death within 1 hour of symptom onset.

☐ **A. <u>CARDIAC</u>** *(Please select only one cardiac classification from the 5 choices below)*

☐ **1. Arrhythmic—Tachy or (Unclear)**

☐ **a. Sudden** (within 1 hr. of symptom onset)
☐ **1.** Without preceding signs or symptoms
***Note: If un-witnessed: at last contact, patient was in usual state of health without complaints or obvious difficulty*.**
☐ **2.** Immediately following lightheadedness or palpitations
☐ **3.** Immediately preceded by chest discomfort or other signs/symptoms of acute myocardial ischemia
☐ **4.** Immediately following ECG or monitor documented VT or VF.
☐ **5.** Occurring in a patient with progressive symptoms of heart failure in the last 2 weeks but death is unexpected.
Note: Applies to patients dying in their sleep after recent progression of CHF.

☐ **b. Non-sudden**
☐ **1.** Incessant VT
☐ **2.** Sequelae of tachyarrhythmic cardiac arrest or VT storm
☐ **3.** Post Ablation or ICD implant mortality
Note: This applies to a post-ablation or post-op ICD death occurring within 30 days of that procedure, that is a direct result of ablation or device implant. (Does not include subsequent, non-ablation or non-implant related arrhythmic events.)

☐ **2. Arrhythmic—Brady**

☐ **a. Sudden** (within 1 hr of symptom onset)
☐ **1.** Without preceding signs or symptoms
***Note: If un-witnessed: at last contact, patient was in usual state of health without complaints or obvious difficulty*.**
☐ **2.** Immediately following lightheadedness or palpitations
☐ **3.** Immediately preceded by chest discomfort or other signs/symptoms of acute myocardial ischemia
☐ **4.** Immediately following ECG monitor documented bradycardia
☐ **b. Non-sudden**
☐ **1.** Sequelae of bradycardia-mediated cardiac arrest

☐ **3. Heart Failure**

☐ **a. Sudden** (within 1 hr of symptom onset)
☐ **1.** Acute, severe pulmonary edema
Note: Events directly related to heart failure therapy AND Events in Patients with survival anticipated to be short (i.e. < 4 months), with severe, progressive CHF will be classified here, even if VT or VF is documented in hospital or by paramedics
☐ **1.** Tachy ☐ **2.** Brady ☐ **3.** Unclear
☐ **2.** Pulseless electrical activity (PEA) observed with first monitoring at or after event onset. This does not include pulseless electrical activity after defibrillation from VF.
☐ **1.** Tachy ☐ **2.** Brady ☐ **3.** Unclear

☐ **b. Non-sudden**
☐ **1.** Event in a patient with severe, progressive congestive heart failure: With survival anticipated to be short (i.e., < 4 months).
Note: Events directly related to heart failure therapy AND Events in Patients with severe, progressive CHF *with survival anticipated to be short (i.e., < 4 months) and* ***can be classified here, even if VT or VF is documented in hospital or by paramedics providing they are sudden***
☐ **1.** Tachy ☐ **2.** Brady ☐ **3.** Unclear
☐ **2.** Pulseless electrical activity (PEA) observed with first monitoring at or after event onset. This does not include pulseless electrical activity after defibrillation from VF.
☐ **1.** Tachy ☐ **2.** Brady ☐ **3.** Unclear

☐ **4. Non-arrhythmic**

☐ **a.** Probable acute MI. Event in a patient with reasonable evidence for an infarction, onset of symptoms within previous 48 hours:
☐ **1.** Symptoms ☐ **2.** ECG ☐ **3.** Enzymes ☐ **4.** Other
☐ **b.** Ischemic, non-MI. Event in a patient with known ischemia (e.g., during unstable angina or exercise with evidence of ischemia, but no myocardial necrosis).
☐ **c.** Arrhythmic event (with ECG documented VT or VF) in a hospitalized patient within 48 hours of a cardiac surgical procedure or PTCA (excluding ventricular arrhythmia control procedures).
☐ **d.** Nonarrhythmic event within 30 days, and a direct result of, a cardiovascular procedure (e.g.,CABG, PTCA), except for ICD implantation.

☐ **B. NON-CARDIAC**

☐ **1. Vascular Event** (thromboembolic event or acute hemorrhage; e.g., pulmonary embolus, dissecting aneurysm, CVA, etc.) ***Note: The final "event" may have been CHF, VT, VF, or bradycardia/asystole, but will be coded here if the patient was admitted for a serious non-cardiac process that was a more proximate cause of the patient's demise.***

If the final "event" is cardiac:

☐ **a.** Arrhythmic ☐ **b.** CHF ☐ **c.** Ischemia ☐ **d.** PEA

☐ **2. Non-vascular Event** (e.g., trauma, renal failure, liver failure, cancer, sepsis, suicide, overdose, etc.) ***Note: The final "event" may have been CHF, VT, VF, or bradycardia/asystole, but will be coded here if the patient was admitted for a serious non-cardiac process that was a more proximate cause of the patient's demise.***

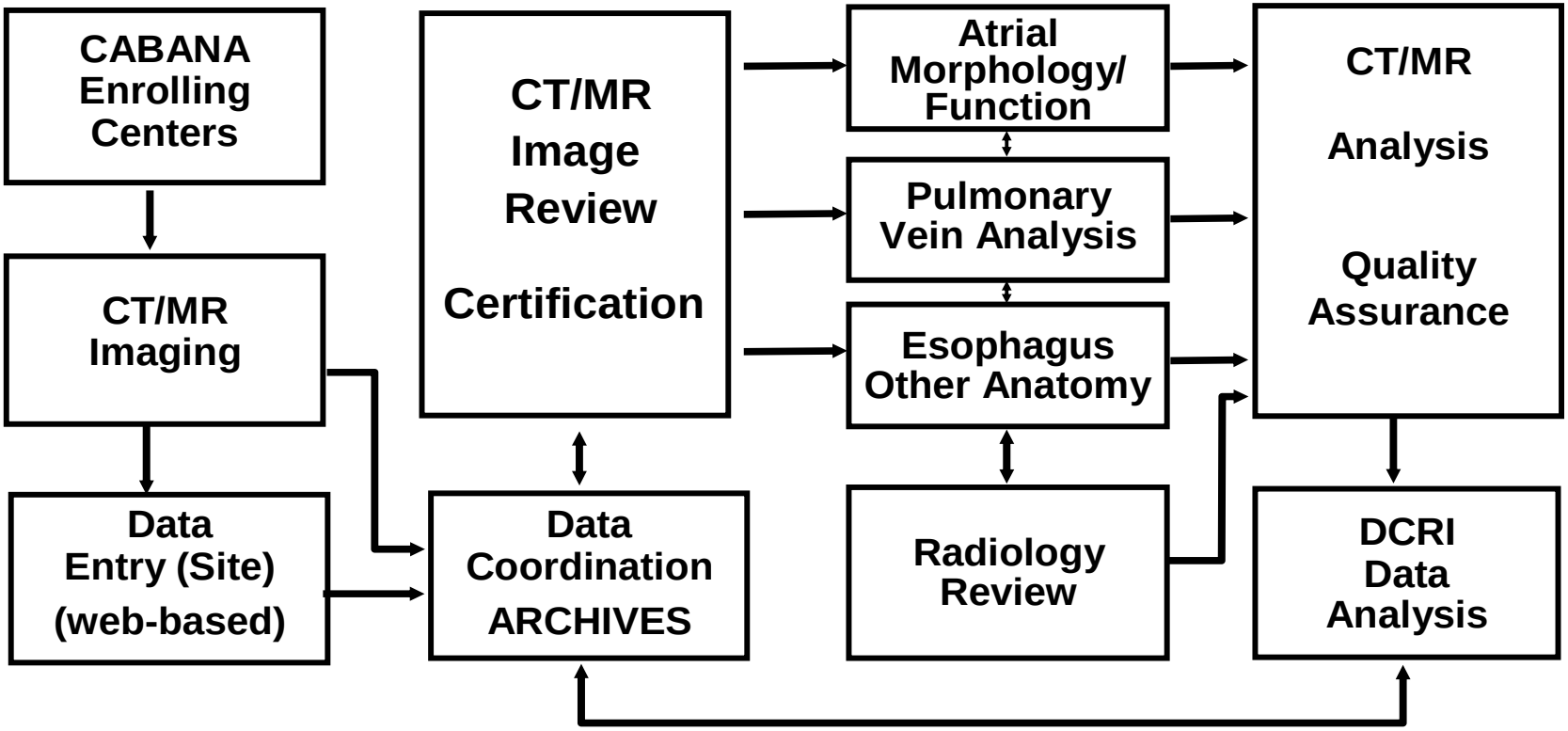
If the final "event" is cardiac:

☐ **a.** Arrhythmic ☐ **b.** CHF ☐ **c.** Ischemia ☐ **d.** PEA

☐ **C. UNKNOWN**

Appendix H

CABANA CT/MR Imaging Core



Impact of Sinus Rhythm on Mortality