Summary of Changes in the Protocol

The following changes listed in Table 1 represent clarification, version control, and corrective changes to the CABANA Protocol, Version 3.1, (August 19, 2009). These changes were approved by the CABANA Leadership Team at Mayo Clinic and Duke Clinical Research Institute (DCRI).

Table 1. Summary of Protocol Changes

Section/Page	Version 3.0 June 19, 2009	Version 3.1 August 19, 2009	Rationale
Title Page	NA	**Grant Number:** 1U01HL089709-01A1 **Grant Number:** 1U01HL089786-01A1 **Grant Number:** 1U01HL089907-01A1 **Grant Number:** 1U01HL089645-01A1	Clarification **No change to study procedures.**
Title Page	Version: 3.0	Version: 3.1	Version control **No change to study procedures.**
Title Page	Date: June 19, 2009	Date: August 19, 2009	Version control **No change to study procedures.**
Footer Throughout	June 19, 2009	August 19, 2009	Version control **No change to study procedures.**
Page 6	CRF 312.64B	CFR 812 (Subpart E).	Correction **No change to study procedures.**
4.4.3/24	Symptom Event Recorder	**CABANA Box** Symptom Event Recorder	Clarification **No change to study procedures.**
8.2.8/41	NA	Bang and Tsiatis	Correction **No change in study procedures.**

Summary of Changes in the Protocol

The following changes listed in Table 1 represent clarification, version control, and corrective changes to the CABANA Protocol, Version 3.2, (24 November, 2009). These changes were approved by the CABANA Leadership Team at Mayo Clinic and Duke Clinical Research Institute (DCRI).

Table 1. Summary of Protocol Changes

Section/Page	Version 3.1 19 August, 2009	Version 3.2 24 November, 2009	Rationale
Title Page / 1	Version: 3.1	Version: 3.2	Version control **No change to study procedures.**
Title Page / 1	Date: 19 August, 2009	Date: 24 November, 2009	Version control **No change to study procedures.**
Footer Throughout	19 August, 2009	24 November, 2009	Version control **No change to study procedures.**
Contacts / 2	Not previously listed	**National Heart Lung and Blood Institute** NHLBI Two Rockledge Centre Suite 8170, MSC 7940 6701 Rockledge Dr. Bethesda, MD 20892-7940 (Fed-Ex Zipcode 20817) **Project Officer:** Alice M. Mascette, MD Phone:301-435-0504 Fax: 301-480-7404 mascetta@mail.nih.gov	Clarification **No change to study procedures.**
Contacts / 3	Phone: 507-284-4937 Not previously listed	Phone: 507-284-2997 **Co-Investigator:** David Holmes, III PhD Phone: 507-284-2997	Clarification **No change to study procedures.**

		Fax: 507-284-1632 Holmes.david3@mayo.edu **Data Management**: Maryam Rettmann, PhD Phone: 507-284-2997 Fax: 507-284-1632 rettmann.maryam@mayo.edu	
TOC / 8	Version 3.1	Updated to version 3.2	Clarification **No change to study procedures.**
4.2 / 23	Baseline economic, functional status, and quality of life data, including SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, and the AF Symptom Checklist will be collected via a structured questionnaire interview conducted by the Site Coordinator prior to randomization.	Baseline functional status, *economic data (including two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer" and asking 5 brief questions)*, and quality of life data *(including a Baseline Questionnaire of validated scales, ie, SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, AF Effects on QOL (AFEQT), Work Productivity and Activity Impairment Instrument (WPAI), and Stanford Presenteeism scale)* will be collected by the Site Coordinator *via structured interview* prior to randomization.	Clarification and to provide outcomes for secondary endpoints and objectives: 9. Medical costs, resource utilization, and cost effectiveness 10. Quality of Life
4.4.1 / 24	1. Historical examination including Drug History assessment 2. Physical examination 3. ECG 4. Blood Tests (INR, creatinine, hemoglobin, hematocrit) 5. 24-hour Holter monitoring 6. Trans-thoracic 2-D echocardiography 7. Trans-esophageal	*1.* Historical examination including Drug History assessment *(within 60 days prior to randomization)* *2.* Physical examination *(within 60 days prior to randomization)* *3.* ECG *(within 60 days prior to randomization)* *4.* Blood Tests (INR, creatinine, hemoglobin, hematocrit) *(within 7 days prior to treatment)* *5.* 24-hour Holter monitoring *(within 12*	Clarification **No change to study procedures.**

	echocardiogram 8. CT /MR evaluation (all ablation patients and 375 Drug patients) 9. Economics and Quality of Life Assessment	*months prior to randomization)* *6.* Trans-thoracic 2-D echocardiography *(within 4 months prior to randomization)* *7.* Trans-esophageal echocardiogram *(within 48 hours prior to treatment)* 8. CT /MR evaluation (all ablation patients and 375 Drug patients) *(within 4 months prior to treatment)* 9. Economics and Quality of Life Assessment *(after consent, prior to randomization)*	
4.4.2 / 24	Follow-up in all patients will occur at 3, 6, and 12 months following randomization during the first year and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below. Economic and QOL data, including SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, the AF Symptom Checklist, Cardiac Self-Efficacy and Stanford Presenteeism scale will be repeated during the 3 month follow-up visit and annually by trained telephone interviewer staff from the EQOL Coordinating Center (EQOL CC) for patients enrolled in North America and by the Site Coordinator in sites outside North America. A Brief Follow-up Questionnaire capturing atrial fibrillation severity and symptoms will be collected at 6, 18, 30 and 42 months.	Follow-up in all patients will occur at 3, 6, and 12 months following randomization during the first year and every 6 months thereafter, with clinic visits, phone follow-up, and other testing as described below. Economic and QOL data, including a *full follow-up questionnaire of validated scales, ie,* SF-36, DASI, Toronto Atrial Fibrillation Severity Scale, AF *Effects on QOL (AFEQT), Work Productivity and Activity Impairment Instrument (WPAI),* and Stanford Presenteeism scale, will be repeated *at 3 months* and annually *from randomization* by trained telephone interviewer staff from the EQOL Coordinating Center (EQOL CC) for patients enrolled in North America and by the Site Coordinator in sites outside North America. A Brief Follow-up Questionnaire capturing atrial fibrillation severity and symptoms, *work productivity/activity/presenteeism* will be collected at 6, 18, 30 and 42 months	Clarification and to provide outcomes for secondary endpoints and objectives: 9. Medical costs, resource utilization, and cost effectiveness 10. Quality of Life

	Medical bills for patients enrolled at US sites will be collected throughout the trial by the EQOL Coordinating Center economic team. The Site Coordinators will complete a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim all-cause hospitalizations, ER visits since last contact and will forward them to the EQOL Coordinating Center for processing.	*post randomization. All above follow-up visits/calls should be completed within 30 days +/- of the due date. (Ex: 3 month visit: completed between 60 days and 120 days of randomization)* Medical bills for patients enrolled at US sites will be collected throughout the trial by the EQOL Coordinating Center economic team. The Site Coordinators will complete a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim all-cause hospitalizations, ER visits since last contact and will forward them to the EQOL Coordinating Center for processing. *As part of the economic data in CABANA, two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer" and asking 5 brief questions will be collected by the Site Coordinator throughout the trial and entered into the e-CRF.*	
4.4.3 / 26	Not previously listed	*5): Hospital discharge or following Drug Therapy initiation*	Clarification **No change to study procedures.**
5.2.2 / 27	Tambacor Tykosin Quini-glute	*Tambocor* *Tikosyn* *Quinaglute/ dex*	Clarification **No change to study procedures.**
5.2.2 / 27	Not previously listed	*Multaq (dronedarone) should not be used in patients with NYHA IV heart failure, or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.*	Clarification in response to FDA letter dated October 14, 2009. **No change to study procedures.**
6.2 / 32	Secondary endpoint events, including composite endpoints of	Relocated this statement as a stand-alone paragraph for clarity:	Clarification **No change to study procedures.**

	mortality, disabling stroke, serious bleeding, or cardiac arrest will be confirmed and adjudicated in a similar manner by the CEC. A Disabling Stroke will be considered present using a modification of A Rankin Stroke score [100], and will be adjudicated by a Neurologic Events Committee. Serious (or Life-threatening) bleeding will be considered present using a modification of the GUSTO bleeding Scale adapted for use in catheter ablation [101]. These events will be tracked regardless of treatment randomization. While hospitalization for AF in both treatment arms will be carefully tracked and compared, it will be considered as an "*AF recurrence"* and counted against efficacy, not safety. The definition for each of these events is listed in the CEC Charter. When there is disagreement between the CEC and the principal investigator, the CEC's decision will be considered final. Procedures for adjudicating events are described in the CEC Charter, which is available upon request.	*While hospitalization for AF in both treatment arms will be carefully tracked and compared, it will be considered as an "AF recurrence" and counted against efficacy, not safety. Therefore, AF recurrence and/or worsening of AF does not need to be reported as an adverse event.*	
11.1.2 / 45	Any site may be terminated from the trial if it fails to comply with the above requirements. Specifically,	Any *activated* site may be terminated from the trial *for failure to enroll any subjects, within a reasonable period of*	Clarification requested by the DSMB. **No change to study procedures.**

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

Summary of Changes in the Protocol

The following changes listed in Table 1 represent clarification, version control, and corrective changes to the CABANA Protocol, Version 3.3, (03 March, 2010). These changes were approved by the CABANA Leadership Team at Mayo Clinic and Duke Clinical Research Institute (DCRI).

Table 1. Summary of Protocol Changes

Section/Page	Version 3.2 24 November, 2009	Version 3.3 03 March, 2010	Rationale
Title Page / 1	Version: 3.2	Version: 3.3	Version control **No change to study procedures.**
Title Page / 1	Date: 24 November, 2009	Date: 03 March, 2010	Version control **No change to study procedures.**
Footer Throughout	24 November, 2009	03 March, 2010	Version control **No change to study procedures.**
TOC / 8	Version 3.2	Updated to version 3.3	Clarification **No change to study procedures.**
4.4.1 / 24	All patients will undergo standard baseline evaluation, including: 1. Historical examination including Drug History assessment (within 60 days prior to randomization) 2. Physical examination (within 60 days prior to randomization) 3. ECG (within 60 days prior to randomization) 4. Blood Tests (INR, creatinine, hemoglobin, hematocrit) (within 7 days prior to treatment) 5. 24-hour Holter monitoring (within 12 months prior to treatment) 6. Trans-thoracic 2-D echocardiography (within 4 months prior to randomization) 7. Trans-esophageal echocardiogram (within 48 hours prior to treatment)	Defining the eligibility of patients for the CABANA Trial will require information generated during the course of routine clinical care as dictated by their attending physician. This information should be, consistent with established guidelines, consensus documents, and good clinical practice. Selected baseline testing data will be collected in order to characterize the type, cause and severity of the patient's AF and the treatments received prior to enrollment. The baseline data will include information from the following clinical evaluations: 1. Relevant medical history including prior and current drug treatment of AF	FDA requested Clarification Delineation between the baseline testing considered part of routine clinical care from that specifically required for the CABANA Trial

	8. CT /MR evaluation (all ablation patients and 375 Drug patients) (within 4 months prior to treatment) 9. Economics and Quality of Life Assessment (after consent, prior to randomization) The trans-thoracic echocardiographic (TTE) studies are designed to characterize the substrate underlying the patient's AF, establishing the presence of LV dysfunction (LVEF), hypertrophy, diastolic dysfunction, or other structural abnormalities. The TTE will also assess LA size and volume, as well as echo measures of atrial function. 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. 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 quantitative LA size, morphology, and function studies, as well as PV and esophageal investigations. In addition, 375 patients randomized to drug therapy will undergo baseline scanning for comparisons in the atrial structure and function studies. These patients will be recruited from centers that are	2. Relevant physical examination 3. 12 lead ECG prior to treatment 4. Blood Tests (INR, creatinine, hemoglobin / hematocrit) (pre-treatment) 5. Trans-thoracic 2-D echocardiography The trans-thoracic echocardiographic (TTE) data will be used to characterize the substrate underlying the patient's AF, establishing the presence of LV dysfunction (LVEF), hypertrophy, diastolic dysfunction, or other structural abnormalities. The TTE will also assess LA size and volume, and provide measures of atrial function. Following a recommended approach consistent with established guidelines, consensus documents, and good clinical practice, a trans-esophageal echocardiographic (TEE) study will be performed within 24 hours prior to ablation in patients with *persistent or longstanding persistent* AF. The TEE may be performed up to 48 hours before the procedure in patients on continuous warfarin at a therapeutic INR or in those appropriately bridged with intravenous un-fractionated or low molecular weight heparin. The performance of a pre-treatment TEE in patients with *paroxysmal* AF is left to the discretion of the investigator (5.4.4), but is not required in CABANA. Data on the performance	

	committed to CT / MR assessment of each enrolled drug patient. Since randomization is performed (stratified) within each site, this component of the study will still benefit from the overall study randomization.	and results of all TEEs performed as part of routine care will be collected in the eCRF, however. TEE data may also be used to confirm atrial size and morphology. The approach to cardioversion in drug treated patients should follow the recommendations of AF Treatment Guidelines [92]. In those centers where routine clinical practice includes the performance of pre-ablation CT / MR studies, relevant data from these studies will be collected to serve as a baseline for comparative quantitative LA size, morphology, and function studies, as well as subsequent follow-up PV and esophageal investigations. In addition at those centers, up to 375 patients randomized to drug therapy will be asked to undergo baseline research CT/MR scanning to allow the CABANA study to evaluate and compare atrial structure and function in response to drug or ablative therapy. These drug-treated patients will be recruited from selected centers that are committed to CT / MR assessment of enrolled drug patients. Since randomization is performed (stratified) within each site, this component of the study will still benefit from the overall study randomization. Optimally, the scans performed in all patients should be within 4 months prior to treatment. In addition to these clinically dictated studies, baseline economic and QOL	

		data will be obtained after informed consent is obtained, but before randomization occurs.	
4.4.2 / 25 para 2	Medical bills for patients enrolled at US sites will be collected throughout the trial by the EQOL Coordinating Center economic team. The Site Coordinators will complete a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim all-cause hospitalizations, ER visits since last contact and will forward them to the EQOL Coordinating Center for processing. As part of the economic data in CABANA, two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer" and asking 5 brief questions will be collected by the Site Coordinator throughout the trial and entered into the e-CRF.	Medical bills for patients enrolled at US sites will be collected throughout the trial by the EQOL Coordinating Center economic team. The Site Coordinators will complete a one page Rapid Report Form (RRF) at each CABANA study visit documenting any interim hospitalizations and/or, ER visits since last contact. These forms will be forwarded to the EQOL Coordinating Center for processing. As part of the economic data in CABANA, two EQ-5D forms that rate the patient's health by using a 0-100 "thermometer" and asking 5 brief questions will be collected by the Site Coordinator at each follow-up visit throughout the trial and entered into the e-CRF.	Clarification Delineation between the baseline testing considered part of routine clinical care from that specifically required for the CABANA Trial
para 3	…(throughout trial)	… (throughout the trial)	
para 4	CT/MR imaging studies will be performed on all ablation subjects at baseline, 3 months post-ablation therapy, and as indicated for PV stenosis management throughout the trial. CT/MR imaging studies will also be performed on 375 drug therapy patients at baseline and 3 months after therapy is fully established (end of blanking period). It is essential that the same imaging modality, acquisition parameters, and imaging techniques be utilized for each subject at all time-points. CT/MR data will	CT/MR imaging studies will be performed where clinically indicated or otherwise part of routine clinical care on ablation subjects at baseline, at 3 months post-ablation therapy, and as indicated for PV stenosis management throughout the trial. At sites where baseline and follow-up CT/MR imaging studies are part of routine care for ablation patients, CT/MR imaging studies will also be performed for research purposes on up to 375 drug therapy patients at baseline and 3 months after therapy is	

	then be electronically transferred to a server at the Mayo Biomedical Imaging Resource, the CABANA Trial Image Analysis Lab. Scans will be anonymized at the site using a software tool provided by the Imaging Center. Each clinical center is required to perform standard site radiology evaluation and assessment of the CT/MR images according to the sites' standard clinical practice.	fully established (end of blanking period). CT/MR data will be electronically transferred to a server at the Mayo Biomedical Imaging Resource, the CABANA Trial Image Analysis Lab. Scans will be anonymized at the site using a software tool provided by the Imaging Center. Each clinical center will also perform standard site radiology evaluation and assessment of the CT/MR images according to the sites' standard clinical practice.	
4.4.3/26	All procedures and laboratory tests required for evaluation of follow-up should be performed whether or not a subject receives treatment according to the protocol.	All procedures and laboratory tests during follow-up should be performed whether or not a subject receives treatment according to the protocol.	Clarification Delineation of testing considered part of routine clinical care from that required for the CABANA Trial
7.1.5 / 34	1. **Device-related:** any adverse event for which a causal relationship between the device and the event is a reasonable possibility. The likelihood that the event is device related will be categorized as listed above, the device-related "cause" will categorized as follows:	1. **Device-related:** any adverse event for which a causal relationship between the device and the event is a reasonable possibility. The likelihood that the event is device related will also be sub-classified using the approach in 7.1.4 above. The event will be further classified as a device failure or malfunction (7.1.5.2) and whether it is unanticipated (7.1.5.3), as described in these sections.	FDA requested Clarification **No change to study procedures.**
Appendix B /60	P95005	P950005	Clarification/Typo **No change to study procedures.**

Summary of Changes in the Protocol

The following changes listed in Table 1 represent clarification, version control, and corrective changes to the CABANA Protocol, Version 3.3, (03 March, 2010). These changes were approved by the CABANA Leadership Team at Mayo Clinic and Duke Clinical Research Institute (DCRI).

Table 1. Summary of Protocol Changes

Sites/Protocol version	**North America and International**	**North America and International**	**International with full Clinical Trial Application (CTA)**	
Section/Page	**Version 3.3 03 March, 2010**	**Version 3.4 08 August, 2011**	**Version 3.4.1 08 April, 2012**	**Rationale for change**
Title Page / 1	Version: 3.3	Version: 3.4	Version: 3.4.1	Language revisions/insert for compliance with US /Foreign Regulatory Authorities
Title Page / 1	Date: 03 March, 2010	Date: 08 August, 2011	Date: 08 April, 2012	
Title Page / 1			EudraCT-Number: 2011-002532-12	BfArM required
Footer Throughout	03 March, 2010	08 August, 2011	08 April, 2012	
Contact / 2	**Project Officer:** Alice M. Mascette, MD Phone:301-435-0504 Fax: 301-480-7404 mascetta@mail.nih.gov	**Project Officer:** Alice M. Mascette, MD Phone:301-435-0477 Fax: 301-480-7971 alice.mascetta@nih.gov	No revision from 3.4	Change of contact details
Contact / 2	**Project Leader**: Kathleen L. Hoffmann, R.N. Phone: 919-668-8277 Cell: 919-818-9461 Fax: 919-668-7105 kathleen.hoffmann@duke.edu	**Project Leader**: Kathleen L. Moretz, R.N. Phone: 919-668-8277 Cell: 919-818-9461 Fax: 919-668-7105 kathleen.moretz@duke.edu	No revision from 3.4	Change of contact details
Synopsis / 5	Enrollment will occur over approximately 3 years, and subjects will be followed a	Enrollment will occur over approximately 4 years, and subjects will be followed a	No revision from 3.4	The enrollment period has been extended

	minimum of 2 years.	minimum of 2 years.		
TOC / 8	Version 3.3	Updated to version 3.4	Updated to version 3.4.1	Change of protocol version
2.2.2 / 20	By reducing the recurrence of AF, the proposed therapies should also reduce all cause and cardiovascular hospitalization.	By reducing the recurrence of AF, the proposed therapies should also reduce cardiovascular hospitalization.	No revision from 3.4	Editorial change to increase the clarity of the text
3.1 / 21	1. Have documented AF episodes ≥1 hour in duration; with ≥2 episodes over 4 months with electrocardiographic documentation of 1 episode or at least 1 episode of AF lasting more than 1 week 4. Be ≥65 yrs of age, or <65 yrs with one or more of the following risk factors for stroke: Hypertension defined as a BP >140/90 mmHg [90], Diabetes defined as a fasting glucose ≥126 mg/dl [91], Congestive heart failure (including systolic or diastolic heart failure), Prior stroke or TIA, LA size >5.0 cm (or volume index ≥ 40 cc/m2), or EF ≤35. Subjects <65 yrs of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify.	1. Have paroxysmal AF episodes ≥1 hour in duration; with ≥2 episodes over the preceding 6 months with ***electrocardiographic documentation*** of at least 1 episode; or 1 persistent or longstanding persistent episode of AF lasting more than 1 week. 4. Be ≥65 yrs of age, or <65 yrs with **one or more** of the following risk factors for stroke: Hypertension (treated and/or defined as a BP >140/90 mmHg) [90], Diabetes (treated and/or defined as a fasting glucose ≥126 mg/dl) [91], Congestive heart failure (including systolic or diastolic heart failure), Prior stroke or TIA, LA size >5.0 cm (or volume index ≥40 cc/m2), or EF ≤35. Subjects <65 yrs of age whose only risk factor is hypertension must have a second risk factor or LV hypertrophy to qualify.		Clarification of the inclusion criteria
3.1 / 22		Patients may have documented atrial flutter in addition to atrial fibrillation and remain eligible	No revision from 3.4	Wording added for clarification that documented atrial

		for enrollment.		flutter is accepted along with atrial fibrillation
3.2 / 22	1. Patients who have failed ≥2 membrane active anti-arrhythmic drugs at a therapeutic dose due to inefficacy or side effects 8. Hypertrophic obstructive cardiomyopathy 10. Other mandated anti-arrhythmic drug therapy 16. Contraindication to warfarin anti-coagulation 20. Participation in any other clinical mortality trial	1. Patients who have failed ≥2 *membrane active* anti-arrhythmic drugs at a therapeutic dose due to inefficacy or side effects (Table 5.2.2) 8. Hypertrophic obstructive cardiomyopathy (outflow track) 10. Other arrhythmias mandating anti-arrhythmic drug therapy (i.e. VT, VF) 16. Contraindication to appropriate anti-coagulation therapy 20. Participation in any other clinical mortality trial (Participation in other non-mortality trials should be reviewed with the clinical trial management center)	No revision from 3.4	Clarification of the exclusion criteria
3.2 / 23		Planned atrial flutter ablation in combination with the left atrial ablation is not an exclusion.	No revision from 3.4	Wording added to clarify that planning/performing an atrial flutter ablation is accepted
4.3 / 23	Randomization will be accomplished by telephone using a centralized, IVRS randomization system.	Randomization will be accomplished by telephone or internet using a centralized, interactive voice and web randomization system (IXRS).	No revision from 3.4	To provide clarifications about the randomization system, with additional information about the internet option.
4.4 / 24	Patients will be followed at 6 and 12-month intervals throughout the trial.	Patients will be followed at 6 and 12-month intervals from randomization throughout the	No revision from 3.4	To clarify the timing for the follow-up procedures

		trial.		
4.4.1 / 24	Following a recommended approach consistent with established guidelines, consensus documents, and good clinical practice, a trans-esophageal echocardiographic (TEE) study will be performed within 24 hours prior to ablation in patients with *persistent or longstanding persistent* AF. The TEE may be performed up to 48 hours before the procedure in patients on continuous warfarin at a therapeutic INR or in those appropriately bridged with intravenous un-fractionated or low molecular weight heparin. In those centers where routine clinical practice includes the performance of pre-ablation CT / MR studies, relevant data from these studies will be collected to serve as a baseline for comparative quantitative LA size, morphology, and function studies, as well as subsequent follow-up PV and esophageal investigations. In addition at those centers, up to 375 patients randomized to drug therapy will be asked to undergo baseline research CT/MR scanning to allow the CABANA study to evaluate and compare atrial structure and function in response to drug or ablative therapy. These drug-treated	Following a recommended approach consistent with established guidelines, consensus documents, and good clinical practice, a trans-esophageal echocardiographic (TEE) study will be performed within 24 hours prior to ablation in patients with *persistent or longstanding persistent* AF. The TEE may be performed up to 48 hours before the procedure in patients on continuous anticoagulation therapy, such as warfarin at a therapeutic INR or in those appropriately bridged with intravenous un-fractionated or low molecular weight heparin. In those centers where routine clinical practice includes the performance of pre-ablation and post-ablation CT/MR studies, relevant data from these studies will be collected to serve as a baseline for comparative quantitative LA size, morphology, and function studies, as well as subsequent follow-up PV and esophageal investigations. In addition at those centers, up to 375 patients randomized to drug therapy will be asked to undergo one ~~baseline~~ research CT/MR scan prior to initiating therapy. This will allow the	No revision from 3.4	The wording has been changed to allow the use of other anticoagulant drugs in addition to warfarine. The timing for performing the baseline CT/MR scans for the ablation patients and for the drug therapy patients at the selected centers has been clarified.

	patients will be recruited from selected centers that are committed to CT / MR assessment of enrolled drug patients. Since randomization is performed (stratified) within each site, this component of the study will still benefit from the overall study randomization. Optimally, the scans performed in all patients should be within 4 months prior to treatment.	CABANA study to evaluate and compare atrial structure and function in response to drug or ablative therapy. These drug-treated patients will be recruited from selected centers that are committed to CT/MR assessment of all enrolled ~~drug~~ patients (both study arms). Since randomization is performed (stratified) within each site, this component of the study will still benefit from the overall study randomization. Optimally, the pre-therapy scans performed in all patients should be within 4 months prior to treatment.		
4.4.2 / 25	CT/MR imaging studies will be performed where clinically indicated or otherwise part of routine clinical care on ablation subjects at baseline, at 3 months post-ablation therapy, and as indicated for PV stenosis management throughout the trial. At sites where baseline and follow-up CT/MR imaging studies are part of routine care for ablation patients, CT/MR imaging studies will also be performed for research purposes on up to 375 drug therapy patients at baseline and 3 months after therapy is fully established (end of blanking period). CT/MR data will be electronically transferred to a server at the Mayo Biomedical	CT/MR imaging studies will be performed where clinically indicated or otherwise part of routine clinical care on ablation subjects ~~at baseline, at 3 months post~~ after ablation therapy (between 90 days post ablation and the 6 month follow-up) and as indicated for PV stenosis management throughout the trial. ~~At sites where baseline and follow-up CT/MR imaging studies are part of routine care for ablation patients~~. The 375 drug therapy patients that received the CT/MR scan prior to initiating drug therapy, ~~imaging studies~~ will also undergo one ~~be performed for~~ research CT/MR scan after therapy is fully	After enrollment, subjects will either receive a single 'CABANA Box' recording system to be used throughout the entire study, or will be examined several times using ambulatory Holter ECG monitoring as generated during the course of routine clinical care as dictated by their attending physician. At sites where the 'CABANA Box' has received the appropriate approvals, all patients enrolled will receive a single 'CABANA Box' recording system to be used for both patient activated event monitoring (throughout the	The Medicomp monitoring system will only be utilized at Institutions or within countries where appropriate approvals have been obtained. Routine monitoring based on clinical care will be recorded within the trial database records. The timing for performing post-therapy CT/MR scans for the

	Imaging Resource, the CABANA Trial Image Analysis Lab. Scans will be anonymized at the site using a software tool provided by the Imaging Center. Each clinical center will also perform standard site radiology evaluation and assessment of the CT/MR images according to the sites' standard clinical practice. Complete follow-up data will also be obtained at the time of treatment discontinuation, with a crossover in treatment strategy, and at the emergence of any primary or secondary endpoints.	established (between 90 days post drug treatment initiation and the 6 month follow-up) ~~(end of blanking period)~~. CT/MR data will be electronically transferred to a server at the Mayo Biomedical Imaging Resource, the CABANA Trial Image Analysis Lab. Scans will be anonymized at the site using a software tool provided by the Imaging Center. Each clinical center will also perform standard site radiology evaluation and assessment of the CT/MR images according to the sites' standard clinical practice. Follow-up data will also be obtained at the time of treatment discontinuation, with a crossover in treatment strategy, and at the emergence of any primary or secondary endpoints.	trial), autodetect/autocapture (AD:AC) event monitoring (one 24 hour period/month and full disclosure Holter monitoring (for 96 hours every 6 months) throughout the entire study. Fingertip recordings as well as AD:AC recordings can be transferred via telephone download from the patient's home to the CABANA monitoring center. Holter recordings will require downloading of information at the enrolling site for data transfer to the CABANA monitoring center. All recordings will be made available to the enrolling center for use in clinical practice.	ablation patients and for the drug therapy patients at the selected centers has been clarified.
5.2.3 / 28		Drugs which have been approved by appropriate regulatory agencies outside of the United States may be used within that jurisdiction.	No revision from 3.4	To explain that the protocol allows the use of new drugs which have been approved by appropriate regulatory agencies outside of the United States within the respective jurisdictions, as a chief aim of the trial is to provide

				relevant, up-to-date information for guiding drug and ablative therapy for AF.
5.2.6 / 28	During follow-up, drug arm patients with recurrences may be treated with additional anti-arrhythmic drugs or alternative rate control agents. Ablative intervention is strongly discouraged. Of note, most patients included to date in single center trials were treated for over one year before undergoing ablation. Patients will be fully informed of this at the time of the consent process. **Crossovers must be approved by the CABANA Trial Administrative Center.**	During follow-up, drug arm patients with recurrences may be treated with additional anti-arrhythmic drugs or alternative rate control agents. Of note, most patients included to date in single center trials were treated for over one year before undergoing ablation. Thus, it is anticipated that most patients will be treated for at least 12 months in the drug therapy arm and that patients will be fully informed of this at the time of the consent process. Cross over ablative intervention is strongly discouraged. **Crossovers must be approved by the CABANA Trial Administrative Center. Before approval is granted for a patient randomized to drug therapy to be crossed over to ablation,** sites will be required to provide rationale and documentation that drug therapy options have been exhausted.	No revision from 3.4	To reinforce that crossover of the patients from the drug therapy arm to ablation therapy is discouraged and subject of approval by the CABANA Trial Administrative Center.
5.3.3 / 29		Catheters which have been approved by appropriate regulatory agencies outside of the United States may be used within that jurisdiction.	No revision from 3.4	To clarify catheters which have been approved by appropriate regulatory agencies

				outside of the United States may be used within that jurisdiction, even if they are not listed in the protocol.
5.4.1 / 31	Patients with risk factors for CVA or peripheral thromboembolic events at the time of enrollment, treated with rate control agents alone, will remain on active anticoagulation therapy with warfarin throughout the duration of the trial [92]. Unlike the AFFIRM trial, patients receiving rhythm control therapy will also be required to receive warfarin anticoagulation for the duration of the trial. In both cases, target INRs of 2 to 3 will be required, unless higher INRs are mandated because of underlying disease.	Patients with risk factors for CVA or peripheral thromboembolic events at the time of enrollment, treated with rate control agents alone, will remain on active anticoagulation therapy ~~with~~ (~~warfarin~~, dabigatran) throughout the duration of the trial [92]. Unlike the AFFIRM trial, patients receiving rhythm control therapy will also be required to receive ~~warfarin~~ adequate anticoagulation (warfarin, dabigatran) for the duration of the trial. In ~~both cases~~ the use of warfarin therapy, target INRs of 2 to 3 will be required, unless higher INRs are mandated because of underlying disease.		Changes have been implemented to allow the use of other anticoagulation drugs (dabigatran).
5.4.2 / 31	Anticoagulation before, during, and after the ablative intervention will follow the guidelines of the AF Ablation Consensus Document [50]. Prior to the ablative intervention, patients with persistent and long-standing persistent AF should receive at least one month of warfarin anticoagulation (INRs: 2-3), or	Anticoagulation before, during, and after the ablative intervention will follow the guidelines of the AF Ablation Consensus Document [50]. Prior to the ablative intervention, patients with persistent and long-standing persistent AF should receive adequate anticoagulation (i.e. at least one month of warfarin	No revision from 3.4	Changes have been implemented to allow the use of other anticoagulation drugs (dabigatran), in accordance with the recent guidelines of the AF Ablation Consensus

	have a TEE excluding intra-atrial thrombus at the time of the intervention. During the ablative intervention, maintaining an ACT between 300 and 400 seconds is strongly recommended. Following the ablative intervention, patients will be started on IV heparin or subcutaneous injections of low molecular weight heparin beginning 4 to 6 hours after all sheaths are removed, and 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, unless the ablation was performed at a therapeutic INR in patients maintained on warfarin through the ablation. Three to six months after ablation, warfarin may be replaced by full dose aspirin in patients with a CHADs score ≤ 1. This would include patients with hypertension without hypertrophy, or those <65 years of age, providing 1) atrial size and function are normal and 2) there is no symptomatic or asymptomatic AF by standard or full-disclosure monitoring. In those patients with a CHADs score ≥2, warfarin is to be continued throughout the trial. Randomization of warfarin	anticoagulation (INRs: 2-3)), or have a TEE excluding intra-atrial thrombus at the time of the intervention. During the ablative intervention, maintaining an ACT between 300 and 400 seconds is strongly recommended. Following the ablative intervention, patients will be started on IV heparin or subcutaneous injections of low molecular weight heparin beginning 4 to 6 hours after all sheaths are removed, and ~~warfarin~~ appropriate anticoagulation reinstituted the evening of the intervention. Thereafter, low molecular weight heparin is to be maintained until anticoagulated appropriately or standard dose warfarin achieves a target INR of 2 to 3, unless the ablation was performed at a therapeutic INR in patients maintained on warfarin through the ablation. One month following the ablation, Dabigatran may be substituted for warfarin, following recently written guidelines. Three to six months after ablation, warfarin may be replaced by full dose aspirin in patients with a CHADs score ≤ 1. This would include patients with hypertension without hypertrophy, or those <65 years of age, providing 1) atrial size		Document.

	discontinuation is precluded by the low post-ablation stroke rates that would require at least 10,000 patients for detecting differences in stroke prevalence. Nevertheless, the characteristics, follow-up monitoring results, and long-term anticoagulation status of ablation patients will be compared to descriptively identify predictors of events and profiles of patients at high risk for warfarin discontinuation. The utility of trans-telephonic, auto-detection / full disclosure, and Holter monitoring, as a future aid in the decision to discontinue anticoagulation will also be critically examined.	and function are normal and 2) there is no symptomatic or asymptomatic AF by standard or full-disclosure monitoring. In those patients with a CHADs score ≥2, adequate anticoagulation ~~warfarin~~ is to be continued throughout the trial. Randomization of warfarin discontinuation is precluded by the low post-ablation stroke rates that would require at least 10,000 patients for detecting differences in stroke prevalence. Nevertheless, the characteristics, follow-up monitoring results, and long-term anticoagulation status of ablation patients will be compared to descriptively identify predictors of events and profiles of patients at high risk for warfarin discontinuation. The utility of trans-telephonic, auto-detection / full disclosure, and Holter monitoring, as a future aid in the decision to discontinue anticoagulation will also be critically examined.		
5.4.3 / 31	It is likely during the course of the trial that newer antithrombotic therapies non-inferior to warfarin will be approved. These agents may be used as replacement therapy for warfarin on approval of Innovative Antithrombotic Therapies/Executive Committees.	It is likely during the course of the trial that newer antithrombotic therapies non-inferior to warfarin or dabigatran will be approved. These agents may be used as replacement therapy for warfarin on approval of Innovative Antithrombotic Therapies/Executive	No revision from 3.4	Changes have been implemented to allow the use of other anticoagulation drugs (dabigatran).

		Committees.		
5.4.4 / 31	Specific items left to the investigators discretion include: 1) specific choice of rate control vs. rhythm control drug therapy and specific drugs to be used; 2) hospitalization to initiate anti-arrhythmic drug therapy; 3) choice of TEE guided direct current cardioversion (DCCV) vs. DCCV after 4 weeks of warfarin to an INR of 2-3; 4) pre-ablation TEE assessment in patients with simple paroxysmal AF and hypertension without hypertrophy; 5) continuation of warfarin to maintain a therapeutic INR at the time of catheter ablation.	Specific items left to the investigators discretion include: 1) specific choice of rate control vs. rhythm control drug therapy and specific drugs to be used; 2) hospitalization to initiate anti-arrhythmic drug therapy; 3) choice of TEE guided direct current cardioversion (DCCV) vs. DCCV after 4 weeks of appropriate anticoagulation therapy, such as warfarin to an INR of 2-3; 4) pre-ablation TEE assessment in patients with simple paroxysmal AF and hypertension without hypertrophy; 5) continuation of warfarin to maintain a therapeutic INR at the time of catheter ablation; 6) selection of warfarin versus dabigatran.	No revision from 3.4	Changes have been implemented to allow the use of other anticoagulation drugs (dabigatran).
6.2 / 32	While hospitalization for AF in both treatment arms will be carefully tracked and compared, it will be considered as an "*AF recurrence"* and counted against efficacy, not safety. Therefore, AF recurrence and/or worsening of AF does not need to be reported as an adverse event.	While hospitalization for AF in both treatment arms will be carefully tracked and compared, it will be considered as an "*AF recurrence"* and counted against efficacy, not safety. Therefore, AF recurrence and/or worsening of AF ~~does~~ **should not** be reported as an adverse event.	No revision from 3.4	Change implemented to increase the clarity of the text.
7.0 / 32	An adverse event (AE) will be considered present if 1) there are untoward signs, symptoms, illnesses, or other medical events that develop or worsen in severity during the course of the study, 2) they are clinically	An adverse event (AE) will be considered present if 1) there are untoward signs, symptoms, illnesses, or other medical events that develop or worsen in severity during the course of the study, 2) they are clinically	No revision from 3.4	The text had been updated to provide additional guidance and clarifications to the investigators for the assessment and reporting of

	relevant and if they are clinically related to the study. Note: Disease, signs symptoms, and or laboratory abnormalities already existing at randomization are not considered adverse events unless they represent an intensity or frequency exacerbation. Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Surgical procedures planned prior to randomization and the conditions leading to these measures are not adverse events.	relevant **and** if they are clinically related to the study. Note: Disease, signs symptoms, and or laboratory abnormalities already existing at randomization are not considered adverse events unless they represent an intensity or frequency exacerbation. An adverse event designation should reflect the reason for a diagnosis or abnormal measurement. ~~Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Surgical~~ Procedures planned prior to randomization and the conditions leading to these measures are not adverse events.		adverse events.
7.0 / 33	The DCRI will evaluate any safety information that is spontaneously reported in the time frame specified in the protocol. For each subject, adverse events occurring after randomization must be recorded on the applicable Adverse Events page(s) in the electronic Case Report Form (eCRF). Recording should be done in a concise manner using standard, acceptable medical terms. The adverse event recorded should	The DCRI will evaluate any safety information that is spontaneously reported in the time frame specified in the protocol. For each subject, adverse events occurring after randomization must be recorded on the applicable Adverse Events page(s) in the electronic Case Report Form (eCRF). Recording should be done in a concise manner using standard, acceptable medical terms. The adverse event	No revision from 3.4	The text had been updated to provide additional guidance and clarifications to the investigators for the assessment and reporting of adverse events.

	not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events.	recorded should not be a procedure or a clinical measurement (i.e., a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. It is the responsibility of the Principal Investigator to oversee the safety of the **patients enrolled in the** study at his/her site. **The responsibility for safety oversight includes careful assessment and appropriate reporting of adverse events. The primary mechanism for reporting adverse events in CABANA is for study personnel at the clinical sites to enter the relevant information and the details and description of each event using the adverse event forms that are part of the InForm electronic data capture (EDC) system being used in the trial.**		
7.1.1 / 33	An anticipated event is one that has been previously identified in previous studies, published literature, or product labeling to be related to the disease state or therapies. A listing of 'Anticipated' events can be found in Appendix A. An unanticipated adverse event is any occurring that has not been previously reported (see	An anticipated event is one that has been previously identified in previous studies, published literature, or product labeling to be related to the disease state or therapies. A listing of '**anticipated/expected'** events can be found in Appendix A. An unanticipated**/unexpected** adverse event is any occurring that has not been reported **in**	No revision from 3.4	The text had been updated to provide additional guidance and clarifications to the investigators for the assessment and reporting of adverse events.

	appendix A).	**previous studies, published literature, or product labeling** (see appendix A).		
7.1.2 / 33	c. 23 hour hospitalizations.	c. 23 hour hospitalizations **(observation)**.	No revision from 3.4	
7.1.3 / 34	1. **Mild**: Any event that results in minimal transient impairment of a body function and does not threaten damage to a body structure, and/or does not require intervention other than monitoring.	1. **Mild**: Any event that results in minimal transient impairment of a body function and does not threaten damage to a body structure, and/or does not require intervention other than monitoring **(easily tolerated).**	No revision from 3.4	The text had been updated to provide additional clarifications to the investigators for the assessment of adverse events.
7.1.4 / 34	1. **Definitely related**: reasonable temporal relationship to study therapy or device a. follows a known response pattern (e.g., study drug, treatment or device is known to cause this AE) b. there is no alternative etiology or explanation for the event 2. **Probably related**: reasonable temporal relationship a. follows a suspected response pattern b. no evidence for a more likely alternative etiology though could be unrelated 3. **Possibly related:** reasonable temporal relationship a. equivocal evidence that the event is study related as opposed to an	**The International Council of Harmonization (ICH) Guidelines (1995) indicate that "reasonable causal relationship" means that "there are facts [evidence] or arguments to suggest a causal relationship." The causality assessment must be made by the investigator based on information available at the time that the adverse event eCRF is completed. The initial causality assessment may be revised as new information becomes available.** 1. **Definitely related**: **there is a** reasonable temporal relationship to study therapy or device a. follows a known response pattern (e.g., study drug, treatment or device is known to	No revision from 3.4	Change implemented to increase the clarity of the text.

	alternative etiology 4. **Probably not related:** does not have a reasonable temporal relationship OR a. good evidence for a more likely alternative etiology 5. **Not related:** does not have a temporal relationship OR a. clear and compelling evidence that the event is due to an alternative etiology b. ICH guidelines (1995) clarify "reasonable causal relationship" to mean that "there are facts [evidence] or arguments to suggest a causal relationship." The causality assessment must be made by the investigator based on information available at the time that the adverse event eCRF is completed. The initial causality assessment may be revised as new information becomes available. All adverse events, serious and non-serious, that occur between the time of randomization and the last study-related procedure/visit will be followed until resolution, stabilization, or until the last subject enrolled	cause this AE) b. there is no alternative etiology or explanation for the event 2. **Probably related**: **there is a** reasonable temporal relationship **which** a. follows a suspected response pattern b. no evidence for a more likely alternative etiology though could be unrelated 3. **Possibly related: there is a** reasonable temporal relationship **but** a. equivocal evidence that the event is study related as opposed to an alternative etiology 4. **Probably not related: there is** not a reasonable temporal relationship OR a. good evidence for a more likely alternative etiology 5. **Not related: there is** not ~~have~~ a temporal relationship OR a. clear and compelling evidence that the event is due to an alternative etiology ~~b. ICH guidelines (1995) clarify "reasonable causal relationship" to mean that "there are facts [evidence] or arguments to suggest a~~		

	completes the follow-up phase of the trial. Adverse events for subjects who discontinue study participation at any time during the study should be collected/reported through at least the time of discontinuation. In addition, required Institutional reporting structure will be followed and/or as described in this protocol.	~~causal relationship." The causality assessment must be made by the investigator based on information available at the time that the adverse event eCRF is completed. The initial causality assessment may be revised as new information becomes available.~~		
7.2 / 35	All adverse events, serious and non-serious, that occur between the time of randomization and the last study-related procedure/visit will be followed until resolution, stabilization, or until the last subject enrolled completes the follow-up phase of the trial. Adverse events for subjects who discontinue study participation at any time during the study should be collected/reported through at least the time of discontinuation. In addition, required Institutional reporting structure will be followed and/or as described in this protocol.	The goal is to have an adverse event reporting process that is (a) clear and simple for site investigators and study coordinators to understand and implement, (b) satisfies all regulatory reporting requirements, (c) eliminates any duplication in data collection and reporting, and (d) has a balanced focus on both the drug and ablation arms of the trial. All related adverse events, serious and non-serious, that occur between the time of randomization and the last study-related procedure/visit will be followed until resolution, stabilization, or ~~until the last subject enrolled completes the follow-up phase of the~~ to trial completion. Adverse events for subjects who discontinue study participation at any time during	No revision from 3.4	The text had been updated to provide additional guidance and clarifications to the investigators for the assessment and reporting of adverse events.

		the study should be collected/reported through at least the time of discontinuation. In addition, the required Institutional reporting structure will be followed and/or as described in this protocol.		
7.3 / 35	Regardless of causality, the investigator will record all serious adverse events occurring between randomization and the last study-related procedure/visit or completion of the trial into the electronic database within 24 hours of knowledge of the event. DCRI will report all unanticipated adverse device effects (UADE) to Mayo Clinic and the DSMB chair within 2 business days of receipt.	Regardless of causality, the investigator will record all serious adverse events occurring between randomization and the last study-related procedure/visit or completion of the trial into the electronic database within 24 hours of knowledge of the event. DCRI will report all unanticipated**/unexpected** adverse **events** to Mayo Clinic and the DSMB chair within 2 business days of receipt.	No revision from 3.4	Change implemented to increase the clarity of the text.
7.4 / 35	Specified events as listed below that meet serious criteria (see section 7.1.2 of the protocol) are unanticipated and probably/definitely related, if occurring between randomization through completion of follow-up (end of trial) require ***expedited*** reporting by the DCRI and in turn to the appropriate regulatory agencies.	Specified events as listed below that meet ***serious*** criteria (see section 7.1.2 of the protocol), ***related*** **(**possibly/probably/definitely) to either study drug or the ablation device or procedure, and are ***unanticipated/unexpected*** if occurring between randomization through completion of follow-up (end of trial) require ***expedited*** reporting **to** the DCRI and in turn to the appropriate regulatory agencies.	No revision from 3.4	The text had been updated to provide additional guidance to the investigators for the assessment of adverse events.
7.4.1 / 35	1. Unanticipated ablation procedure related events	**1. Unexpected, SAE related to study drug**	No revision from 3.4	The text had been updated to clarify

	2. Unanticipated Adverse Device Effect events (UADEs) 3. Device Failures or Malfunctions 4. **Events of Interest (EOI)**: Ablation therapy or Procedure related events (index and/or follow-up): All events that resulted in death, myocardial perforation with tamponade requiring intervention, esophageal atrial fistula, and/or severe pulmonary vein stenosis that were life threatening or classified as severe in nature.	2. Unanticipated ablation procedure related events 3. Unanticipated Adverse Device Effect (UADEs) 4. Device failures or malfunctions 5. **Events of Interest (EOI)**: Drug or ablation therapy or ablation procedure related events (index and/or follow-up): All events that resulted in death, pro-arrhythmic events, myocardial perforation ~~with~~ / tamponade requiring intervention, esophageal atrial fistula, and/or severe pulmonary vein stenosis that were life threatening or classified as severe in nature.		that unexpected adverse events related to study drug also require expedited reporting.
7.5 / 36	Expedited Events must be entered on the appropriate eCRF pages or if the electronic database is unavailable reported on an *Expedited Event Form* and faxed to DCRI Safety Surveillance within 24 hours of knowledge of the event. When available, the event must be entered into the electronic data base. **DCRI Safety Surveillance** Telephone: 1-919-668-8624 Toll Free: 1-866-668-7799 Fax: 1-919-668-7138 Toll Free Fax: 1-866-668-7138 **Safety Surveillance Medical Reviewer** Lynda Szczech, M.D. Telephone: 1-919-668-8918	Expedited Events must be entered on the appropriate eCRF pages or if the electronic database is unavailable for more than 24 hours, the event would be reported on an *Expedited Event Form* and faxed/emailed to DCRI Safety Surveillance within 24 hours of knowledge of the event. When available, the event must be entered into the electronic data base. **Safety Surveillance** hone: 1-919-668-8624 ree: 1-866-668-7799 l: Safetysurveillance@mc.duke.ed 1-919-668-7138	No revision from 3.4	The text had been updated to provide clarifications to the investigators for reporting adverse events to DCRI Safety Surveillance

	Toll Free Fax: 1-866-668-7138			
7.6 / 36	The DCRI Safety Surveillance Medical Monitor will review all SAEs for expectedness.		No revision from 3.4	The text had been removed as the information is also provided in section 7.6.2.
7.6.1 /36	Since the CABANA Trial is not under an Investigational New Drug Application, the principle investigator and/or designee at the site will be required to complete and submit form 3500A for reporting serious adverse events (SAEs) that are drug related and unexpected via the FDA's MedWatch Adverse Event Reporting program, DCRI Safety Surveillance and/or their designee. 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. DCRI Safety Surveillance will be responsible for notifying the NIH. Sites should fax a copy of the completed MedWatch form and a cover sheet documenting the date and time the MedWatch form was submitted.	**Physician Reporting of Drug or Device Adverse Events** **Physician reporting of drug or device-related unexpected/unanticipated serious adverse events (as mandated by regulatory authorities) using MedWatch or Council for International Organizations of Medical Sciences (CIOMS) forms, should continue independently of any CABANA reporting.** **It is anticipated that physicians and/or the appropriate healthcare professional will complete this reporting by, 1) MedWatch- submit form 3500 for drug or device via the FDA's MedWatch Adverse Event Reporting program online at www.fda.gov/MedWatch/report.htm, by phone 1-00-FDA-1088, or by returning the postage-paid FDA form 3500 downloaded from ww.fda.gov/MedWatch/getforms.htm by mail to MedWatch, 5600 Fishers Lane, Rockville,**	No revision from 3.4	The text had been updated to provide additional guidance and clarifications to the investigators for reporting of adverse events.

	All Events of Interest: (as identified above) will require expedited reporting to the NIH by the DCRI Safety Surveillance within 5 business days of initial notification.	**MD 20852-9787 or fax 1-800-FDA-0178, 2) CIOMS- using http://www.cioms.ch/index.htm, postal address: c/- World Health Organization, Avenue Appia, 20 CH - 1211 Geneve, 27 Switzerland, telephone: +41 (0) 22 791 34 13 or fax: +41 (0) 22 791 42 86.**		
7.6.2 / 36	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 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. MedWatch surveillance will remain the responsibility of the site using the same approach as noted above.	**CABANA Reporting of Drug or Device Adverse Events For CABANA trial purposes, adverse events will be reported through the eCRF submission process designed to facilitate notification to DCRI Safety Surveillance and/or their designee.** The DCRI Safety Surveillance Medical Monitor **(a physician trained and experienced in safety reporting)** will review all SAEs for **expectedness. potential expected/unexpected; anticipated/unanticipated status.** The decision regarding ultimate classification will be made by individuals within CABANA Leadership with expertise in antiarrhythmia and ablation therapies and clinical trial experience. **All Events of Interest**: (as identified above) will require expedited reporting to the NIH by the DCRI Safety Surveillance within 5 business	No revision from 3.4	The text had been updated to clarify the process followed by DCRI Safety Surveillance for the assessment of adverse events.

		days of initial notification.		
7.6.3 / 36	The CABANA exclusion criteria specifically excludes women of childbearing potential unless post-menopausal or surgically sterile. If a pregnancy does occur during the follow-up period, please notify the DCRI Safety Surveillance at 919-668-8624. Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs if they occur during the study follow-up period according to the protocol.	~~The CABANA exclusion criteria specifically excludes women of childbearing potential unless post-menopausal or surgically sterile. If a pregnancy does occur during the follow-up period, please notify the DCRI Safety Surveillance at 919-668-8624. Pregnancies are not considered adverse events.~~	No revision from 3.4	The section about women of childbearing potential was removed, as it is not applicable for this study.
8.1 / 37	Another important factor that must be considered in these calculations is the extent to which patients randomized to the drug arm may **cross over** to receive an ablation during the course of their follow-up (because the AF and its symptoms are not adequately controlled by drugs).	Another important factor that must be considered in these calculations is the extent to which patients randomized to the drug arm may **cross over** to receive an ablation during the course of their follow-up (~~because~~if the AF and its symptoms are not adequately controlled by drugs).	No revision from 3.4	Editorial changes to increase the clarity of the text.
8.2.1 / 39	The log-rank test will be the primary analytic tool for comparing mortality differences between the two therapies. Kaplan-Meier estimates of cumulative mortality rates as a function of follow-up time will be calculated and displayed.	The log-rank test will be the primary analytic tool for comparing mortality differences between the two therapies. Kaplan-Meier estimates of cumulative mortality rates as a function of follow-up time will be calculated and displayed.	No revision from 3.4	Editorial changes to increase the clarity of the text.

	Relative risks will be expressed as hazard ratios with 95% confidence intervals using the Cox proportional hazards model	Relative risks will be expressed as hazard ratios with 95% confidence intervals generated using the Cox proportional hazards model		
11.1 / 45	During monitoring visits, the Monitor will perform a one hundred percent (100%) review of all Inclusion/Exclusion criteria, informed consent, HIPAA Authorization, all events meeting criteria for expedited event reporting as well as safety and efficacy endpoints. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Key variables (demographics, inclusion/exclusion criteria, and safety) on the eCRFs) will be compared with each subject's source documents. Any discrepancies will be noted and resolved.	During monitoring visits, the Monitor will perform a **ten** percent (10%) review of all Inclusion/Exclusion criteria **of the randomized subjects since last periodic monitoring visit. Review of 100% of the** informed consent **forms**, HIPAA Authorization, all events meeting criteria for expedited event reporting as well as **10% of SAE's and** Events of Interest **EOI will be performed**. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Key variables (demographics, inclusion/exclusion criteria, and safety) on the eCRFs) will be compared with each subject's source documents. Any discrepancies will be noted and resolved.	No revision from 3.4	The text had been updated to clarify the expectations during site monitoring visits
13.0 / 47	6. Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).	6. Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study drug or device, outcome and treatment for adverse event).	No revision from 3.4	Editorial changes to increase the clarity of the text.
14.0 / 48	Investigators will maintain	No revisions for 3.3	Investigators will maintain	Editorial changes to

	documentation of the dates and reasons for each deviation from the protocol, in compliance with Code of Federal Regulations (CFR) 812.140.		documentation of the dates and reasons for each deviation from the protocol, in compliance with the ICH-GCP guidelines, Code of Federal Regulations (CFR) 812.140 and national legislation.	reflect the accurate legislation locally for all sites within all their countries respectively
16.0 / 49	Upon completion of the study (defined by all subjects have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved, DCRI and/or their designee will notify the site of closeout and a study closeout visit will be performed. The DCRI monitor and/or their designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous correspondences have been resolved. Other issues to be reviewed at the closeout visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.	No revisions for 3.3	The end of trial is defined as the day of the last visit of the last subject in the trial. For clinical trial sites located in the EU, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC. For sites located in countries outside the EU, local regulations will be followed. Upon completion of the study ~~(defined by all subjects have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved,)~~ DCRI and/or their designee will notify the site of closeout and a study closeout visit will be performed. The DCRI monitor and/or their designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous correspondences have been resolved. Other issues to be reviewed at the	Editorial changes defining the end of the trial. Language inserted for regulatory compliance

			closeout visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.	
18.0 / 50	The principal investigator or IRB-documented members of the research team will approach the patient to obtain written informed consent. The underlying rationale for the study, the procedures to be followed, the potential benefits, risks, alternatives, and other issues mandated by the consent process will be fully disclosed. Written informed consent will be documented on an informed consent form (ICF) approved by the same IRB responsible for approval of this protocol, The ICF will conform to FDA regulations in 21 CFR Part 50, and to the institutional requirements for informed consent and applicable regulations. The investigator agrees to obtain approval from DCRI and/or their designee of any ICF intended for use in the study, prior to submission for IRB approval.	No revisions for 3.3	The principal investigator or IRB-documented members of the research team will approach the patient to obtain written informed consent on an informed consent form (ICF) approved by the same IRB/EC responsible for approval of this protocol. The informed consent document will conform to FDA regulations in 21 CFR Part 50, and/or to the national requirements for informed consent. It must include all elements required by law, local regulations, GCP and International Conference on Harmonization guidelines and study specific procedures. The underlying rationale for the study, the procedures to be followed, the potential benefits, risks, alternatives, and other issues mandated by the consent process will be fully disclosed. If new information become available during the course of the trial that may be relevant to the subject's consent, the Informed Consent Form will be revised and the revised version will be	Language revised/ inserted for regulatory compliance

			submitted for EC/IRB approval before use. ~~Written informed consent will be documented on an informed consent form (ICF) approved by the same IRB responsible for approval of this protocol. The ICF will conform to FDA regulations in 21 CFR Part 50, and to the institutional requirements for informed consent and applicable regulations.~~	
19.0 / 50	Subject information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Assurance Portability and Accountability Act and as mandated in Title 45 CFR, Parts 160 and 164. All records will be kept confidential and the subject's name will not be released by study staff at any time. Subject records will not be released to anyone other than DCRI and/or their designee, and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected.	No revisions for 3.3	Subject information collected in this study ~~will comply with the standards for protection of privacy of individually identifiable jhealth information as promulgated in the Health Assurance Portability and Accountability Act and as mandated in Title 45 CFR, Parts 160 and 164~~ and all records will be kept confidential and the subject's name will not be released by study staff at any time. ~~Subject records will not be released to anyone other than DCRI and/or their designee, and responsible regulatory authorities.~~ The subject must be informed that his/her personal trial-related data will be used by the sponsor in accordance with the local data	Language revised/ inserted for accuracy and regulatory compliance

			protection legislation. The subject will also be informed that, when requested, his / her medical records may be examined by authorized monitors (DCRI and/or their designee) or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IRB / IEC members and by domestic and foreign regulatory authorities. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected.	
20.0 / 51	An Authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule [45 CFR § 164.102 *et seq*] will be obtained from every trial subject prior to, or at the time of, enrollment.	No revisions from 3.3	~~A~~ For clinical trial sites located in the US, an Authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule [45 CFR § 164.102 *et seq*] will be obtained from every trial subject prior to, or at the time of, enrollment.	Language revised/ accuracy and regulatory compliance
22.0 / 51	The appropriate IRB/EC must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide DCRI or their designee with documentation that the IRB has approved the study *before* the study may begin.	No revisions from 3.3	This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / EC and competent authority (CA) according to national and international regulations. ~~The appropriate IRB/EC must approve the protocol and informed consent documents, agree to monitor the conduct~~	Language revised/ accuracy and regulatory compliance

	In addition, the investigator must provide the following documentation to DCRI or their designee. 1. IRB annual re-approval of the protocol, per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonization guidelines. 2. IRB approval of revisions to the informed consent documents or any amendments to the protocol. Any revisions to the protocol that may increase subject risk exposure must be approved prior to implementation. Administrative changes (such as a change in address or phone number) must be sent to IRBs/Ethics Committees but do not require their approval. The investigator will provide DCRI or their designee with documentation of all approvals.		~~of the study, and agree to review study progress periodically, at intervals not to exceed 1 year.~~ The investigator will provide DCRI or their designee with the study approval documentation before the study may begin. ~~documentation that the IRB has approved the study *before* the study may begin.~~ The same is applicable for the implementation of changes introduced by amendments. Where applicable~~, In addition~~, the investigator must also provide to DCRI and/or their designee the following ~~documentation to DCRI or their designee.~~ 1. A copy of IRB annual re-approval of the protocol, per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonization guidelines. 2. IRB approval of revisions to the informed consent documents ~~or any amendments to the protocol. Any revisions to the protocol that may increase subject risk exposure must be approved prior to implementation.~~ Administrative changes (such as a change in address or phone number) must be sent to IRBs/Ethics	

			Committees but do not require their approval. ~~The investigator will provide DCRI or their designee with documentation of all approvals.~~ 3. The investigator must submit periodic status reports to their EC as required, as well as notification of completion of the study and a final report where applicable. 4. The investigator will provide DCRI or their designee with documentation of all approvals.	
24.0 / 52		**24.0 Sub-Studies** **24.1 CABANAgene** CABANAgene: a resource that will accumulate DNA samples from CABANA subjects to enable subsequent genotype-phenotype studies. Appendix C, page 62, the CABANAgene protocol, provides the rationale for studies and approaches that are anticipated. The major goal of CABANAgene is to create the resource. Specific projects to use the samples would require approval of the CABANA study group, and phenotypes to be studied would be those collected by and adjudicated by the CABANA	**24.0 Sub-Studies** All activated sites will be given the opportunity to participate or not participate. All proposed sub-studies will be first submitted for review and approval to the respective IRB / EC and competent authority (CA) based on national and international regulations. It is further acknowledged that subjects enrolled in CABANA will have the choice to participate or to not participate in sub-studies.	Language added for clarity that all Sub-Studies are optional for activated sites and enrolled subjects. CABANA is comparing two major approaches for management of atrial fibrillation (AF): drugs to maintain sinus rhythm and ablation. As in all other large clinical trials, responses to therapy will be variable in both treatment arms. Abundant evidence

		study group. The CABANAgene project is included in the Pharmacogenetics Research Network (PGRN) arrhythmia site renewal. Participation under the PGRN umbrella also provides access to advanced genotyping and genetic statistical methods to investigators accessing the CABANAgene resource. Examples of issues that CABANAgene could address include: 1) predictors of response to antiarrhythmic or rate control drug therapies; 2) predictors of response to warfarin therapy; 3) predictors of response to ablation therapy and; 4) clinical and genetic approaches to defining AF subtypes.		points to genetic factors as a contributor to such variability in important human phenotypes such as response to treatment, and the goal of CABANAgene is the creation of a large resource linking to test hypotheses that relate genetic variation to disease susceptibility and treatment responses. Collecting DNA from patients in CABANA will address questions such as which patients are most likely to respond to ablation or drug therapy and which patients are most likely to develop complications with ablation or drug therapy.
Appendix A / 60	Deleted (see below)	Added (see below)		The list of Anticipated Events has been updated according to the most recent clinical data.

Appendix C / 62		Sub study CABANAgene (see protocol V3.4, Appendix C)		Same as above in 24.0

~~Appendix A~~ DELETED

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

Medical Therapy events

1. Bradycardia
2. Heart Block
3. Bundle Branch block
4. Intraventricular conduction delay
5. Hypotension
6. Dizziness / light headedness
7. Syncope
8. Shortness of breath
9. Fatigue
10. Wheezing
11. Asthma exacerbation
12. Nausea/vomiting
13. Depression
14. Impotence
15. Peripheral edema
16. Heart failure
17. Skin rashes
18. Diarrhea
19. Constipation
20. Poor appetite
21. Alteration of color vision
22. Blurred / double vision
23. Deteriorating vision
24. Blindness
25. Unusual metallic taste or changes in taste
26. Hyperthyroidism
27. Hypothyroidism
28. Abnormal liver functions
29. Photosensitivity
30. Bluish / gray skin tone
31. Unsteady gait / imbalance
32. Lung toxicity/interstitial inflammation
33. Drug related nonsustained VT
34. Sustained VT
35. Prolonged QT/Torsade des pointes
36. Proarrhythmia; new or worsened
37. Ventricular fibrillation
38. Ventricular tachycardia
39. Stroke / thromboembolic event
40. Renal failure
41. Seizure
42. Allergic reaction or anaphylaxis

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

Ablation Therapy or procedure related events:

1. Related to catheter insertion:
    a. Infection
    b. Sepsis
    c. Bleeding
    d. Bruising / ecchymosis
    e. Pain
    f. Hematoma (not requiring blood transfusion)
    g. Pseudoaneurysm
    h. A-V fistula
    i. Vessel trauma
    j. DVT
    k. Urinary tract infection
2. Pulmonary embolism
3. Pneumothorax
4. Hemothorax
5. Pleural effusion
6. Pneumonia

DELETED

1. Related to medications: as listed under Medical therapy with the following additions:
    a. Allergic reaction (skin rash, SOB)
    b. Hypotension
    c. Kidney damage
    d. Respiratory depression
    e. Left ventricular dysfunction
    f. Headache / nausea
    g. Bleeding from heparin
    h. Visual migraine
    i. Complete AV block
    j. Transient AV block
    k. Permanent AV block
    l. Volume overload
2. Related to catheter manipulation:
    a. Myocardial perforation
    b. Pericardial effusion
    c. Tamponade
    d. Myocardial infarction
    e. Other ischemic event
    f. Coronary artery spasm
    g. Coronary artery occlusion
    h. Coronary artery dissection
    i. Stroke
    j. TIA
    k. Peripheral thromboembolic event
    l. Cardiac thromboembolic event
    m. Air embolism
    n. Heart valve damage
    o. Clinically relevant sinus node block
    p. Clinically relevant AV node dysfunction
    q. Damage to Pacemaker or pacemaker leads
3. Related to ablation:
    a. Chest pain during energy delivery
    b. Pericarditis
    c. Radiation skin burn
    d. Radiation related cancers
    e. Phrenic nerve damage
    f. Pulmonary vein stenosis
    g. Pulmonary vein damage/dissection
    h. Pulmonary vein thrombus
    i. Pulmonary edema
    j. Pulmonary hypertension
    k. Esophageal atrial fistula
    l. New or worsened Gastroesophageal reflux
    m. Pleuritic chest pain
    n. Elevated creatinine phosphokinase (CPK)
    o. Temperature elevation
    p. Vasovagal reaction
    q. Esophagus or stomach erosion disorder, esophageal achalasia, esophageal ulcers, or stomach emptying disorder

Appendix A Adverse Events

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

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

Appendix A Adverse Events (continued)

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

CATEGORY	ANTICIPATED EVENT	
PULMONARY		
	76 Asthma exacerbation	84 Pulmonary hypertension
	77 Hemothorax	85 Pulmonary vein damage/dissection
	78 Lung toxicity	86 Pulmonary vein stenosis
	79 Pleural effusion	87 Pulmonary vein thrombus
	80 Pneumonia	88 Respiratory depression
	81 Pneumothorax	89 Shortness of breath/dyspnea
	82 Pulmonary edema	90 Wheezing
	83 Pulmonary embolism	91 Pleuritic chest pain
PERIPHERAL VASCULAR		
	92 A-V fistula	98 Peripheral edema
	93 Bleeding	99 Peripheral thromboembolic event
	94 Bleeding from heparin	100 Pseudoaneurysm
	95 Bruising / ecchymosis	101 Thromboembolic event
	96 DVT	102 Vessel trauma
	97 Hematoma	

Summary of Changes in the Protocol

The following changes listed in Table 1 represent clarification, version control, and corrective changes to the CABANA Protocol, Version 3.5, (22 November, 2013). These changes are approved by the CABANA Leadership Team, Mayo Clinic and Duke Clinical Research Institute (DCRI).

Table 1. Summary of Protocol Changes

Section/Page	Version 3.4.1 08 April, 2012	Version 3.5 22 November, 2013	Rationale
Title Page	Version: 3.4.1	Version: 3.5	
Title Page	Date: 08 April, 2012	Date:22 November, 2013	
Footer Throughout	08 April, 2012	22 November, 2013	
Contact	**Project Officer:** Alice M. Mascette, MD Phone:301-435-0477 Fax: 301-480-7971 alice.mascette@nih.gov	**Project Officer:** Yves D. Rosenberg, MD, MPH Phone: 301-435-1292 Fax: 301-480-3667 rosenbey@nih.gov	Personnel Change
Synopsis DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Subjects who have new onset or under-treated paroxysmal, persistent, or longstanding persistent AF who warrant therapy for their arrhythmia, with (1) documented atrial fibrillation (AF) ≥1 hour in duration, (2) ≥2 episodes over the preceding ***6*** months with ***electrocardiographic documentation*** of at least 1 episode; or 1 persistent or longstanding persistent episode of AF lasting more than 1 week, (3) are eligible for catheter ablation, (4) are eligible for ≥2 sequential rhythm control and/or ≥3 rate control drugs, and (5) are ≥65 yrs of age, or <65 yrs with **one or more** of the following risk factors for stroke: (Hypertension, Diabetes, Congestive heart failure, Prior stroke or TIA, LA size >5.0 cm or volume index ≥40 cc/m2, or EF ≤35). See main protocol for complete inclusion/exclusion criteria.	Subjects who have new onset or under-treated paroxysmal, persistent, or longstanding persistent AF who **warrant therapy** for their arrhythmia, that (1) Over the preceding **6** months have: a) ≥2 paroxysmal episodes (***electrocardiographic documentation*** of at least 1 episode) lasting ≥1 hour in duration: (that terminate spontaneously within 7 days or cardioversion is performed within 48h of AF onset) b) ***electrocardiographic documentation*** of 1 persistent AF episode: (sustained for ≥7 days or cardioversion is performed more than 48h after AF onset) c) ***electrocardiographic documentation*** of 1 longstanding persistent AF episode: (continuous AF of duration >1 year). (2) are eligible for catheter ablation, (3) are eligible for ≥2 membrane active drugs and/or ≥2 rate control drugs, and (4) are ≥65 yrs of age or <65 yrs with one or more risk factors for stroke	Clarification of entry criteria and required documentation for each of the 3 AF types. To improve enrollment, the DSMB suggested the

		(hypertension, diabetes, heart failure, prior stroke or TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), or left atrial diameter ≥ 5.0 cm or left atrial volume ≥ 40 cc/m^2). Eligible subjects with persistent or long-standing persistent AF will require at least 1 documented episode. See main protocol for complete inclusion/exclusion criteria.	addition of CHADS-VASc criteria and decrease rate control drugs to ≥2.
STUDY HYPOTHESIS	The treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality (primary endpoint) and decreasing the composite endpoint of total mortality, disabling stroke, serious bleeding, and cardiac arrest (secondary endpoint) in subjects with untreated or incompletely treated AF warranting therapy.	The treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing a) the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (primary endpoint; previously the key secondary endpoint) and decreasing total mortality (secondary endpoint; previously the primary endpoint) in subjects with untreated or incompletely treated AF warranting therapy.	Due to a lower than expected aggregated mortality rate, the DSMB suggested: change the primary endpoint of the trial from total mortality to the original key secondary endpoint consisting of the composite of death, disabling stroke, serious bleeding, or cardiac arrest
DURATION OF STUDY PARTICIPATION	Enrollment will occur over approximately 4 years, and subjects will be followed a minimum of 2 years.	Enrollment will occur over approximately 4 years, and subjects will be followed for an average of approximately 5 years.	Due to the accrual of patients at a slower rate than projected DSMB suggested: decreasing the sample size and extend the follow-up
NUMBER OF SUBJECTS	3000 with a 1:1 randomization ratio	2000-2200 with a 1:1 randomization ratio	
NUMBER OF SITES	Total number: 140 North American Sites: 100 Non-North American Sites: 40	Total number: approximately 180 North American Sites: approximately 120 Non-North American Sites: approximately 60	Possible number and distribution of sites needed to complete the Trial
PRIMARY ENDPOINT	Total mortality	Composite of: 1) total mortality, 2) disabling stroke, 3) serious bleeding, or 4) cardiac arrest.	DSMB suggested: Primary secondary a composite
SECONDARY	Cardiovascular death, Cardiovascular	Total mortality,	DSMB suggested:

OUTCOMES	death or disabling stroke, Arrhythmic death or cardiac arrest, Heart failure death, Freedom from recurrent AF, Cardiovascular hospitalization, Medical costs and resource use and cost effectiveness, Quality of life, Composite adverse events, LA size, morphology and function.	Total mortality or cardiovascular hospitalization, Total mortality or stroke or cardiovascular hospitalization, Cardiovascular death, Cardiovascular death or disabling stroke, Arrhythmic death or cardiac arrest, Heart failure death, Freedom from recurrent AF, Cardiovascular hospitalization, Medical costs and resource use and cost effectiveness, Quality of life, Composite adverse events, LA size, morphology and function.	Secondary endpoint revised
TOC /8		Updated to version 3.5	
1.0 /12 Introduction	An ablation trial evaluating overall mortality, conducted within a population at increased risk, will provide the most compelling evidence for guiding the therapy of this malady. The completion of the 60 patient CABANA Pilot Study provides solid evidence of the feasibility of this landmark study. The primary aim of the CABANA Trial is to test the hypothesis that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing total mortality	An ablation trial evaluating overall mortality and major AF related events, conducted within a population at increased risk, will provide the most compelling evidence for guiding the therapy of this malady. The completion of the 60 patient CABANA Pilot Study provides solid evidence of the feasibility of this landmark study. The primary aim of the CABANA Trial is to test the hypothesis that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art therapy with either rate control or rhythm control drugs for reducing: 1) total mortality, disabling stroke, serious bleeding, or cardiac arrest as the primary endpoint and 2) total mortality as the secondary endpoint in patients with untreated or incompletely treated AF.	DSMB suggested revisions to the primary and secondary outcomes
1.1.2 /13 Progression of AF	There is also reason to anticipate an increasing impact of this arrhythmia on mortality.	There is also reason to anticipate an increasing impact of this arrhythmia on mortality, stroke, bleeding and cardiac arrest.	DSMB suggested revisions
1.4 /17	These studies taken together, along with	These studies taken together, along with	DSMB suggested

Rationale for Maintaining Sinus Rhythm	data from population-based studies, provide the rationale for a large, multi-center trial to prospectively examine the impact of sinus rhythm on overall mortality in patients with AF.	data from population-based studies, provide the rationale for a large, multi-center trial to prospectively examine the impact of sinus rhythm on total mortality, disabling stroke, serious bleeding and cardiac arrest in patients with AF.	revisions
1.8 /19 Significance of the Trial	Scientifically, the trial will determine whether the attainment of normal sinus rhythm is a mortality advantage.	This study will also assess the role of earlier therapy for AF and the related utility of ablation as first line therapy in patients warranting treatment. Scientifically, the trial will determine whether the attainment of normal sinus rhythm is a mortality and stroke advantage.	DSMB suggested revisions
2.0 /20 Objectives		**Changes to the Protocol from the Original Study Design** Although CABANA was originally mandated to be a mortality trial, a careful assessment of the progress of the trial was undertaken by the study leadership in early 2013. Completely blinded to any treatment-specific outcome data, the two major issues addressed by the leadership group were (1) a lower than expected aggregated mortality rate, and (2) accrual of patients at a slower rate than projected. Careful consideration of these issues led to a decision to (a) change the primary endpoint of the trial from total mortality to the original key secondary endpoint consisting of the composite of death, disabling stroke, serious bleeding, or cardiac arrest, and (b) reduce the sample size to a number that was consistent with the new primary endpoint and more realistically achievable within the funding period of the trial. There may still be a mortality difference between treatment groups. This was not revealed in the interim review. These changes will be highlighted in the sections of the protocol that follow.	Clarity and overview of the protocol revisions

2.1 /20 Primary Objective and Hypothesis	The primary hypothesis of the CABANA trial is that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art medical therapy with either rate control or rhythm control drugs for reducing total mortality (primary endpoint) and decreasing the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (key secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy. It is anticipated that treatment with percutaneous left atrial catheter ablation will reduce mortality ≥30% compared to drug therapy. All endpoints will be carefully assessed and analyzed on an intention to treat basis.	The primary hypothesis of the CABANA trial is that the treatment strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) is superior to current state-of-the-art medical therapy with either rate control or rhythm control drugs for decreasing the incidence of the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest (primary endpoint) and reducing total mortality (secondary endpoint) in patients with untreated or incompletely treated AF warranting therapy. It is anticipated that treatment with percutaneous left atrial catheter ablation will reduce the incidence of this endpoint by ≥30% compared to drug therapy. To properly interpret this composite endpoint, the incidence of each of the individual components will also be descriptively examined to assess its relative contribution to the overall composite outcome. The primary endpoint and all secondary endpoints will be carefully assessed and analyzed on an intention to treat basis.	DSMB suggested revisions to the primary outcomes
2.2 /20 Secondary Endpoints/Objectives	1. Total mortality, disabling stroke, serious bleeding, or cardiac arrest 2. Total mortality or cardiovascular hospitalization	1. Total mortality 2. Total mortality or cardiovascular hospitalization 3. Total mortality, stroke, or CV hospitalization (for heart failure or acute ischemic events)	DSMB suggested revisions to the secondary outcomes
2.2.1 /21 ~~Composite Morbidity~~ / Total Mortality	This trial will determine whether catheter ablation for the elimination of AF has an impact on the composite end point of total mortality, disabling stroke, serious bleeding, or cardiac arrest, when compared to drug therapy. This is the key secondary endpoint. The hypothesis regarding this endpoint is that catheter ablation for AF will result in a significant	Because of the vital importance of assessing the impact of left atrial catheter ablation on total mortality, this endpoint (which is a component of the primary endpoint) will be a specific secondary endpoint in the trial. *Hypothesis:* Catheter ablation for AF will reduce total mortality by ≥30% compared to state-of-the-art pharmacologic therapy.	DSMB suggested revisions to the secondary outcomes

	(>25%) reduction in the incidence of this composite endpoint. To detect the relative contribution of these component events, the incidence of each individual component will also be descriptively examined to aid in the interpretation of the composite outcome. Because of a mechanistic concordance of events, arrhythmic death and cardiac arrest will be considered together as a composite secondary endpoint. Cardiovascular death and disabling stroke will be similarly grouped.		
2.2.2 /21 Composite Mortality / Cardiovascular Hospitalization	By reducing the recurrence of AF, the proposed therapies should also reduce cardiovascular hospitalization. Additional secondary endpoints, including cardiovascular hospitalization and the composite of total mortality and cardiovascular hospitalization, will therefore be examined. *Hypothesis*: Catheter ablation for AF will be significantly (>=25%) more effective than pharmacologic therapy, in reducing cardiovascular hospitalization and the composite of total mortality or cardiovascular hospitalization.	By reducing the recurrence of AF, the proposed therapies should also reduce cardiovascular hospitalization. Additional secondary endpoints, including cardiovascular hospitalization and the composite of total mortality and cardiovascular hospitalization, will therefore be examined. The composite of total mortality, stroke or cardiovascular hospitalization will also be assessed. *Hypothesis*: Catheter ablation for AF will be significantly (≥25%) more effective than pharmacologic therapy, in reducing cardiovascular hospitalization, the composite of total mortality or cardiovascular hospitalization, and the composite of total mortality, stroke or cardiovascular hospitalization.	DSMB suggested revisions to the secondary outcomes
2.2.4 /21 Freedom from Recurrent Atrial Fibrillation	Time to second AF recurrence and AF burden will also be established.	Time to second AF recurrence and AF burden will also be established. Freedom from AF after each ablation performed in an individual subject will be separately tracked.	Clarification as it relates to the tracking of recurrent AF for ablation therapy
3.1 /22 Inclusion Criteria	1. Have paroxysmal AF episodes ≥1 hour in duration; with ≥2 episodes over the preceding 6 months with ***electrocardiographic documentation***	1. Over the preceding **6** months have a) paroxysmal AF episodes (that terminate spontaneously within 7 days or cardioversion is performed within 48h of	Clarification of entry criteria and required documentation for each of the 3 AF types.

	of at least 1 episode; or 1 persistent or longstanding persistent episode of AF lasting more than 1 week. 2. Warrant active therapy beyond simple ongoing observation 3. Be eligible for catheter ablation and ≥2 sequential rhythm control and/or ≥3 rate control drugs. 4. Prior stroke, TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size >50 NOTE: providing they remain realistically eligible for ≥2 membrane active drugs and/or ≥3 rate control agents.	AF onset): that is ≥1 hour in duration with ≥2 episodes with ***electrocardiographic documentation*** of at least 1 episode; or b)***electrocardiographic documentation*** of 1 persistent AF episode: (sustained for ≥7 days or cardioversion is performed more than 48h after AF onset) or c) ***electrocardiographic documentation*** of 1 longstanding persistent AF episode: (continuous AF of duration >1 year). 2.Warrant active therapy (within the past 3 months) beyond simple ongoing observation 3. Be eligible for catheter ablation and ≥2 sequential rhythm control and/or ≥2 rate control drugs. 4. Prior stroke, TIA or systemic emboli, Atherosclerotic vascular disease (previous MI, peripheral arterial disease or aortic plaque), LA size >50 NOTE: providing they remain realistically eligible for ≥2 membrane active drugs and/or ≥2 rate control agents. Patients receiving new drug therapy initiated within the previous 3 months may continue that therapy if randomized to the drug therapy arm.	To improve enrollment, the DSMB suggested the addition of CHADS-VASc criteria and decrease rate control drugs to ≥2. Protocol clarification
3.2 /23 Exclusion Criteria	4. More than one week of amiodarone treatment in the past 3 months 5. An efficacy failure of full dose amiodarone treatment ≥12 weeks duration at any time. NOTE: Prior ablation of the cavo-tricuspid isthmus alone is not an exclusion if the patient develops subsequent recurrent AF. Planned atrial flutter ablation in combination with the left atrial ablation is not an exclusion.	4. REMOVED 4. An efficacy failure of full dose amiodarone treatment ≥8 weeks duration at any time. NOTE: Exclusion Criterion #3 includes failed membrane active antiarrhythmic drugs started within 3 months prior to enrollment. Prior ablation of the cavo-tricuspid isthmus alone is not an exclusion if the patient develops subsequent recurrent AF. Planned atrial flutter ablation in combination with the left atrial ablation is not an exclusion	To enhance enrollment Protocol clarification
4.1 /23 Trial Design and	This multi-center study will randomize 3000 patients in a 1:1 fashion to a	This multi-center study will randomize 2000-2200 patients in a 1:1 fashion to a	DSMB suggested to decrease the sample

Time Line	strategy of catheter ablation vs. state-of-the-art drug therapy for either rate or rhythm control, as outlined in Figure 2. Each will have untreated or incompletely treated AF, which in the opinion of the investigator warrants therapy. CABANA enrollment will occur over approximately 3 years, beginning in the 3rd quarter of 2009. All CABANA patients will be followed a minimum of 2 years. Assuming criteria for early termination are not reached, the major trial results are expected to be reported in 2015.	strategy of catheter ablation vs. state-of-the-art drug therapy with either rate or rhythm control, as outlined in Figure 2. Each patient will have untreated or incompletely treated AF, which in the opinion of the investigator warrants therapy. CABANA enrollment will occur over approximately 4 years. All CABANA patients will be followed an average of approximately 5 years. Assuming criteria for early termination are not reached, the major trial results are expected to be reported in early 2018.	size
4.2 /24 Screening and Pre-Randomization Procedures	The principal investigator or documented members of the research team will discuss the underlying rationale for the study Work Productivity and Activity Impairment Instrument (WPAI), Stanford Presenteeism scale will be collected	The principal investigator or documented members of the research team approved by local Institutional Review Board (IRB) or Ethics Committee (EC) will discuss the underlying rationale for the study, Work Productivity and Activity Impairment Instrument (WPAI), Stanford Presenteeism scale and Mayo AF Symptom Index (MAFSI)) will be collected	Protocol clarification
4.4 /24 Post Randomization Procedures	and patients followed for a minimum of approximately 2 years.	and patients followed for an average of approximately 5 years.	DSMB suggested Extension of the follow-up
4.4.1 /25 Baseline testing	up to 375 patients randomized to drug therapy will be asked to undergo one research CT/MR scan	up to 150 patients randomized to drug therapy will be asked to undergo one research CT/MR scan	Recalculation of numbers to meet objectives
4.4.2 /25 Patient Follow Up	A brief Follow up Questionnaire capturing atrial fibrillation severity and symptoms, work productivity/activity/presenteeism will be collected at 6, 18, 30, and 42 months post randomization. Follow-up visits/calls should be completed within 30 days +/- of the due date asking 5 brief questions and Mayo Atrial Fibrillation Symptom Index (MAFSI) will	REMOVED Follow-up visits/calls at 3 and 6 months should be completed within 30 days +/- of the due date Follow-up visits/calls at 12 months and every 6 months thereafter should be completed within 60 days +/- of the due date (Ex: 12 month visit: completed between 300 days and 420 days of randomization). asking 5 brief questions and Mayo Atrial Fibrillation Symptom Index (MAFSI) will be collected by the Site Coordinator at 3	Extension of the follow-up window to allow more flexibility Reduction in number of surveys/patient to reduce subject burden

	be collected by the Site Coordinator at each follow up visit throughout the trial and entered into the e-CRF. All patients enrolled will receive a single 'CABANA Box' recording system to be used for both patient activated event monitoring (throughout the trial), autodetect/autocapture (AD:AC) event monitoring (one 24 hour period/month) and full disclosure Holter monitoring for 96 hours every 6 months throughout the study. The 375 drug therapy patients	and 12 months following randomization during the first year and yearly thereafter throughout the trial and entered into the e-CRF. After enrollment, subjects will either receive a single 'CABANA Box' recording system to be used throughout the entire study, or will be followed using ambulatory event and Holter ECG monitoring as generated during the course of routine clinical care as dictated by their attending physician. At sites where the 'CABANA Box' has received appropriate approval, all patients enrolled will receive a single 'CABANA Box' recording system to be used for both patient activated event monitoring (throughout the trial), 24 hour autodetect/autocapture (AD:AC) event monitoring *and* 96 hour full disclosure Holter monitoring throughout the study. During year one, subjects will be asked to record their heart rhythm each month. After the first year, they will be asked for a 24 hour recording twice a year and a 96 hour recording twice a year. Follow up monitoring with an alternative system will be required in centers unable to use the "CABANA Box". The 150 drug therapy patients After completion of the 60 month follow-up, subjects will be asked to extend their participation. If agreed upon, subjects will be asked about their current state of health and any clinical events every 6 months by telephone until the last subject enrolled reaches approximately 36 months follow-up.	The Medicomp monitoring system will only be utilized at Institutions or within countries where appropriate approvals have been obtained. Routine monitoring based on clinical care will be recorded within the trial database records. To decrease subject burden, use of the heart monitor (CABANA Box) has been reduced. Recalculation of numbers to meet objectives. Extended follow-up to achieve an approximate trial wide follow-up of an average of 5 years.
4.4.3 /27		Updated Schedule of Assessment	Clarification

5.4 /32 Guidelines for Anti-thrombotic Therapy	(warfarin, dabigatran) These agents may be used as replacement therapy for warfarin on approval of Innovative Antithrombotic Therapies/Executive Committees.	(warfarin, dabigatran, rivaroxiban or apixaban) These agents may be used as replacement therapy for warfarin on approval of local regulatory agencies and the Innovative Antithrombotic Therapies/Executive Committees.	Innovative Drug Therapy committee approved new anticoagulation drugs for use within CABANA
6.1 /33 Primary Endpoints	The primary endpoint event of mortality, will be adjudicated by an independent Clinical Events Committee (CEC) and the most proximate cause of that event established. The CEC will also confirm whether a death is cardiac/vascular/non-cardiovascular in origin; as well as witnessed/un-witnessed; or sudden/non-sudden. Cardiac mortality will be further categorized as tachyarrhythmic, bradyarrhythmic, heart failure, or due to other cardiac causes using the events adjudication form.	The primary endpoint is the composite of total mortality, disabling stroke, serious bleeding or cardiac arrest. All components will be adjudicated by an independent Clinical Events Committee (CEC) and the most proximate cause of the event established. A Disabling Stroke will be considered present using a modification of a Rankin Stroke score [100], and will be adjudicated by a Neurologic Events Committee. Serious (or Life-threatening) bleeding will be considered present using a modification of the GUSTO bleeding Scale adapted for use in catheter ablation [101]. These events will be tracked regardless of treatment randomization. The definition for each of these events is listed in the CEC Charter. When there is disagreement between the CEC and the principal investigator, the CEC's decision will be considered final. Procedures for adjudicating events are described in the CEC Charter, which is available upon request. The CEC will also confirm whether a death is cardiac/vascular/non-cardiovascular in origin; as well as witnessed/un-witnessed; or sudden/non-sudden. Cardiac mortality will be further categorized as tachyarrhythmic, bradyarrhythmic, heart failure, or due to other cardiac causes using the events adjudication form. Hospitalization will also be tracked with specific reason for admission (heart failure, acute ischemic	DSMB suggested revisions to the primary outcomes Placement within protocol changed Placement within protocol changed

		event, etc) determined by the site principal investigator as reported in the eCRF.	
6.2 /34 Secondary Endpoints & Safety Endpoints	Secondary endpoint events, including composite endpoints of total mortality, disabling stroke, serious bleeding, or cardiac arrest will be confirmed and adjudicated in a similar manner by the CEC. A Disabling Stroke will be considered present using a modification of a Rankin Stroke score [100], and will be adjudicated by a Neurologic Events Committee. Serious (or Life-threatening) bleeding will be considered present using a modification of the GUSTO bleeding Scale adapted for use in catheter ablation [101]. These events will be tracked regardless of treatment randomization. The definition for each of these events is listed in the CEC Charter. When there is disagreement between the CEC and the principal investigator, the CEC's decision will be considered final. Procedures for adjudicating events are described in the CEC Charter, which is available upon request. While hospitalization for AF in both treatment arms	Secondary endpoint events, including total mortality and a composite of total mortality or cardiovascular hospitalization will be confirmed. REMOVED While hospitalization for any atrial fibrillation, atrial flutter or atrial tachycardia in both treatment arms	DSMB suggested revisions to the secondary outcomes. Secondary endpoints as listed will be confirmed but not adjudicated by the CEC.
7.1.1 /35 Anticipated Adverse Events	A listing of 'anticipated/expected' events can be found in Appendix A. An unanticipated/unexpected adverse event is any adverse event that has not been reported in previous studies, published literature, or product labeling (see appendix A).	A listing of commonly occurring 'anticipated/expected' events in the population being studied can be found in Appendix A. An unanticipated/ unexpected adverse event is any adverse event that has not been reported in previous studies, published literature, product labeling, or which is not anticipated in the population being studied (see appendix A).	The text had been updated to provide additional guidance and clarifications to the investigators for the assessment and reporting of adverse events.
7.3 /36	DCRI will report all unanticipated/	DCRI will report all unanticipated/	

Serious Adverse Event Reporting	unexpected adverse events to Mayo Clinic and the DSMB chair	unexpected study related serious adverse events to Mayo Clinic, NHLBI and the DSMB chair	
7.4.1 /37 Expedited events include	**Events of Interest (EOI)**: Drug or ablation therapy or ablation procedure related events (index and/or follow-up): All events that resulted in death, pro-arrhythmic events, myocardial perforation / tamponade requiring intervention, esophageal atrial fistula, and/or severe pulmonary vein stenosis that were life threatening or classified as severe in nature.	**Events of Interest (EOI)**: Drug or ablation therapy or ablation procedure related events (index and/or follow-up): The related events that resulted in death, and the following events if they are life-threatening or severe in nature; pro-arrhythmic events, myocardial perforation / tamponade requiring intervention, esophageal atrial fistula, and/or severe pulmonary vein stenosis that were life threatening or classified as severe in nature.	
7.6.2 /38 CABANA Reporting of Drug or Device Adverse Events	For CABANA trial purposes, adverse events will be reported through the eCRF submission process designed to facilitate notification to DCRI Safety Surveillance and/or their designee. The DCRI Safety Surveillance Medical Monitor (a physician trained and experienced in safety reporting) will review all SAEs for potential expected/unexpected; anticipated/unanticipated status. The decision regarding ultimate classification will be made by **individuals within CABANA Leadership** with expertise in antiarrhythmia and ablation therapies and clinical trial experience. DCRI Safety Surveillance will notify the NIH within 1-2 business days of an unexpectedness/unanticipated event DCRI Safety Surveillance will notify the NIH within 5 business days of all reported Events of Interest (as identified above).	For CABANA trial purposes, adverse events will be reported through the eCRF submission process designed to facilitate notification to DCRI Safety Surveillance and/or their designee. DCRI Safety Surveillance will review and code all SAEs. The Safety Surveillance Medical Monitor (a physician trained and experienced in safety reporting) will review Events of Interest, and unexpected/unanticipated SAEs related to ablation therapy or CABANA approved rate or rhythm control drugs. The decision regarding ultimate classification will be made by **individuals within CABANA Leadership** with expertise in antiarrhythmia and ablation therapies and clinical trial experience. DCRI Safety Surveillance will notify the NHLBI and Mayo within 1-2 business days of an unexpectedness/unanticipated event DCRI Safety Surveillance will notify the NHLBI within 5 business days of all reported Events of Interest (as identified above).	The text had been updated to clarify the process followed by DCRI Safety Surveillance for the assessment of adverse events.
8.1 /39	Second, important secondary endpoints	Second, important secondary endpoints	Reporting of new

Sample Size and Power Considerations	were considered, including the key composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest. crossovers of drug-arm patients to receive ablation will have the impact of reducing the mortality rate of patients If we assume that patients who cross over receive a similar reduction in mortality as the benefit hypothesized for patients initially randomized to ablation, the 3.5 year control-arm event rate will	were considered. As described in Section 2.0, the study was originally designed with total mortality as the primary endpoint. However, in early 2013 a careful assessment of the progress of the trial was undertaken by the study leadership. Completely blinded to any treatment-specific outcome data, the two major issues addressed by the leadership group were (1) a lower than expected aggregated mortality rate, and (2) accrual of patients at a rate much slower than projected. Careful consideration of these issues led to a decision to (a) change the primary endpoint of the trial from total mortality to the key secondary endpoint consisting of the composite of death, disabling stroke, serious bleeding, or cardiac arrest, and (b) reduce the sample size to a number that was consistent with the new primary endpoint. The following paragraphs, which outlined the key considerations in determining the original sample size, are also relevant for the revised sample size. the most reliable estimates of mortality and other endpoint events applicable to the drug arm of CABANA With the original secondary endpoint elevated to become the primary endpoint, the incidence of the new primary endpoint is expected to be higher than the mortality rates. crossovers of drug-arm patients to receive ablation will have the impact of reducing the event rate of patients REMOVED	calculations based on revised primary and secondary endpoints

	drop from 15% to approximately 12-13%. The treatment effect will also be reduced. the method of Schoenfeld [104]. To provide an adequate number of patients in the trial that will be relatively robust under various assumptions regarding the control-arm event rates and the magnitude of the treatment benefit, 3,000 patients will be enrolled. This number will provide 90% power for detecting a 30% mortality reduction, allowing for a 2% loss to follow-up. Thus, the study will have high power for detecting an important benefit if the control arm event rate is consistent with or even slightly lower than expected based on previous studies. This number will also provide power > 80% for detecting a 25% reduction in mortality with ablation if the 3.5-year event rate in the drug arm is 13% or higher. Thus we have good power for detecting a more conservative estimate of the mortality benefit if the control arm event rate is consistent with previous studies. A 25-30% mortality reduction will be highly important from a clinical and public health standpoint, given the large population of patients in this country and throughout the world who suffer from AF. Since the event rates for the key composite secondary endpoint will be higher than the primary mortality endpoint, 3000 patients will also provide >90% power for detecting a 25% reduction in the important secondary endpoint consisting of the composite of total mortality, disabling stroke, serious bleeding, or cardiac arrest.	the method of Schoenfeld [104] developed for the proportional hazards model. To provide an adequate number of patients in the trial that will be relatively robust under various assumptions regarding the control-arm event rates and the magnitude of the treatment benefit, 2,000-2,200 patients will be enrolled. With a minimum follow-up of 3 years (amounting to an average follow-up of approximately 5 years), 2200 patients will provide 90% power for detecting a 30% reduction in the new primary endpoint, and 2000 patients will provide 80% power, assuming a 3-year event rate in the drug arm of 12% and allowing for a 2% loss to follow-up. Thus, the study will have high power for detecting an important benefit if the control arm event rate is consistent with the rate expected based on previous studies. A sample size in this range will also provide acceptable power (86% with 2200 patients and 82% with 2000 patients) for detecting a 25% reduction with ablation in the primary endpoint if the 3-year drug arm event rate is 15%. Thus we will have good power for detecting a more conservative estimate of the benefit in the composite endpoint if the control arm event rate is higher, but still consistent with previous studies. A 25-30% reduction in primary events will be highly important from a clinical and public health standpoint, given the large population of patients in this country and throughout the world who suffer from AF.	

		This number of patients (2,000-2,200) will also provide adequate power for detecting a 25% reduction in other important secondary composite endpoints listed in section 2.2 such as the endpoints that involve cardiovascular hospitalization where the incidence is expected to be higher than for the primary endpoint.	
8.2.1 /41 Analysis of the Primary Endpoint	The log-rank test will be the primary analytic tool for comparing mortality differences between the two therapies. Kaplan-Meier estimates of cumulative mortality rates as a function of follow-up time will be calculated and displayed. Relative risks will be expressed as hazard ratios with 95% confidence intervals generated using the Cox proportional hazards model. Supplementary analysis involving covariate adjustment will be performed with the Cox model. Such adjustment will be limited to a relatively small, prospectively defined set of patient characteristics that are known *a priori* to have a strong prognostic relationship with mortality. The covariate-adjusted analysis will serve as a prelude to supplementary analyses examining differential treatment effects. The covariates will include age, sex, race, heart failure class, presence/absence of structural heart disease, whether the patients' AF is paroxysmal, persistent or long-standing persistent, duration of AF, presence/absence of hypertension, and ejection fraction. Cox model analyses may also be performed using appropriate groupings of sites as a stratification factor.	The log-rank test will be the primary analytic tool for comparing outcome differences between the two therapies. Kaplan-Meier estimates of cumulative event rates as a function of follow-up time will be calculated and displayed. Relative risks will be expressed as hazard ratios with 95% confidence intervals generated using the Cox proportional hazards model. Supplementary analysis involving covariate adjustment will be performed with the Cox model. Such adjustment will be limited to a relatively small, prospectively defined set of patient characteristics that are known *a priori* to have a strong prognostic relationship with the primary endpoint. The covariate-adjusted analysis will serve as a prelude to supplementary analyses examining differential treatment effects. The covariates will include age, sex, race, heart failure class, presence/absence of structural heart disease, whether the patients' AF is paroxysmal, persistent or long-standing persistent, duration of AF, presence/absence of hypertension, and ejection fraction. Cox model analyses may also be performed using appropriate groupings of sites as a stratification factor.	Language revised based on change in primary and secondary endpoints.
8.2.2 /41 Analysis of Secondary Endpoints	Secondary endpoints including the important mortality/morbidity composite endpoint consisting of death, disabling	Secondary endpoints, including total mortality and secondary endpoints 2 through 9 listed in Section 2.2, will all	Language revised based on change in primary and secondary endpoints.

	stroke, serious bleeding, or cardiac arrest, and secondary endpoints 2 through 8 listed in Section 2.2 all involve time-to-event analyses and thus will be analyzed similar to the primary endpoint using the log-rank test, Cox model, and Kaplan-Meier event rate estimates	involve time-to-event analyses and thus will be analyzed similar to the primary endpoint using the log-rank test, Cox model, and Kaplan-Meier event-rate estimates.	
8.2.6 /43 Interim Analyses	interpretation of statistical significance associated with treatment comparisons of key study endpoints will be guided using the group sequential stopping boundaries outlined above. After approximately 25% of the total events have occurred, conditional power for the primary treatment comparison	interpretation of statistical significance associated with treatment comparisons will be guided using the group sequential monitoring boundaries outlined above. After approximately 50% of the total events have occurred, conditional power for the primary treatment comparison	Language revised based on change in primary and secondary endpoints.
8.2.7 /44 Multiple Comparisons	overall level of significance for the assessment of the primary mortality endpoint will be 0.05,	overall level of significance for the assessment of the primary composite endpoint will be 0.05,	Language revised based on change in primary and secondary endpoints.
11.1 /47 Site Selection and Monitoring	As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of Good Clinical Practice and applicable regulations, a DCRI study monitor or their designee will visit study sites regularly. They will maintain frequent telephone and written communication.	As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of Good Clinical Practice and applicable regulations, the Monitoring Plan is being revised with Executive Committee approval. A DCRI study monitor or their designee will no longer perform on-site visits to Active study sites regularly and throughout the study. Rather they will maintain frequent telephone and written communication, as well as perform on-site visits to a subset of sites to ensure data integrity.	Accurate communication of the Site monitoring process.
18.0 /50 Informed Consent	obtain written informed consent. The underlying rationale for the study, the procedures to be followed, the potential benefits, risks, alternatives, and other issues mandated by the consent process will be fully disclosed.	obtain written informed consent on an informed consent form (ICF) approved by the same IRB/EC responsible for approval of this protocol. The informed consent document will conform to FDA regulations in 21 CFR Part 50, and/or to the national requirements for informed consent. It must include all elements required by law, local regulations, GCP and International Conference on	Language revised/ inserted for regulatory compliance

	Written informed consent will be documented on an informed consent form (ICF) approved by the same IRB responsible for approval of this protocol, The ICF will conform to FDA regulations in 21 CFR Part 50, and to the institutional requirements for informed consent and applicable regulations.	Harmonization guidelines and study specific procedures. The underlying rationale for the study, the procedures to be followed, the potential benefits, risks, alternatives, and other issues mandated by the consent process will be fully disclosed. If new information becomes available during the course of the trial that may be relevant to the subject's consent, the Informed Consent Form will be revised and the revised version will be submitted for EC/IRB approval before use. REMOVED	
19.0 /51 Confidentiality of Subjects	Subject information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Assurance Portability and Accountability Act and as mandated in Title 45 CFR, Parts 160 and 164. All records will be kept confidential and the subject's name will not be released by study staff at any time. Subject records will not be released to anyone other than DCRI and/or their designee, and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected.	Subject information collected in this study REMOVED and all records will be kept confidential and the subject's name will not be released by study staff at any time. REMOVED When requested patient medical records may be examined by authorized monitors (DCRI and/or their designee) or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IRB / IEC members and by domestic and foreign regulatory authorities. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected. Furthermore; for clinical trial sites located in the US, the NHLBI has issued CABANA a Certificate of Confidentiality to protect the privacy of research subjects	Language revised/ inserted for regulatory compliance. Please note; for clinical trial sites located in the US, CABANA now has a Certificate of Confidentiality

		by withholding their identifiable information from all persons not connected with this research.	
22.0 /52 IRB / EC Committee Review	The appropriate IRB/EC must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide DCRI or their designee with documentation that the IRB has approved the study *before* the study may begin. In addition, the investigator must provide the following documentation to DCRI or their designee. 1. IRB annual reapproval of the protocol, per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonization guidelines. 2. IRB approval of revisions to the informed consent documents or any amendments to the protocol. Any revisions to the protocol that may increase subject risk exposure must be approved prior to implementation. Administrative changes (such as a change in address or phone number) must be sent to IRBs/Ethics Committees but do not require their approval. The investigator will provide DCRI or their designee with documentation of all approvals.	This study will be initiated only after all required documentation has been reviewed and approved by the respective IRB/EC and competent authority (CA) according to national and international regulations. The investigator will provide DCRI or their designee with the study approval documentation before the study may begin. The same is applicable for the implementation of changes introduced by amendments. Where applicable, the investigator must also provide to DCRI and/or their designee the following documentation: 1. A copy of IRB annual re-approval of the protocol per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonization guidelines. 2. IRB approval of revisions to the informed consent documents. Administrative changes (such as a change in address or phone number) must be sent to IRBs/Ethics Committees but do not require their approval. 3. The investigator must submit periodic status reports to their EC as required, as well as notification of completion of the study and a final report where applicable. 4. The investigator will provide DCRI or their designee with documentation of all approvals.	Language revised/ accuracy and regulatory compliance
Appendix A /61		Added 26. Persistent PFO/iatrogenic ASD	The list of Anticipated Events has been updated according to the most recent clinical data.
Appendix B/63		Biosense Webster ThermoCool® SF Medtronic Cryocath LP Arctic Front®	Updated approved catheter list

		Medtronic Cardiac Ablation System	
Appendix C /64 CABANAgene Appendix A: CABANA Inclusion/Exclusion Criteria	Sample size 3000 2 year follow-up	Revised accordingly in sections referring to sample size (2,000-2,200) and duration follow-up (an average of approximately 5 years). Revised per CABANA protocol Version3.5	Reflection of the changes within the main CABANA Trial population, follow-up timeline, and Inclusion/Exclusion