Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92. DOI: 10.1056/NEJMoa1313731

This supplement contains the following items:

1. Original Protocol, Revised Protocol, Final Protocol
2. Original SAP, Final SAP

Treatment **O**f **P**reserved **C**ardiac function heart failure with an **A**ldosterone an**T**agonist

TOPCAT

IND Number:

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Funded by the National Heart, Lung, and Blood Institute, NIH/DHHS

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PROTOCOL SIGNATURE PAGE

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drug and the conduct of the study.

I will use the informed consent form approved by the National Heart, Lung and Blood Institute and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and as specified in the Manual of Procedures (MOP) and, in particular, I agree to report any adverse events, serious adverse events, and unanticipated adverse drug effects (UADEs) as defined in Sections C.5.4 – C.5.6 of this protocol.

I further agree that the National Heart, Lung and Blood Institute, the appropriate regulatory authorities and staff from the regional coordinating centers have access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including study drug) provided by the National Heart, Lung and Blood Institute and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local regulations; and to accept respective revisions conducted by authorized personnel of National Heart, Lung and Blood Institute and by competent authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Principal Investigator(s)		
Principal Investigator(s)		

TRIAL OF ALDOSTERONE ANTAGONIST THERAPY IN ADULTS WITH PRESERVED EJECTION FRACTION CONGESTIVE HEART FAILURE

TABLE OF CONTENTS

PROTOCOL OVERVIEW (ABSTRACT)

This trial is a multicenter, international, randomized, double blind placebo-controlled trial of the aldosterone antagonist, spironolactone, in 4500 adults with heart failure and left ventricular ejection fraction of at least 45%, recruited from over 150 clinical centers. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Secondary endpoints include all-cause mortality, new onset of diabetes mellitus, atrial fibrillation, and quality of life. The trial duration is 4.5 years, with 2.5 years for subject enrollment and an additional 2 years of follow-up, for an average subject follow-up of 3.25 years. Dynamic balancing by clinical center at the time of randomization will be used to ensure that the distribution of clinical centers are similar in the two treatment groups. The study population will include those who meet the inclusion criteria, some of which are:

- Male or female age 50 years or older;
- Heart failure defined as one symptom and one sign present in the last 12 months (described in protocol);
- Left ventricular ejection fraction $\geq$ 45% (per local reading);
- Controlled systolic blood pressure (SBP), defined as: SBP < 140 mm Hg or SBP from 140-160 mm Hg if subject is being treated with 3 or more medications;
- Serum potassium < 5.0 mmol/L prior to randomization;
- At least one hospitalization in the last 12 months for which heart failure was a major component of the hospitalization OR elevated BNP or N-terminal pro-BNP within the last 30 days;
- Willing to comply with scheduled visits, as outlined in the protocol;
- Signed informed consent form.

Exclusion criteria can be found in Section C.1.2.

Study drug dosing will start at 15 mg/day and may be titrated up to 45 mg according to subject tolerance, safety parameters, and symptoms, and will be continued throughout the trial. Following each change in the dosing regimen, subjects will have blood drawn for safety labs 1 week later. Subjects will take study medication every day according to specific instructions. All other treatments will follow accepted local standards for medical care for specific morbidities as described by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) Practice Guidelines, as appropriate. Such treatments may also be adjusted by the local medical practitioner, if necessary. All randomized subjects will be followed even if study drug is discontinued ahead of schedule, except in the case that the subject refuses to participate further in the study.

Follow-up study visits to monitor symptoms, medications, and events and to dispense study drug will occur every 4 months during the first year and every 6 months thereafter. Quality of life will be assessed three times in the first year of the trial and annually thereafter. An electrocardiogram (ECG) will be performed at baseline only. Blood, DNA, and urine samples will be collected from a subset of subjects and stored in a repository for later use in ancillary studies. All clinical endpoints will be adjudicated by a clinical events committee in a blinded fashion. Continual safety surveillance has been built into the study by means of the proposed dosing and safety assessment regimen described in the protocol. The 15 mg dose of spironolactone was formulated to reduce the risks and side-effects associated with this drug. The Data and Safety Monitoring Board (DSMB) will meet regularly, at least twice a year. The DSMB chair will be notified of any events considered probable or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required. The

study will be conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and applicable national and local regulations.

A. SPECIFIC AIMS

A.1 Primary Aim

To determine if treatment with spironolactone can produce a clinically meaningful reduction in cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Primary Outcome Measure: Cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite. Treatment arms will be compared using time-to-event analysis.

Secondary Outcome Measures:

- All-cause mortality
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

A.2 Secondary Aim #1

To determine if treatment with spironolactone can produce a clinically meaningful reduction in new clinical diagnoses compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- New onset of diabetes mellitus
- Development of atrial fibrillation
- New onset MI (fatal + non-fatal)
- New onset stroke (fatal + non-fatal)
- Deterioration of renal function
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

A.3 Secondary Aim #2

To evaluate the relative impact of spironolactone versus placebo on functional status and quality of life in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- Quality of life, as measured by the:
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) – Primary quality of life outcome measure
  - EuroQOL (EQ5D) visual analog scale
  - McMaster Overall Treatment Evaluation (OTE)
  - Patient Health Questionnaire (depression scale)

A.4 Secondary Aim #3

To determine if treatment with spironolactone is safe, compared with placebo, in adults with heart failure and left ventricular ejection of at least 45%.

Safety Outcome Measures:

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function.

B. BACKGROUND

B.1 Prior Literature/Studies

Chronic heart failure (CHF) is a broad syndrome characterized by the relative inability of the heart to adequately meet metabolic demands of tissues without an abnormal elevation in filling pressure, which contributes to the clinically recognizable constellation of signs and symptoms. Although the etiologies of CHF are diverse, the premature mortality, incumbent morbidity, and associated healthcare burdens are not cause specific. Regardless of the etiology, CHF represents a progressive disorder that afflicts approximately 10% of the elderly and is the most common reason for hospitalization of patients over 65 years old (Hunt et al., 2001), with a prevalence of 4.9 million people in the United States, and 550,000 new cases diagnosed annually (American Heart Association, 2003). Epidemiologic and hospital-based studies have demonstrated that among patients with newly diagnosed CHF in the community, 43% to 54% of patients have preserved systolic function (PSF) (Senni et al., 1998; Vasan et al., 1999; Ahmed et al., 2002; McDermott et al., 1997). CHF patients without low ejection fractions have been variably described as having HF-PSF, heart failure with preserved ejection fraction, or diastolic heart failure. Although each term has relative merits, they do not completely characterize the complex interactions between systolic and diastolic function, vascular-ventricular coupling, neuroendocrine activation, and cardiorenal adaptations that result in the syndrome of heart failure. Pragmatically, since a quantitative left ventricular ejection fraction (LVEF) is used to define the well-studied systolic dysfunction (LVEF<40%) component of the heart failure population, an LVEF ≥40% can be used to identify the remaining proportion of heart failure patients with relatively PSF.

Relative to systolic dysfunction CHF, HF-PSF has a higher proportion of women and elderly. The Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials, with concurrent screening for both systolic dysfunction and HF-PSF, found a similar incidence of atrial fibrillation and diabetes mellitus across ejection fraction groups but a lower frequency of prior myocardial infarction in those with HF-PSF (McMurray et al., 2003). In the Cardiovascular Health Study, approximately 67% of women older than 65 years of age had PSF compared with 42% of men (Kitzman et al., 2001). The estimate of the prevalence of this syndrome varies dramatically based upon the study design with a range from 13 to 74% reported (Ahmed et al., 2002). The annual mortality rate has been estimated to be between 1.3 and 17.5% (Vasan et al., 1995). In the recently completed CHARM-Preserved trial, involving 3025 patients with symptomatic heart failure and an LVEF greater than 40% (median 54%), the mortality rate was 5.5 per 100 person-years, which though less than the approximately 10 per 100 person-years for heart failure with depressed LVEF, was still threefold higher than age-matched subjects without heart failure (Yusuf et al., 2003). These patients also have significant morbidity. CHF patients with PSF (HF-PSF) have a high risk of re-hospitalization for HF and functional decline, reduced exercise performance, and worse quality of life than non-HF patients (Hundley et al., 2001; Kitzman et al., 2002; Smith et al., 2003).

B.2 Rationale for This Trial

B.2.1 Rationale for Investigation of New Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors in CHF Patients with PSF

This randomized double-blind placebo-controlled trial is designed to test the hypothesis that the addition of a mineralocorticoid receptor blocker to conventional therapy would improve clinical outcomes as assessed by reduced risk of death and hospitalizations for major cardiovascular events in patients with symptomatic heart failure and a quantitative LVEF at or above 45%. Despite the persistent advances over the past two decades in the treatment and prevention of cardiovascular diseases, the incidence of heart failure continues to increase. In some respects, this increase is a consequence of successes in the management of other fatal cardiovascular disorders, producing a larger reservoir of older individuals surviving with coexisting major cardiovascular comorbidities. Moreover, patients with heart failure and PSF have a particularly high rate of recurrent hospitalizations for a variety of major cardiovascular complications. The efficacy demonstrated with two separate mineralocorticoid receptor blockers, reducing the risk of death and hospitalizations for heart failure in patients with symptomatic heart failure and reduced ejection fraction, and acute MI complicated by heart failure, (spironolactone and eplerenone, respectively), provides a strong rationale for testing a mineralocorticoid receptor blocker in patients with heart failure and relatively preserved systolic ejection fraction. In addition to the potential reductions of individual risks of cardiovascular morbidity and mortality, the benefits achieved in this understudied population that utilizes considerable health care resources, would have major public health implications – reductions in both mortality and in costly hospitalizations.

B.2.2 Rationale for Use of Spironolactone

There are two candidates for aldosterone inhibition: the more familiar generic drug spironolactone and the newer eplerenone (owned by Pfizer). The important clinical benefits of these two mineralocorticoid receptor blockers is supported by mechanistic animal studies demonstrating that these agents reduce interstitial fibrosis, ventricular remodeling, vascular oxidative stress, improved endothelial function and have other favorable actions that could be anticipated to translate into clinical benefits in patients with heart failure and PSF. Both drugs have demonstrated improvement in survival in high-risk cardiovascular patients by mechanisms that likely go well beyond the renal effects of aldosterone inhibition. Spironolactone has an associated 10% rate of gynecomastia in males, which is not a side effect of eplerenone. However, from the Randomized Aldactone Evaluation Study (RALES) trial experience, this side effect resulted in negligible discontinuance of the drug. In the TOPCAT trial, gynecomastia will not be an issue as the population recruited for the trial will include a large number of females, many of whom are postmenopausal.

C. STUDY DESIGN AND METHODS

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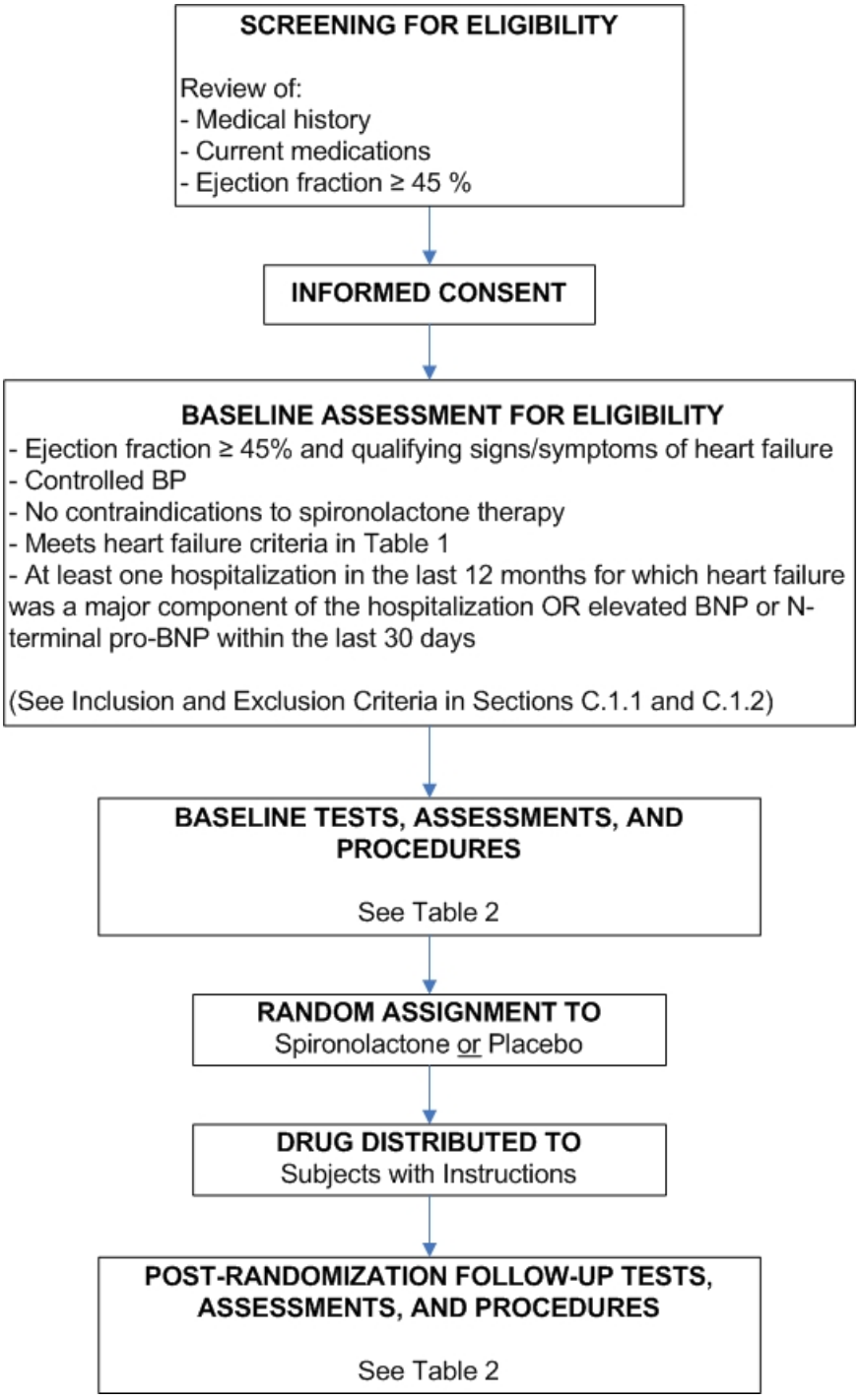
Figure 1
SUBJECT FLOW IN TRIAL



C.1 Participants

C.1.1 Inclusion Criteria

In order for a subject to be eligible for inclusion in the trial, all of the following criteria must be met:

1. Male or female; Age 50 years or older;
2. Heart failure as defined in Table 1. One symptom must be present at the time of screening and one sign must be present in the last 12 months;
3. Left ventricular ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable) ≥ 45% (per local reading). The ejection fraction must have been obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction;
4. Controlled systolic BP, defined as a target systolic BP < 140 mm Hg. Subjects with BP up to and including 160 mm Hg are eligible for enrollment if on 3 or more medications to control BP.
5. Serum potassium < 5.0 mmol/L prior to randomization;
6. At least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization. Transient heart failure in the context of myocardial infarction (MI) does not qualify.

   OR

   Brain natriuretic peptide (BNP) in the last 30 days ≥ 100 pg/ml or N-terminal pro-BNP ≥ 360 pg/ml and not explained by another disease entity;
7. Women of child-bearing potential must have a negative serum/urine pregnancy test within 72 hours prior to randomization, must not be lactating, and must agree to use an effective method of contraception during the entire course of study participation.
8. Willing to comply with scheduled visits, as outlined in Table 2;
9. Informed consent form signed by the subject.

TABLE 1. Criteria for Diagnosing Heart Failure

SYMPTOMS (at least one must be present at the time of screening)	SIGNS (at least one in last 12 mo.)
• Paroxysmal nocturnal dyspnea • Orthopnea • Dyspnea on mild or moderate exertion	• Any rales post cough • Jugular venous pressure (JVP) ≥ 10 cm H_2O • Lower extremity edema • Chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly

C.1.2 Exclusion Criteria

If a subject meets any one of the following criteria then he/she is ineligible for enrollment in the trial:

1. Severe systemic illness with life expectancy judged less than three years;
2. Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator;
3. Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;
4. Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial;

5. Atrial fibrillation with a resting heart rate > 90 bpm;
6. Myocardial infarction in past 90 days;
7. Coronary artery bypass graft surgery in past 90 days;
8. Percutaneous coronary intervention in past 30 days;
9. Heart transplant recipient;
10. Currently implanted left ventricular assist device;
11. Stroke in past 90 days;
12. Systolic blood pressure (SBP) > 160 mm Hg;
13. Known orthostatic hypotension;
14. Gastrointestinal disorder that could interfere with study drug absorption;
15. Use of any aldosterone antagonist or potassium sparing medication in last 7 days;
16. Known intolerance to aldosterone antagonists;
17. Current lithium use;
18. Current participation (including prior 30 days) in any other therapeutic trial;
19. Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol;
20. History of hyperkalemia (serum potassium ≥ 5.5 mmol/L) in the past six months or serum potassium ≥ 5.0 mmol/L within the past two weeks;
21. Severe renal dysfunction, defined as an estimated glomerular filtration rate (GFR) < 30 ml/min (per the Modification of Diet in Renal Disease (MDRD) 4-component study equation). Subjects with serum creatinine ≥ 2.5 mg/dl are also excluded even if their GFR is ≥ 30 ml/min;
22. Known chronic hepatic disease, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels > 3.0 times the upper limit of normal as read at the local lab.

C.1.3 Human Subjects Considerations

C.1.3.a Informed Consent

A waiver of consent will be requested from the Institutional Review Board/Ethics Committee (IRB/EC) of each clinical center in order to submit to the Clinical Trial Coordinating Center (CTCC) a completed screening form on non-randomized subjects. Written informed consent will be obtained from all potentially eligible trial subjects. Consent from a surrogate will not be permitted.

The repository will be a side-arm study of the main protocol. All sites participating in the side-arm study will approach all potentially eligible trial subjects for consent. A separate informed consent for each stored specimen will be obtained prior to randomization.

Other than random assignment to either spironolactone or placebo, all subjects will undergo routine care for heart failure with PSF.

Before any trial-related procedure is performed, the investigator will obtain informed consent from the study subject by means of a dated and signed consent approved by the local IRB/EC in his/her country.

The informed consent process will be performed in accordance with the ICH guidelines for Good Clinical Practice (GCP), local laws and regulations.

The process will involve two steps. In the first step, potential study subjects will be given an information sheet and adequate time to study the information. The second step, obtaining informed consent, may only take place after the potential study subject has had adequate time

to study the information sheet, ask any questions and to decide whether or not to participate in the trial. Both the consent and the patient information sheet will be provided to the subject in the local language.

The informed consent process includes individual discussion with the subject about what study participation will involve. The information to be discussed will include all the information provided in the TOPCAT trial patient information sheet. The discussion process includes informing the study subject both verbally and in writing that:

-if he/she refuses to participate in the study, the quality of medical care he/she receives will not be affected and
-he/she may withdraw at any time without giving reason and without affecting their future care and
-without disclosing his/her name, relevant medical and personal data will be disclosed to the sponsor and regional coordinating centers who are obliged to use the information anonymously and solely for scientific purposes and
-his/her medical records may be reviewed during on-site monitoring, and may be inspected by auditors and/or regulatory authorities who are obliged to confidentiality and
-confidentiality will be maintained at all times according to local data protection laws.

Both the date a potential study subject is given the information sheet and the date the study subject gives informed consent must be recorded. The study subject will be given a copy of the signed informed consent form and information sheet.

After informed consent has been provided by the study subject, the declaration of consent will be kept in the patient file at the clinical site and will be made available for audit purposes. If the filing of the original signed consent form in the subject's hospital file is not permitted by the hospital or clinical setting, it must be filed in the investigator files and an indication that consent was obtained (with the date specified) should be noted in the medical files.

C.1.3.b Patient Confidentiality

Patient confidentiality will be maintained according to ICH guidelines for GCP and applicable local and national data protection laws. A study identification number will be assigned to each subject. The link between patient name and I.D. number will be stored only at the clinical center where the subject receives his/her care, thereby ensuring that all data transferred from a subject's medical records to a study report form and any process derived from the study report form is handled confidentially.

C.1.3.c DNA Confidentiality

The whole blood sample prepared for DNA abstraction will be sent to the repository. The sample will not have the original study I.D. number, the patient's name, or any other information that could identify the subject. The specific procedures will be detailed in the Manual of Procedures (MOP).

C.1.3.d Potential Risks

Spironolactone has been licensed for the treatment of heart failure in all of the countries participating in the TOPCAT trial for many years. The most common risks of taking spironolactone include hyperkalemia (observed at < 1.0% in the RALES trial with no serious consequences), hyponatremia, headache, drowsiness, lethargy, diarrhea, cramps, bleeding, gastritis, vomiting, anorexia, nausea, rash, pruritis, urticaria. Gynecomastia, erectile dysfunction, and post-menopausal bleeding are less common. Hirsutism, agranulocytosis, and hyperchloremic metabolic acidosis have also been reported.

Although breast tenderness and gynecomastia have been reported in up to 10% of male patients treated with spironolactone, the risk of this side effect is dose-related and uncommon in patients treated with daily doses of 50 mg or less (as targeted in this trial). In the RALES trial, gynecomastia resulted in negligible discontinuance of the drug and the condition is expected to be less of a problem in the TOPCAT trial as the study will be investigating patients with HF-PSF, a large proportion of whom are post-menopausal women.

A potentially serious side effect sometimes seen in patients treated with spironolactone is hyperkalemia. People with impaired renal function are considered to be at higher risk of hyperkalemia- an observation used to define the exclusion criteria of first the RALES trial and now TOPCAT. The investigators in the RALES trial attributed the observed incidence of hyperkalemia (1% in the placebo group and 2% in the spironolactone-treated group) to the exclusion of patients with elevated serum creatinine and potassium at baseline (and also to the relatively low treatment dose of spironolactone: the mean dose was 26 mg). Similar exclusion criteria will be used in the TOPCAT trial; however, the starting dose of spironolactone will be lower and renal function will be more accurately and reliably defined at baseline by estimated GFR. By careful evaluation of the pre-disposing factors for hyperkalemia and use of close monitoring of serum potassium during the study, it is anticipated that the rate of clinically significant hyperkalemia seen in TOPCAT will be similar to or possibly lower than that observed in the RALES trial.

Therapeutic trials investigating heart failure have been performed to date almost exclusively on patients with systolic dysfunction. However, now there is a growing awareness that a large proportion of patients with heart failure have preserved systolic function and that survival of these patients is also adversely affected. While treatment has been shown to be useful in patients with heart failure with systolic dysfunction, this is an area which has been understudied in those heart failure patients with PSF. Consequently much still remains to be learned about HF-PSF and its treatment.

C.1.3.e Potential Benefits

Subjects enrolled in this trial who are receiving active drug may receive a benefit. Also, there may be considerable benefit to future patients with HF-PSF as a result of the medical knowledge obtained from this study.

C.2 Trial Enrollment

C.2.1 Recruitment Protocol

The Principal Investigator at each private practice or clinical center, his or her designee, and the coordinator will have the responsibility for case finding and subject recruitment. The coordinator will conduct a chart review, while complying with local institution Health Insurance Portability and Accountability Act (HIPAA) requirements, to identify potentially eligible subjects. The coordinator will contact the subject per local guidelines to assess interest in the trial and to schedule an office or clinic visit for determination of full eligibility. Subjects may also be approached for participation while in-hospital if the subject is potentially eligible based on chart review. It should be noted that a subject may be screened for trial eligibility more than once during the accrual period.

C.2.2 Stratification

Due to the large number of clinical centers and potentially small number of enrolled subjects at some sites, dynamic balancing (Zelen, 1974) rather than stratified randomization across sites will be utilized to ensure that the distributions of clinical centers are similar in the two treatment groups. This approach will prevent the creation of excessively small stratum sizes. In addition, subjects will be stratified on inclusion criterion #6. Stratum I will include subjects selected based on a hospitalization in the 12 months prior to enrollment with a heart failure diagnosis and stratum II will include those subjects not reporting a hospitalization in the prior 12 months for which heart failure was a major component (for whom elevated BNP is required).

C.2.3 Blinding

Subjects and treating physicians will be blinded to whether subjects are receiving spironolactone or placebo. Because the trial has a double-blind design, safety laboratory tests will be performed for each subject for the duration of the trial, regardless of treatment arm. Similarly, monitoring of potential side effects will be continuous and irrespective of treatment assignment. While unmasking of the drug assignment for an individual subject is not anticipated given the proposed dosing and safety-monitoring regimen described in Section C.3, a procedure for unblinding will be included in the Manual of Procedures (MOP).

C.2.4 Randomization

Subjects will be randomly assigned in a 1:1 ratio using permuted blocks to receive either spironolactone or placebo after written informed consent is obtained. Randomization will be accomplished over the Internet using randomization software accessed via a secure website. After verifying key eligibility criteria and supplying clinical center information, the randomization software will return a Treatment Allocation Code corresponding to either spironolactone or placebo. The nurse coordinator will utilize a master list of Treatment Allocation Codes to determine which labeled study drug packet to provide to the subject. Paired labels containing treatment allocation code will be on the drug packet and on a verification form to ensure correct assignment.

C.3 Treatment

C.3.1 Description of Study Medication

Study drug supplies will be provided by the Department of Health and Human Services (DHHS) Program Support Center in Perry Point, MD. Shipments will consist of the following:

1. Bottles containing 150 spironolactone 15 mg tablets
2. Bottles containing 150 placebo tablets, identical in size and appearance to the 15 mg spironolactone tablets.

Both the spironolactone 15 mg tablets and matching placebo are manufactured by URL Mutual Pharmaceutical in Philadelphia, PA, USA in accordance with federal regulations and ICH guidelines for Good Manufacturing Practices.

C.3.2 Randomization Procedures

Subjects will be assigned in the order they are enrolled into the study, to receive the allocated treatment according to a computer-generated randomization schedule prepared at NERI prior to the start of the study. The Treatment Allocation Code is not the same as the subject identification number.

C.3.3 Study Drug Administration

Study medication will be dispensed at Randomization, 4 Month visit, 8 Month visit, 12 Month visit, and every 6 months thereafter. Previously dispensed drug supplies are to be returned at each subsequent visit to verify drug compliance. The volume of unused tablets will be recorded on the appropriate case report form (CRF). Site personnel will instruct the subject on the importance of compliance.

The first dose of study drug will be administered as soon as possible after written informed consent has been obtained, baseline procedures have been performed, and there is confirmation that laboratory results are within acceptable parameters.

C.3.4 Study Drug Titration and Dosing Regimen

All subjects randomized into the study will begin on an initial dose of 15 mg daily (i.e. one tablet by mouth every day). The titration schedule and safety assessment intervals are illustrated in Figure 2. After 4 weeks, the dose should be increased to 30 mg daily (i.e. two tablets by mouth every day) if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the treating physician has the option to increase the dose to 45 mg daily at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily. Safety labs (i.e., electrolytes and chemistries) will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

Once the subject is appropriately titrated, the dosing regimen (i.e., 15 mg, 30 mg, or 45 mg by mouth every day) should remain stable **unless** scheduled laboratory results exceed the safety parameters. The flowchart in Figure 2 illustrates the various pathways for dose titration of the study drug as follows:

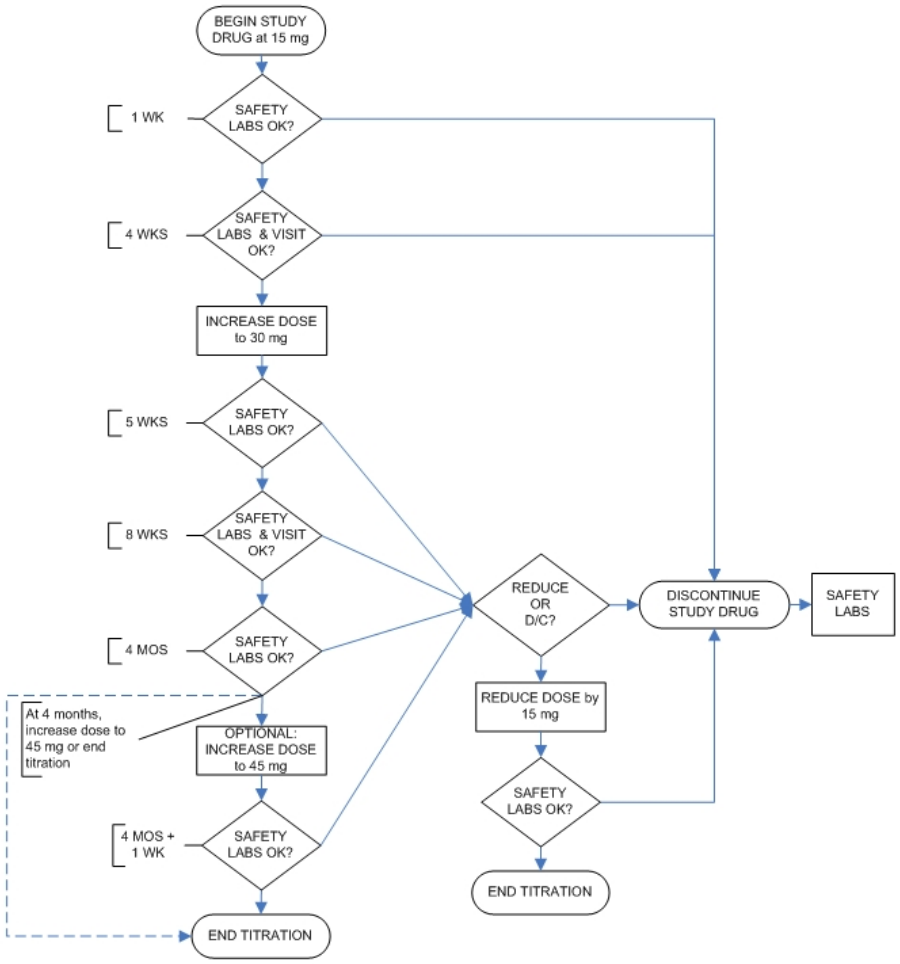
1. Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; and if the subject is already on the lowest dose (i.e. 15 mg), then the study drug should be permanently discontinued. Once a downward dose adjustment has been made, the drug should not be uptitrated beyond this level for the trial duration.

2. Discontinue study drug permanently if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen.
3. Reinitiate study drug, at the discretion of the treating physician, if the dosing regimen is interrupted due to non-compliance. If a subject is eligible for study drug reinitiation, the physician should choose from one the following three options:
    - Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation)
    - Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable.
    - Do not reinitiate study drug

If possible, drug should be reinitiated within one week of drug discontinuation. The number of times that drug can be reinitiated is at the discretion of the treating physician.

Figure 2. Study Drug Titration and Safety Assessment Schedule

The study drug titration and safety assessment schedule is illustrated in this figure.



Titration: Initial dose: **15 mg/day.** After 4 weeks, the dose should be increased to **30 mg/day** if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the investigator has the option to increase the dose to **45 mg/day** at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily.

Reduce drug: Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; if the subject is already on the lowest dose (i.e. 15 mg), the study drug should be permanently discontinued. Once a downward dose adjustment has been made, the study drug should not be uptitrated beyond this level for the trial duration.

Discontinue drug: Permanently discontinue study drug if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen.

Safety labs: Collect safety labs (i.e., electrolytes and chemistries) at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

Reinitiation (after non-compliance): If the dosing regimen is interrupted due to non-compliance, study drug may be reinitiated at the discretion of the treating physician. If a subject is eligible for drug reinitiation, the physician should choose from one the following three options:

- Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation); or
- Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable; or
- Do not reinitiate study drug

If possible, study drug should be reinitiated within one week of drug discontinuation. The number of times study drug may be reinitiated after non-compliance is at the discretion of the treating physician.

C.3.5 Concomitant Medication

Subjects will be treated with other medications at the discretion of their cardiologist and/or primary care provider. All medications will be recorded on the study forms. If a subject begins open-label use of any aldosterone antagonist or potassium-sparing diuretic, withdrawal from study drug is required.

The following drug interactions have been observed with spironolactone:

- ACE inhibitors or ARB – may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics – may be associated with hypokalemia
- Corticosteroids, ACTH – may be associated with hypokalemia
- Pressor amines (e.g. norepinephrine) – may reduce vascular responsiveness
- Skeletal muscle relaxants – may amplify muscle relaxant responsiveness
- Lithium – may lead to lithium toxicity
- NSAIDs – may be associated with hyperkalemia
- Cardiac glycosides (e.g. digoxin) – may lead to digoxin toxicity
- Anticoagulants (e.g. warfarin, heparin) – may reduce the effects of anticoagulation

C.3.6 Indications for Permanent Discontinuation of Study Drug

- Persistent hyperkalemia (potassium ≥ 6.0 mmol/L)
- Potassium ≥ 5.5 mmol/L and subject on lowest dose of study drug (15 mg)
- Anaphylactoid reaction or intolerance
- Serum creatinine $\geq$ 3.0 mg/dl, or at a lower threshold per local physician judgment
- Open label use of any aldosterone antagonist or potassium-sparing diuretic that cannot be discontinued for valid clinical reason
- Other adverse events that require discontinuation of study drug in the judgment of the study investigator, such as a medical course that is incompatible with the concomitant use of spironolactone.

The reason and the circumstances for permanent discontinuation of study drug will be documented. If study drug is permanently discontinued, the subject will continue to be followed until the end of the trial period.

C.3.7 Indications for Withdrawal From the Study

- Subject refusal to continue in the study
- Heart transplantation

All protocol-specified visits and follow-up procedures should be performed for every subject enrolled in the trial, even if the study drug is discontinued. If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. The reason for withdrawal will be documented for all subjects withdrawn from the study. If the withdrawing subject is unwilling to have his/her medical records reviewed until the end of the trial period (to document vital status and cause of death), he/she must submit a written refusal. Subjects may withdraw consent from the sub-study but continue participating in the main study. Subjects who withdraw consent from the main study are automatically withdrawn from the sub-study.

C.3.8 Study Completion

A subject will be considered to have completed the study if he/she has completed follow-up until the end of the trial period, undergoes heart transplantation, or dies. All subjects will be followed for a minimum of 2 years and a maximum of 4.5 years.

C.3.9 Subject Compliance

Study drug compliance will be assessed at each study visit by comparing the expected vs. actual consumption of study drug tablets. The subject will bring all remaining study drug to the follow-up visit. The study coordinator will measure and record the volume of remaining tablets, and a new 4 or 6 month supply (depending on the visit schedule) will be dispensed.

C.3.10 Drug Accountability Log

All study drug supplies (i.e. spironolactone 15 mg and corresponding placebo tablets and bottles) provided by the DHHS Program Support Center to the investigator for use in the clinical study must be accounted for in written documentation that must be maintained by the investigator and that will be monitored by the CTCC.

Forms to record dispensing of study medication will be provided with the initial shipment of the study medication. A copy of the complete records of study drug accountability for all supplies received for the study must be provided to the CTCC as part of the close-out procedure for the study. The drug accountability records must be retained by the investigator along with the subjects' study records.

C.3.11 Code Break

The Treatment Allocation Code may be broken if an emergency situation arises that in the Investigator's opinion requires knowledge of the code.

A request for unblinding should only be made in situations where knowledge of the treatment assignment will actually affect the subsequent care or decision-making process for care of the trial subject. It should be assumed that the trial subject will remain in the trial and will continue adherence to the trial protocol after the event is resolved. Therefore, every effort should be made to maintain trial participation in a blinded nature. It is anticipated that all assignments will remain blinded for the trial duration and that all subjects will be appropriately monitored for safety.

Refer to the Manual of Procedures (MOP) for a description of the process for code break.

C.4 Measurements

C.4.1 Schedule of Measurement

See next page.

Table 2. Schedule of Trial Measurements

	Record Screening	Baseline Screening	Randomization and Drug Distribution	1 Week	4 Weeks	5 Weeks	8 Weeks	4 Months	8 Months	12 Months	18 Months	24, 36, 48 Months	30, 42, 54 Months
Medical History	X	X											
Current Medications	X	X			X		X	X	X	X	X	X	X
Echocardiogram*	X												
Physical Exam, Wt., Vital Signs		X			X		X	X	X	X	X	X	X
Assessment of Study Drug Compliance				X	X	X	X	X	X	X	X	X	X
Blood Studies**		X		X***	X	X	X	X	X	X	X	X	X
ECG		X											
Adverse Event Monitoring				X	X	X	X	X	X	X	X	X	X
Urine Microalbuminuria		X								X		X	
QOL****		X						X		X		X	
Repository Specimens													
Urine Specimen		X								X			
Blood Specimen		X								X			
DNA Specimen		X											

* Ejection fraction obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction.

** Blood Studies (local lab):

- Baseline blood studies include: CBC, electrolytes, BUN, creatinine, blood glucose, and LFTs.
- Follow-up safety blood studies include: electrolytes, BUN and creatinine.

*** Safety labs will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

**** OTE instrument will only be administered at the 4 and 12 month visits; KCCQ and EQ-5D instruments will only be administered at Baseline, 4 and 12 month visits and annually thereafter; Patient Health Questionnaire instrument will only be administered at Baseline and 12 month visits and annually thereafter.

C.4.1.a Record Screening (Table 2)
Record screening will include review of past medical history and current medications. The most recent echocardiogram from the past 6 months will be evaluated to determine if ejection fraction is ≥ 45% (per local reading). It is preferred that the qualifying ejection fraction be obtained by echocardiography. The echocardiogram (video copy or digital image is acceptable) utilized for screening must be submitted to the CTCC. The Echocardiography Core Laboratory will read all pre-eligibility echocardiograms for a central interpretation of ejection fraction to be used in analyses. Ejection fraction obtained by radionuclide ventriculography or angiography is also acceptable in instances where an echocardiogram suitable for quantification is not available.

C.4.1.b Baseline Screening (Table 2)
At the baseline screening visit, the subject will have a physical examination, including vital signs. Blood will be drawn for CBC, electrolytes, BUN, creatinine, blood glucose, and liver function tests (LFTs). A urine test for microalbuminuria will be conducted. Creatinine, potassium, and LFTs, as well as the blood pressure measurements will be used to confirm eligibility. Current medication use will be reviewed to confirm that the subject does not meet exclusion criteria. Age, gender, race, and serum creatinine concentration will be obtained in order to calculate an estimated GFR using the 4-component MDRD Study prediction equation. The GFR estimate will be used to determine whether a subject has acceptable renal function to be enrolled in this study (see exclusion criterion 21). The initial medical history will focus on demographics, cardiac risk factors, and the prior 12 months for recent hospitalizations and procedures. An electrocardiogram (ECG) will be obtained at baseline. The subject will be asked to complete the first quality of life questionnaires. Procedures for the physical examination, blood draw, and urine test will be detailed in the Manual of Procedures (MOP).

All subjects from sites participating in the sub-study will be approached for consent to provide blood and urine samples for the repository, including a whole blood sample for DNA extraction. After randomization and confirmation that lab studies are acceptable, the first 30 days of study drug will be dispensed with instructions.

C.4.1.c Follow-Up Visits (Table 2)
Health status and study drug compliance will be evaluated at scheduled visits throughout the study. Subjects must plan to have blood drawn for safety labs at 1 week post drug initiation/dose change. They will be scheduled to have an office visit and safety labs at 4 weeks post drug initiation/dose change. If the study drug is increased at this time, they will have blood work one week after dose change (week 5), and then full evaluation at 8 weeks. Subsequent planned visits will be scheduled every four months for the first year and every six months thereafter. Specifics for study drug titration are described in Section C.3.4 and Figure 2. Unplanned visits will be determined by the treating physician for symptoms, abnormal lab work, or other reasons.

At each office visit, the following will be obtained by short interview: current signs/symptoms consistent with HF and with administration of study drug, and current medications (subjects will be asked to bring these to each visit for accurate inventory). Blood pressure will be taken and recorded. Every effort should be made to control blood pressure throughout the course of follow-up. Body weight will be recorded. Electrolytes, BUN, and creatinine, will be drawn to assess study drug safety. A urine test for microalbuminuria will be conducted annually.

Four quality of life instruments will be administered to trial subjects in the appropriate language according to the Schedule of Measurement (Table 2).

Blood and urine specimens for the repository will be obtained at baseline and 12 months from a subset of subjects.

If drug reduction/discontinuance is indicated by the chemistry panel results, a follow-up visit will be scheduled within one week at which time the subject will be evaluated for change in course of therapy.

Towards the end of the trial accrual and follow-up period, the Social Security or National Death Index will be searched for any subjects of unknown vital status in the U.S. Similar procedures will be implemented as feasible in other countries, with the assistance of the Regional Leaders.

C.4.1.d Windows for Visits

The acceptable windows for study visits are shown in Table 3. Safety monitoring during the titration period must be conducted at the study site. If for some reason a subject is unable to complete a study visit in person for a visit at Month 4 or later, the QOL instruments will be mailed to the subject along with a hospital-addressed stamped envelope for return of the completed questionnaires to the clinical site. The QOL instruments will be assigned for analysis to the nearest available window based on completion date.

Table 3. Acceptable Windows for Study Visits

Visit	**Window**
Week 1, 4, 5, 8	± 3 days
Month 4	±2 weeks
Month 8, 12	± 2 weeks
Later Visits	± 4 weeks

C.4.2 Outcome Variables

Outcome variables have been chosen that will best capture the multi-faceted impact of spironolactone on heart failure with relatively PSF, a disease with significant morbidity, mortality, and associated costs. The primary trial endpoint is **a composite of** cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Table 4 provides a summary of all outcome measures for the trial. In addition, all components of composite endpoints will be reported.

Table 4. Trial Outcome Measures

Primary Outcome

- Cardiovascular (CV) mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite.

Secondary Outcomes

Morbidity and Mortality

- **All-cause mortality**
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

New Clinical Findings

- New onset of diabetes mellitus
- Development of atrial fibrillation
- New onset MI (fatal + non-fatal)
- New onset stroke (fatal + non-fatal)
- Deterioration of renal function (see Section C.4.2.b)
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

Quality of Life

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol (EQ5D) visual analog scale
- McMaster Overall Treatment Evaluation (OTE)
- Patient Health Questionnaire (depression scale)

Safety Measures

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function

C.4.2.a Morbidity and Mortality

Vital and hospitalization status will be monitored through subject contacts and by interview and medical record review at the clinic site. If a death occurs, the nurse coordinator will complete a death form indicating the date, time, and official cause of death, as well as a description of events leading up to the death.

Selected outcome forms and supporting documentation will be forwarded from the CTCC to the Clinical Endpoints Committee (CEC) for review as described in the TOPCAT Manual of Procedures (MOP).

C.4.2.b New Clinical Findings

New onset of diabetes mellitus will be assessed by physical exam, symptoms, and defined by measurement of blood glucose and introduction of anti-diabetic medication. New diagnosis of atrial fibrillation will be made by reported symptoms and clinically indicated monitoring of heart rhythm. Deterioration of renal function is defined as a twofold increase in baseline serum creatinine level. Stroke and MI will be centrally adjudicated and defined in the CEC Manual of Procedures (MOP).

C.4.2.c Quality of Life

The primary goals of heart failure management are improving patient function, slowing disease progression, and improving quality of life. The quantification of this latter treatment goal requires the use of a health-related quality of life instrument, typically including a range of domains of health status. Four instruments will be administered to trial subjects in the appropriate language according to the Schedule of Measurement (Table 2). The overall quality of life assessment typically will not exceed 12-15 minutes per subject.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be used as the primary endpoint for evaluation of functional status and quality of life in this trial. The KCCQ is a self-administered 23-item questionnaire taking approximately 4-6 minutes that measures physical limitation, symptoms (frequency, severity and recent change over time), quality of life, social interference, and self-efficacy. The KCCQ has been used in several recent and ongoing heart failure trials, including the EPHESUS trial.

In addition to the KCCQ, a brief generic health status measure, the "feeling thermometer" from the EuroQOL Health Status Questionnaire (EQ-5D; Brazier et al., 1993), which is a visual analog (0-100) scale, ranging from the worst imaginable health state (0) to the best imaginable health state (100) will be administered, as well as the McMaster Overall Treatment Evaluation (OTE) (Juniper et al. 1994). The OTE has 3 items addressing the overall effect of the treatment according to whether a subject has improved or deteriorated with respect to symptoms related to heart failure since the treatment started (therefore this instrument will not be part of the baseline QOL battery). If subjects indicate an improvement or deterioration, they will be asked to score the magnitude and the importance of the perceived change on a 7-point scale. The items will be combined to form a 15-graded scale, ranging from the worst deterioration (-7) to the highest improvement (+7) with "No change" (0) as the middle score. The OTE will be administered only at the 4 and 12 month follow-up visits.

Finally, the Patient Health Questionnaire, a 9-item health scale derived from the PRIME-MD that includes a measure of depression severity, will be administered.

C.4.3 Event Adjudication

New England Research Institutes, Inc. (NERI) as the CTCC will serve as the primary liaison to the sites for reporting of study endpoints and will be responsible for ensuring the required endpoint-related data are collected. The Clinical Endpoint Committee at the Brigham and Women's Hospital in Boston will serve as the CEC and will be responsible for reviewing and adjudicating all suspected study endpoints consisting of cardiovascular vs. non-cardiovascular death, hospitalization for congestive heart failure, cardiac arrest, myocardial infarction, and stroke.

The primary objective of the CEC is consistent and unbiased review and adjudication of study endpoints throughout the course of the trial. At the CEC, each event will be reviewed independently by two Reviewers assigned to each event and their adjudications compared with any discrepancies presented in Committee. In certain instances, the Chairman will generate a case precedent, an internal consistency measure, for difficult or noteworthy events that set a precedent for how future events should be regarded.

For each endpoint, the Physician Reviewers are responsible for providing a final adjudication for each event along with appropriate chart documentation describing the key details related to the event as well as rationale supporting their adjudication. The CEC maintains strict internal quality assurance measures in order to maintain the high-level quality of adjudicated data and in addition, all operations are conducted under the International Conference on Harmonization Good Clinical Practices (ICH/GCP) and Code of Federal Regulations (21 CFR 312, 21 CFR 50, 21 CFR 56). The CEC maintains Standard Operating Procedures for all functions and procedures and is subject to review and audit by the sponsor, or their representatives, and regulatory authorities. A 10% sample for re-adjudication will be randomly and blindly inserted in the review process by the CTCC and the results will be reported at CEC meetings. Details of CEC procedures will be included in the TOPCAT trial Manual of Procedures (MOP).

C.4.4 Repository

The repository will be a sub-study of the main protocol and subjects will be asked to provide additional informed consent to participate. For those subjects who consent, urine and blood specimens will be collected at baseline and 12 months, spanning an interval when most events and physiological changes are likely to occur. A whole blood sample for DNA extraction will also be collected at baseline for those subjects who consent. The proposed collections are summarized in Table 5. SeraCare BioServices will serve as the repository. SeraCare BioServices will provide all collection and shipping containers to the clinical centers. The repository specimens will be stored for later use in ancillary studies yet to be approved and funded.

TABLE 5. Specimen Collection	
Serum	• Up to three 10 ml tubes whole blood, collected and processed for storage of plasma or serum as detailed in the Manual of Procedures (MOP) • Temporary storage in pre-labeled shipping tubes at -20^{o}C • Shipment to repository when shipping rack filled
Urine	• 20 ml urine (mid-stream, time of day recorded but unrestricted) • Temporary storage in pre-labeled shipping tube at -20^{o}C • Shipment to repository as above
DNA	• Whole blood will be used for the DNA extraction.

C.5 Adverse Events

C.5.1 Definition

For purposes of this study, an adverse event (AE) is any untoward medical occurrence in a subject which is possibly, probably or definitely related to study drug (spironolactone or placebo).

C.5.2 Classification of Adverse Events

C.5.2.a Severity

The severity (intensity) of each AE will be assessed according to the following definitions:

Mild: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity/intensity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

Severe: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the drug. Treatment for symptom(s) may be given.

Life-threatening: Symptom(s) of a sufficient severity/intensity to cause the subject to be at immediate risk of death. Treatment for symptom(s) may be given.

C.5.2.b Relationship

The temporal/causal relationship between the study drug (spironolactone or placebo) will be determined by the investigator according to the following definitions:

Definite: Clearly related to the study drug.

Probable: Likely (high suspicion) related to the study drug.

Possible: May be related to the study drug.

Unrelated: Clearly not related to the study drug.

C.5.3 Data Collection Procedures for Adverse Events

Adverse events will be recorded according to the date and time of first occurrence, severity, and duration, as well as any treatment prescribed. Following initiation of study drug dosing, all new or continuing adverse events that were not present at enrollment will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, worsening of a medical condition that was present at the initial visit will be considered a new adverse event and reported if there is suspicion of causal relationship with study drug. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE Form and assessed in terms of severity and relationship to study drug. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded on the AE Form beyond baseline.

C.5.4 Serious Adverse Events (SAEs)

Serious adverse event is defined to serve as a guide for regulatory reporting requirements and should not be confused with the severity (intensity) of an event. An AE is considered serious for this trial if it meets one or more of the following criteria:

- Fatal
- Life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/ birth defect

- Results in permanent impairment/damage of a body function/structure
- Requires intervention to prevent permanent impairment of a body function/structure

SAEs will be reported for the first 30 days the subject is on study drug (spironolactone or placebo). The subject must be monitored carefully until the condition disappears and/or the etiology is defined. All events included in trial outcomes are considered SAEs.

C.5.5 Unanticipated Adverse Drug Effects (UADEs)

An Unanticipated Adverse Drug Effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with the study drug, if that effect, problem, or death was:

- Not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or
- Any other unanticipated serious problem that relates to the rights, safety, or welfare of subjects.

We anticipate UADEs to be a rare event as this study drug is well-documented.

C.5.6 Reporting Procedures

All SAEs and UADEs will be considered time-sensitive events reportable to the TOPCAT CTCC within 48 hours in order to meet FDA reporting guidelines as specified by regulations. A summary of all other adverse events will be reported to the FDA at the time of the annual report and semi-annually to the DSMB.

Sponsor reporting of UADEs and other safety information requiring reporting to regulatory authorities and ethics committees in other participating countries will occur according to the local requirements of that country.

The sponsor will also inform all investigators concerned of relevant information about UADEs that could adversely affect the safety of study subjects.

C.6 Statistical Methods

C.6.1 Sample Size and Power

The primary composite endpoint of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure will be analyzed as the time to first occurrence of any such event, utilizing all follow-up data (censored at trial end) and a two-sided log rank test (.05 Type I error). The sample size calculation also assumes an average of 3.25 years follow-up across all subjects (minimum 2 years and maximum of 4.5 years with uniform accrual). It should also be noted that the CHARM-Preserved trial data suggest that the 3.5 year rate of CV deaths combined with heart failure hospitalization is approximately 27%. We expect that few patients will have aborted cardiac arrest as their first event for the composite endpoint, so placebo event rates in this study are expected to be only slightly higher than those in CHARM. A rate of 25.82% for an average of 3.25 years of follow-up corresponds to an event rate of 27.5% for an average of 3.5 years of follow-up. A 20% reduction in the number of such events can be observed with 90% power using 2,957 subjects (Shih, 1995). After 3% inflation of the sample size to account for interim looks at the data, 3,046 subjects would be necessary for this scenario (Table 6). The target sample size for this trial is 4,500 subjects, to maintain power in the possible setting of a Placebo combined event rate slightly lower than 25.82%, resulting in a slightly lower absolute difference between groups.

Because quality of life is a continuous measure, there will be high power to detect moderate to small differences in the change scores of the two treatment groups using a sample size of 4,500.

Table 6. Required Total Sample Size assuming 18.71% to 32.97% event rate in the placebo group over 3.25 years average follow-up, equal number of subjects in each treatment arm, Type I error = .05, two-sided test, 10% loss to follow-up, and 3% inflation for interim monitoring. Shading indicates inadequate power in the study.

3.25-YEAR Event Rate		Relative Reduction	80% Power N	85% Power N	90% Power N
Placebo*	**Treatment**				
18.71	14.97	20.0%	3410	3900	4564
21.08	16.86	20.0%	2948	3372	3944
23.44	18.75	20.0%	2580	2950	3452
25.82	20.65	20.0%	2276	2604	3046
28.19	22.55	20.0%	2024	2316	2710
30.58	24.46	20.0%	1810	2072	2424
32.97	26.38	20.0%	1628	1862	2178

*These placebo event rates correspond to event rates of 20.0%, 22.5%, 25.0%, 27.5%, 30.0%, 32.5%, and 35.0% over 3.5 years average follow-up.

C.6.2 Primary Endpoint Analysis Plan

C.6.2.a Primary Analysis of the Primary Endpoint

The primary analysis of all study endpoints will be conducted according to intention-to-treat (with no covariate adjustment). The primary endpoint, a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, at the end of the 4.5 year subject accrual and follow-up period, will be compared by trial arm (spironolactone vs. placebo) using a logrank test of time to first event from the time of randomization. For this composite endpoint the time to event will be the time at which the first observed event component of the composite endpoint is observed. This method will utilize all available follow-up (ranging from 2 to 4.5 years for subjects who complete the trial) to provide the most powerful treatment comparison.

For all time-to-event analyses, subjects will be censored at the time of their last contact, unless they undergo a heart transplant. If a patient undergoes a heart transplant, their time-to-event measurement for any trial outcome will be censored at the date of heart transplant or last contact, whichever occurs earlier. Every effort will be made to obtain vital status on all trial subjects whose last contact was earlier than planned (dropouts), initially through telephone tracking by site staff, and at the end of the trial using National Death Index and/or Social Security Death Index search (for U.S. subjects).

C.6.2.b Secondary Analysis of the Primary Endpoint

Secondary analyses of the primary study endpoint will be of three types:

1) Comparison of spironolactone vs. placebo will be made as a function of treatment compliance (randomized treatment taken at correct current dose on at least 80% of study days vs. less than 80% of study days). This method attempts to better estimate the magnitude of the true treatment effect although parameter estimates are at risk due to subject selection bias created by evaluation of treatment outside of the original randomization structure. We will also examine individual component events from all composite endpoints (CV mortality, CV-related hospitalization, sudden death, aborted cardiac arrest, and hospitalization for the management of heart failure incidence rate).

2) Cox proportional hazards regression (Cox, 1972) will be used to most efficiently estimate the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure (Pocock, 2002). For this analysis, age, diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes), and hospitalization for the management of heart failure in the 6 months prior to enrollment will be used for covariate adjustment, based on risk factor analyses of CHARM-Preserved trial data.
3) A descriptive dose response analysis, using currently prescribed mg/kg as a time-varying covariate in a Cox proportional hazards model, will be performed for subjects randomized to the active treatment. (Subjects randomized to the active treatment but currently taken off study drug will be assigned a current dose of 0 mg/kg.) The dose per kilogram may be confounded with how well a patient's CHF responds to the drug, and also confounded with how a patient's safety markers respond to the drug. Therefore, descriptive analyses of safety markers by currently prescribed mg/kg will also be performed.

C.6.2.c Interim Analyses

A group sequential analysis plan with four looks at the data including the final analysis is planned, with interim looks conducted at roughly equal intervals in terms of statistical information (number of observed events). An early stopping rule based on a Lan-Demets version of an O'Brien- Fleming group sequential plan (Lan et al., 1983; DeMets et al., 1994, O'Brien et al., 1979) is recommended. The final group sequential stopping rule will be determined by the DSMB.

The stopping boundaries for analysis of the primary endpoint, in conjunction with secondary endpoint comparisons and evaluation of safety (adverse event rates, including abnormal laboratory findings, all-cause mortality, and hospitalization for any reason) will all be considered by the DSMB to determine whether to stop a trial early. The TOPCAT trial will actively recruit subjects for 2.5 years. Maximum length of time on study will be 4.5 years, minimum 2 years.

C.6.2.d Subgroup Analyses

In order to identify the subject subgroups for whom spironolactone may be most or least beneficial, several pre-specified subgroup analyses will be conducted based on the subject's status at the time of randomization, namely:

- Ejection fraction based on local reading, above vs. below the median
- Age 50-64 vs. 65-74 vs. $\geq$ 75 years
- Male vs. female
- History of hypertension vs. no history of hypertension
- Diabetes mellitus (insulin-treated) vs. diabetes mellitus (non-insulin-treated) vs. no diabetes mellitus
- New York Heart Association congestive heart failure class II vs. (III or IV)
- Systolic blood pressure below vs. above median
- Systolic blood pressure < 140 mm Hg vs. systolic blood pressure $\geq$ 140 mm Hg (entry into trial with controlled vs. uncontrolled blood pressure)
- Use vs. no use of cardiac medications, specifically beta-blockers, ACE inhibitors, aspirin, angiotensin receptor blockers, and lipid-lowering agents, diuretics
- Use vs. no use of blood pressure lowering medication
- Pulse pressure above and below median
- Estimated GFR above and below median
- BMI above and below median
- Analysis by region: Americas, EU (including Israel), E. Europe
- Prior MI vs. no prior MI

Covariate by treatment group interaction tests will be performed to test whether the treatment effect is homogenous across subgroups. Statistical testing within subgroups will not be conducted unless the interaction test p-value is < 0.05.

C.6.3 Secondary Endpoints Analysis Plan

Secondary endpoints further characterizing the morbidity and disease-specific mortality of this patient population will also be analyzed using time-to-event methods as described in Section C.6.2.a for the primary trial endpoint. These secondary endpoints include: all-cause mortality, CV mortality and CV hospitalization composite, all components of composite endpoints, hospitalization for any reason, new onset of diabetes mellitus, development of atrial fibrillation, deterioration of renal function (twofold increase in baseline serum creatinine), new onset MI, new onset stroke, sudden death and/or aborted cardiac arrest. To account for multiple hospitalizations per subject, an incidence rate for hospitalization for heart failure in the two groups will be compared using a two-sample test based on the binomial distribution.

Laboratory indices of renal and metabolic function to assess drug safety will be analyzed using longitudinal linear regression methods, with normalizing transformations as appropriate.

Two general approaches to the analysis of quality of life and health status data will be taken. Analyses examining the influence of treatment on quality of life outcomes at specific follow up time points will be carried out through the use of analysis of covariance, adjusting for baseline status and other covariates. In order to utilize all available data describing the trajectory of subjects' functioning during the follow-up period, statistical models developed specifically for the analysis of longitudinal repeated measures data will also be used in secondary analyses to analyze the repeated quality of life measurements.

In addition to the general linear model described above, a generalized estimating equation model for ordinal multinomial data will be used to analyze repeated NYHA functional status measurements.

A challenge in the analysis of quality of life data relates to the unavoidable problem of missing data (due to death, incapacity, subject refusal, or loss to follow up). The proposed analytic strategy assumes that measurements are missing at random (Rubin, 1976), however it is possible that subjects with impaired quality of life may be less likely to complete the interviews. We will examine the sensitivity of our results to a variety of alternative assumptions regarding the relationship between quality of life and the likelihood of completing the instruments. Potential approaches will include imputing missing values with the natural "worst case" score for each of the quality of life endpoints and application of multiple imputation techniques (Schafer, 1997).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be the primary measure of quality of life (QOL). However, each QOL measure captures somewhat different aspects of QOL. Each QOL measure will be analyzed in a similar fashion. Qualitative agreement or disagreement in the direction of spironolactone's effect on each QOL measure will be described.

C.6.4 Site and Cohort Differences

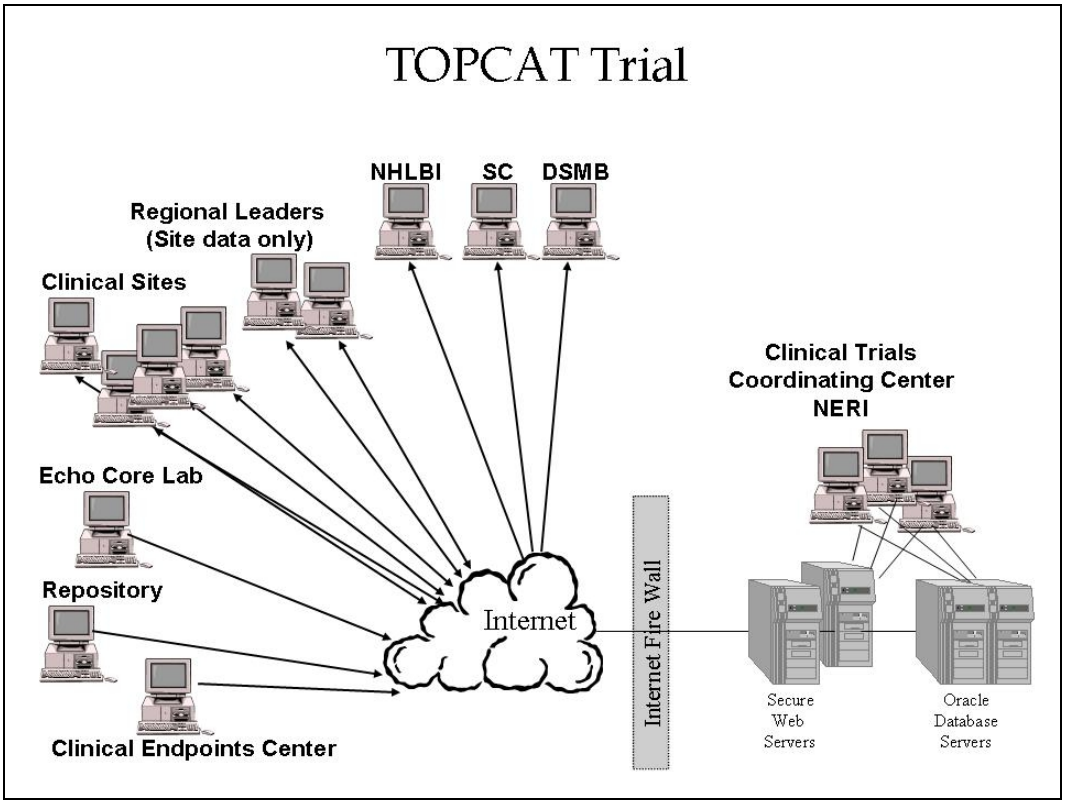
During the ongoing trial, analyses will be conducted on a periodic basis to assess geographic and site differences in protocol violation rates, enrollment rates, subject characteristics and adverse event rates. Differences identified may lead to a site visit to review subject data. The characteristics of subjects who are screened for but do not participate in the trial will also be compared with enrolled subjects. This analysis will allow assessment of the generalizability of trial findings and whether the enrolled subject cohort is representative of the entire patient population.

C.7 Data Management

C.7.1 Information Flow

Data will be sent to and received from several sources, including the clinical sites, the repository, the CEC, and the Echocardiography Core Laboratory. The flow of data among the units in this trial is illustrated in Figure 3. Clinical sites will enter data over the Internet using the Advanced Data Entry and Protocol Tracking (ADEPT) software, a customized and secure Web application. Sites will send blood and urine specimens directly to the repository for central processing, and records of receipt of such samples and final volumes stored will be electronically transmitted to the CTCC and stored in the ADEPT Data Management System (DMS). Echocardiograms stored on videotape or CD-ROM will be submitted to the CTCC. The CTCC will forward the echocardiograms to the Echocardiography Core Laboratory by FedEx. Results of interpretations/analyses performed by the Echocardiography Core Laboratory will be directly uploaded to an Oracle database at the CTCC or entered electronically using the ADEPT DMS.

Figure 3. Information Flow



C.7.2 Overview of Data Management System

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at the CTCC, and then stores these data centrally at the CTCC. Information entered into the data entry system will be by study I.D. number; names will not be linked with subject data in the database. Clinical sites will maintain records linking the patient name with the I.D. assigned for the study in locked files. Sites will have full access to their own data and be able to view this data remotely, over the Internet.

All study data will be stored on NERI's Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. Oracle archiving and backup system ensures minimal data loss.

C.7.3 Protocol Management and Reporting

In addition to providing robust data entry capabilities, ADEPT includes numerous features to streamline field operations and facilitate protocol adherence. Specifically, information regarding study protocol and relative order of study events (e.g., medical exams, questionnaires) are programmed into ADEPT. Web-based, real time reports in both graphical and tabular format are available to the funding agency, Executive Committee, DSMB, and site management staff to track participant accrual and data quality. Standard ADEPT reports include:

- Upcoming appointments;
- Study Instruments pending entry;
- Study Instruments pending edit resolution;
- Missing data rates;
- Time to physically key each study instrument;
- Audit logs for all edits to study data;
- Subjects with overdue visits;
- Protocol violations

In addition to these standard reports, custom reports can be readily developed within the ADEPT system. The CTCC will provide sites, laboratories and the sponsor on-line access to a variety of reports designed to summarize recruitment, retention and compliance with the study protocol.

C.8 Quality Assurance

C.8.1 Site Certification

C.8.1.a Regulatory Documentation:

The investigator(s) who are responsible for the conduct of this study, in compliance with this protocol, are identified on the FDA Form 1572 Statement of Investigator. The following regulatory documentation will be collected from each site prior to study initiation:

- IRB or EC approval of the protocol and informed consent form
- FDA Form 1572 Statement of Investigator ensuring compliance with 21 CFR 312 Investigational New Drug Application (or country equivalent)
- Curriculum vitae and current medical licenses from all investigators (PI and Sub-investigators)
- IRB/EC membership list and Federal Wide Assurance (FWA) certification ensuring compliance with 21 CFR 50 Protection of Human Subjects and 21 CFR 56 Institutional Review Boards

- Laboratory certification(s) as appropriate, and list of normal ranges
- Financial Disclosure and Conflict of Interest forms for all investigators (PI and Sub-investigators)
- Protocol Signature Page

C.8.1.b Site Contracts: Two contracts are required per site. One is legally binding and includes references to any insurance policy (Western European Regions). This is signed by a Clinical Center Administrator or by the Regional Leader. The second is the Investigator contract, signed by all Clinical Investigators. This contract obligates the Investigator to follow trial protocol and protocol related documents, adhere to GCPs, properly store and control study drug, accommodate and assist with site monitoring visits, complete any required reporting and make the best effort to recruit a minimum number of subjects at the site. All contracts will be translated as required.

C.8.1.c Training: Training will be completed on-line via a website established by the CTCC, or via a CD-ROM from the CTCC. Each training module will be followed by exercises to be completed by each individual to be certified for that module.

C.8.2 Site Monitoring

All sites will be visited at least once during the trial by representatives from the CTCC, Regional leader teams, and/or the sponsor. Additional visits will generally be reserved for sites with problems (audits for cause). The monitoring visit consists of reviewing and evaluating three separate components: conformance to IRB/EC and consent form requirements, compliance to trial protocol, and source document data verification. Any site found to be Unacceptable or Acceptable/Needs Follow-up on any monitoring visit is required to submit a written response and/or corrective action plan to the CTCC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension. Procedures for the termination/closure of a clinical site will be provided in the Manual of Procedures (MOP).

C.9 Close Out Procedures

C.9.1 Site Close Out Procedures

The CTCC will be responsible for notifying the regulatory authorities and ethics committees in the participating countries that the clinical trial has ended according to the laws and regulations of those countries. The trial may terminate at the planned target of 4.5 years after recruitment begins or at an earlier date if circumstances warrant. All visits must be scheduled and completed by June 30, 2010 and details regarding the study closeout period will be provided in the Manual of Procedures (MOP). The objectives of the closeout phase are to:

1) Evaluate the data as fully as possible to permit assessment of the effect of spironolactone on the primary endpoint.
2) Fulfill ethical obligations to trial participants.
3) Exploit the scientific value of study data as fully as possible.

C.9.2 Study Related Closeout Procedures

Closeout procedures will be developed by the Steering Committee and disseminated by the CTCC. Regardless of the timing and circumstances of the end of the study, closeout will proceed in two stages: An interim period for analysis and documentation of study results, and a final reporting of the main study results:

1) Interim - About 3-4 months will be needed to complete data collection and to prepare a manuscript for submission to an appropriate journal, reporting on the trial's main results.
2) Reporting of study results - The study results will be released to participating physicians, referring physicians, subjects, and the general community.

D. STUDY ORGANIZATION & POLICIES

D.1 Organization

The trial is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI is responsible for the overall direction of the trial. Day-to-day management of the study will be the responsibility of the NHLBI Project Office, the CTCC, and the Executive Committee. The Executive Committee (EC) consists of the Steering Committee Chair, the NHLBI, and the CTCC Principal Investigators. In addition to day-to-day management of the trial, their role is to make recommendations to the Steering Committee regarding study conduct. The Steering Committee (SC) has as its voting members the SC Chair, the NHLBI project officer, the CTCC PI, and other investigators appointed by NHLBI. The SC oversees all aspects of the study, including monitoring trial progress and review of trial results. The SC may also establish subcommittees to facilitate the conduct of the trial. The SC will meet at least twice a year.

The Clinical Trial Coordinating Center has responsibility for contracting clinical centers for the trial, developing the Manual of Procedures (MOP), data collection forms, and all related systems. The CTCC is responsible for all reports needed for Committee meetings, and for interim and final statistical analyses.

The Data and Safety Monitoring Board (DSMB) is composed of independent experts in cardiology, biostatistics, and ethics who are appointed by the Director of the NHLBI to monitor the conduct of the trial including enrollment, safety, and efficacy outcomes. The DSMB will meet regularly, at least twice a year. The DSMB chair will be notified of any events considered probable or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required.

The Drug Distribution Center is based in the U.S. and provides tablets of spironolactone and placebo. They are responsible for the packaging and distribution of study drug in collaboration with the CTCC.

The Regional Leaders for the trial are based in Boston, Switzerland, and Russia (see Table 7). The leaders will coordinate up to 110, 85, and 50 trial sites, respectively.

TABLE 7. Regional Leaders/Drug Distributors

Region	Leader	Drug Distributor
A. North and South America	CTCC	DHHS, Perry Point, MD
B. EU (including Israel)	SOCAR, Switzerland	Nottingham Clinical Research Group, UK
C. E. Europe	Evidence, Inc., Russia	Evidence Inc., Russia

Each Leader organization will be responsible within its Region for:

- Identification of country leaders (HF specialists) as required;
- Site recruitment and support of site certification (the CTCC will provide the materials and database access);
- Support and triage of site queries – especially clinical;
- Disbursement of site payments (funds and instructions provided by the CTCC);
- Site monitoring as requested by the CTCC;
- Region C: All data entry and editing.

D.2 Publications Policy

The Steering Committee will review all publications following the guidelines given below.

D.2.1 Data Analysis and Release of Results

The scientific integrity of the project requires that data from all of the sites be analyzed study-wide and reported as such. An individual center is expected not to separately report its data. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee. Additionally, all presentations and publications are expected to protect the integrity of the major study objectives. With the exception of interim analyses for the DSMB, endpoint data will not be presented prior to the release of the main study results. Recommendations as to the timing of presentation of endpoint data and the meetings at which they are presented will be provided by the Steering Committee.

D.2.2 Review Process

Each manuscript or abstract must be submitted to the Steering Committee for review of its scientific merit and appropriateness for submission. The Steering Committee may recommend changes to the authors and will make a final decision about submission. Each manuscript should also be sent to the NHLBI for review prior to submission.

D.2.3 Primary Outcome Papers, Abstracts and Presentations

The primary outcome papers are defined as those that present outcome data for the entire trial cohort. The determination of whether or not a particular analysis represents a primary outcome report will be made by the Steering Committee. Authorship on the baseline and primary outcome papers will be "The TOPCAT TRIAL Investigators." For such manuscripts, there will be an appendix containing the names of all participants in the study and their organizational affiliation. Papers and abstracts that are not primary outcome papers will have named authors based upon involvement and ending with the phrase "for the TOPCAT TRIAL Investigators." The same appendix will be appended to non-primary outcome manuscripts as for primary outcome papers. All manuscripts for submission must be approved by the Steering Committee.

D.3 Substudies

D.3.1 Introduction

Two types of substudies will be considered: ancillary studies and databank studies. Ancillary studies are those that require data collection beyond the primary protocol and/or propose using specimens in the trial repository, while Databank studies are based upon data collected as part of the main study. Participation in the substudies is open to all study investigators. In order to assure that all substudies are of high scientific merit, the DSMB will review applications for ancillary studies and make recommendations regarding merit to the Steering Committee. Databank studies will be considered directly by the Steering Committee or a designated subcommittee.

D.3.2 Ancillary Studies

An ancillary study uses trial participants in an investigation that is not described in the trial protocol and involves collecting new data that are not part of the trial data set. Such studies must be carried out by applicant investigators or in conjunction with trial investigators. In general, any such study will require an independent consent form, IRB/EC approval, and an independent funding source. Ancillary studies must be approved by the Steering Committee and any external review committees. All applications for ancillary studies must be submitted in writing to the Steering Committee. The scientific merit of the application will be reviewed and assurance provided that the timing of the resulting publication(s) will not interfere with the main publications of the study.

D.3.3 Databank Studies

A databank study utilizes data that have been collected as part of the main trial in order to answer a question different from that posed by the main protocol. It usually involves only data analysis and generally does not require supplemental funding because it uses the resources of the CTCC. Such studies require the approval of the Steering Committee, are based on scientific merit of the application, assurance that reporting of the databank study will not interfere with the main publications of the study, and availability of CTCC resources.

D.3.4 Application Review Process

The Steering Committee (or designated subcommittee) will review applications for substudies in a timely fashion. If several applications for similar substudies are received, collaboration and joint resubmission will be encouraged. Applications from non-trial investigators will be entertained but will be assigned lower priority than similar applications from trial investigators.

D.3.5 Other Competing Studies

Simultaneous participation by trial subjects in other prospective investigations requires the prior approval of the Steering Committee and is generally to be discouraged. It is recognized that the exigencies of patient care may require that the subject be entered into a compassionate use protocol. If this occurs, the CTCC should be notified within 10 days.

D.3.6 Data Storage and Analysis

All data collection forms for ancillary studies will be stored at the sites and the final dataset will be copied to the CTCC for merging into the primary dataset.

E. REFERENCES

Ahmed A, Roseman JM, Duxbury AS, Allman RM, DeLong JF. Correlates and outcomes of preserved left ventricular systolic function among older adults hospitalized with heart failure. *Am Heart J* 2002;144:365-72.

Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169-80

Cox DR. Regression and life tables (with discussion). *J Roy Stat Soc Series B* 1972; 34, 187-202.

DeMets DL and Lan KKG. Interim analysis: the alpha spending function approach. *Statistics in Medicine* 1994; 13:1341-1352.

Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc* 1987;82:171-200.

Efron B. Bootstrap methods: another look at the Jackknife. *Ann Stat* 1979;7:1-26.

Heart Disease and Stroke Statistics--2003 Update. Dallas: American Heart Association.

Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; 22:6A-13A.

Hsiao WC, Braun P, Dunn D, et al. Results and policy implications of the resource-based relative value scale. *N Engl J Med* 1988;319:881-888.

Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796-802.

Jeunemaitre X, Chatellier G, Kreft-Jais C et al. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol 1987; 60:820-825

Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.

Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144-50.

Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; 70:659-663.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-70.

McDermott MM, Feinglass J, Lee PI, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997;134:728-36.

McMurray J et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Programme. *Eur J Heart Failure* 2003; 5:261-70.

O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; 35:549-566.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341(10):709-17.

Pitt B, Remme W, Zannad F, et al, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-1321.

Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment, and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in Medicine* 2002; 21: 2917-30.

Rubin DB. Inference and missing data. *Biometrika* 1976;63:581-592.

Schafer JL. *Analysis of incomplete multivariate data.* London, Chapman and Hall, 1997.

Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-9.

Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Controlled Clinical Trials* 1995;16:395-407.

Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol* 2003;41:1510-8.

Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.

Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.

Yusuf S, Pfeffer M, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* September 2003, 362(9386):777-81.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis* 1974; 27:365-375

Treatment **O**f **P**reserved **C**ardiac function heart failure with an **A**ldosterone an**T**agonist

TOPCAT

IND Number: 71,883

Version 1.6 – April 20, 2007

Funded by the National Heart, Lung, and Blood Institute, NIH/DHHS

New England Research Institutes, Inc.
9 Galen Street
Watertown, MA 02472 USA

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PROTOCOL SIGNATURE PAGE

I have read the following protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drug and the conduct of the study.

I will use the informed consent form approved by the National Heart, Lung and Blood Institute and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and as specified in the Manual of Procedures (MOP) and, in particular, I agree to report any adverse events, serious adverse events, and unanticipated adverse drug effects (UADEs) as defined in Sections C.5.4 – C.5.6 of this protocol.

I further agree that the National Heart, Lung and Blood Institute, the appropriate regulatory authorities and staff from the regional coordinating centers have access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including study drug) provided by the National Heart, Lung and Blood Institute and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance with the protocol and Good Clinical Practice guidelines, as well as local regulations; and to accept respective revisions conducted by authorized personnel of National Heart, Lung and Blood Institute and by competent authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Principal Investigator(s)		
Principal Investigator(s)		

TRIAL OF ALDOSTERONE ANTAGONIST THERAPY IN ADULTS WITH PRESERVED EJECTION FRACTION CONGESTIVE HEART FAILURE

TABLE OF CONTENTS

New England Research Institutes, Inc.
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PROTOCOL OVERVIEW (ABSTRACT)

This trial is a multicenter, international, randomized, double blind placebo-controlled trial of the aldosterone antagonist, spironolactone, in 4500 adults with heart failure and left ventricular ejection fraction of at least 45%, recruited from over 150 clinical centers. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Secondary endpoints include all-cause mortality, new onset of diabetes mellitus, atrial fibrillation, and quality of life. The trial duration is 4.25 years, with 2.0 years for subject enrollment and an additional 2.25 years of follow-up, with an average subject follow-up of 3.0 years. Dynamic balancing by clinical center at the time of randomization will be used to ensure that the distribution of clinical centers are similar in the two treatment groups. The study population will include those who meet the inclusion criteria, some of which are:

- Male or female age 50 years or older;
- Heart failure defined as one symptom and one sign present in the last 12 months (described in protocol);
- Left ventricular ejection fraction $\geq$ 45% (per local reading);
- Controlled systolic blood pressure (SBP), defined as: SBP < 140 mm Hg or SBP from 140-160 mm Hg if subject is being treated with 3 or more medications;
- Serum potassium < 5.0 mmol/L prior to randomization;
- At least one hospitalization in the last 12 months for which heart failure was a major component of the hospitalization OR elevated BNP or N-terminal pro-BNP within the last 30 days;
- Willing to comply with scheduled visits, as outlined in the protocol;
- Signed informed consent form.

Exclusion criteria can be found in Section C.1.2.

Study drug dosing will start at 15 mg/day and may be titrated up to 45 mg according to subject tolerance, safety parameters, and symptoms, and will be continued throughout the trial. Following each change in the dosing regimen, subjects will have blood drawn for safety labs 1 week later. Subjects will take study medication every day according to specific instructions. All other treatments will follow accepted local standards for medical care for specific morbidities as described by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) Practice Guidelines, as appropriate. Such treatments may also be adjusted by the local medical practitioner, if necessary. All randomized subjects will be followed even if study drug is discontinued ahead of schedule, except in the case that the subject refuses to participate further in the study.

Follow-up study visits to monitor symptoms, medications, and events and to dispense study drug will occur every 4 months during the first year and every 6 months thereafter. Quality of life will be assessed three times in the first year of the trial and annually thereafter. An electrocardiogram (ECG) will be performed at baseline only. Blood, DNA, and urine samples will be collected from a subset of subjects and stored in a repository for later use in ancillary studies. All clinical endpoints will be adjudicated by a clinical events committee in a blinded fashion. Continual safety surveillance has been built into the study by means of the proposed dosing and safety assessment regimen described in the protocol. The 15 mg dose of spironolactone was formulated to reduce the risks and side-effects associated with this drug. The Data and Safety Monitoring Board (DSMB) will meet regularly, at least twice a year. The DSMB chair will be notified of any events considered probably or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required. The

study will be conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and applicable national and local regulations.

A. SPECIFIC AIMS

A.1 Primary Aim

To determine if treatment with spironolactone can produce a clinically meaningful reduction in cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Primary Outcome Measure: Cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite. Treatment arms will be compared using time-to-event analysis.

Secondary Outcome Measures:

- All-cause mortality
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

A.2 Secondary Aim #1

To determine if treatment with spironolactone can produce a clinically meaningful reduction in new clinical diagnoses compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- New onset of diabetes mellitus
- Development of atrial fibrillation
- Myocardial infarction (fatal and non-fatal)
- Stroke (fatal and non-fatal)
- Deterioration of renal function
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

A.3 Secondary Aim #2

To evaluate the relative impact of spironolactone versus placebo on functional status and quality of life in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- Quality of life, as measured by the:
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) – Primary quality of life outcome measure
  - EuroQOL (EQ5D) visual analog scale
  - McMaster Overall Treatment Evaluation (OTE)
  - Patient Health Questionnaire (depression scale)

A.4 Secondary Aim #3

To determine if treatment with spironolactone is safe, compared with placebo, in adults with heart failure and left ventricular ejection of at least 45%.

Safety Outcome Measures:

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function.

B. BACKGROUND

B.1 Prior Literature/Studies

Chronic heart failure (CHF) is a broad syndrome characterized by the relative inability of the heart to adequately meet metabolic demands of tissues without an abnormal elevation in filling pressure, which contributes to the clinically recognizable constellation of signs and symptoms. Although the etiologies of CHF are diverse, the premature mortality, incumbent morbidity, and associated healthcare burdens are not cause specific. Regardless of the etiology, CHF represents a progressive disorder that afflicts approximately 10% of the elderly and is the most common reason for hospitalization of patients over 65 years old (Hunt et al., 2001), with a prevalence of 4.9 million people in the United States, and 550,000 new cases diagnosed annually (American Heart Association, 2003). Epidemiologic and hospital-based studies have demonstrated that among patients with newly diagnosed CHF in the community, 43% to 54% of patients have preserved systolic function (PSF) (Senni et al., 1998; Vasan et al., 1999; Ahmed et al., 2002; McDermott et al., 1997). CHF patients without low ejection fractions have been variably described as having HF-PSF, heart failure with preserved ejection fraction, or diastolic heart failure. Although each term has relative merits, they do not completely characterize the complex interactions between systolic and diastolic function, vascular-ventricular coupling, neuroendocrine activation, and cardiorenal adaptations that result in the syndrome of heart failure. Pragmatically, since a quantitative left ventricular ejection fraction (LVEF) is used to define the well-studied systolic dysfunction (LVEF<40%) component of the heart failure population, an LVEF ≥40% can be used to identify the remaining proportion of heart failure patients with relatively PSF.

Relative to systolic dysfunction CHF, HF-PSF has a higher proportion of women and the elderly. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Trials, with concurrent screening for both systolic dysfunction and HF-PSF, found a similar incidence of atrial fibrillation and diabetes mellitus across ejection fraction groups but a lower frequency of prior myocardial infarction in those with HF-PSF (McMurray et al., 2003). In the Cardiovascular Health Study, approximately 67% of women older than 65 years of age had PSF compared with 42% of men (Kitzman et al., 2001). The estimate of the prevalence of this syndrome varies dramatically based upon the study design with a range from 13 to 74% reported among those with heart failure (Ahmed et al., 2002). The annual mortality rate has been estimated to be between 1.3 and 17.5% (Vasan et al., 1995). In the recently completed CHARM-Preserved trial, involving 3025 patients with symptomatic heart failure and an LVEF greater than 40% (median 54%), the mortality rate was 5.5 per 100 person-years, which though less than the approximately 10 per 100 person-years for heart failure with depressed LVEF, was still threefold higher than age-matched subjects without heart failure (Yusuf et al., 2003). These patients also have significant morbidity. CHF patients with PSF (HF-PSF) have a high risk of re-hospitalization for HF and functional decline, reduced exercise performance, and worse quality of life than non-HF patients (Hundley et al., 2001; Kitzman et al., 2002; Smith et al., 2003).

B.2 Rationale for This Trial

B.2.1 Rationale for Investigation of New Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors in CHF Patients with PSF

This randomized double-blind placebo-controlled trial is designed to test the hypothesis that the addition of a mineralocorticoid receptor blocker to conventional therapy would improve clinical outcomes as assessed by reduced risk of death and hospitalizations for major cardiovascular events in patients with symptomatic heart failure and a quantitative LVEF at or above 45%. Despite the persistent advances over the past two decades in the treatment and prevention of cardiovascular diseases, the incidence of heart failure continues to increase. In some respects, this increase is a consequence of successes in the management of other life-threatening cardiovascular disorders, producing a larger reservoir of older individuals surviving with coexisting major cardiovascular comorbidities. Moreover, patients with heart failure and PSF have a particularly high rate of recurrent hospitalizations for a variety of major cardiovascular complications. The efficacy demonstrated with two separate mineralocorticoid receptor blockers, reducing the risk of death and hospitalizations for heart failure in patients with symptomatic heart failure and reduced ejection fraction, and acute MI complicated by heart failure, (spironolactone and eplerenone, respectively), provides a strong rationale for testing a mineralocorticoid receptor blocker in patients with heart failure and relatively preserved systolic ejection fraction. In addition to the potential reductions of individual risks of cardiovascular morbidity and mortality, the benefits achieved in this understudied population that utilizes considerable health care resources, would have major public health implications – reductions in both mortality and in costly hospitalizations.

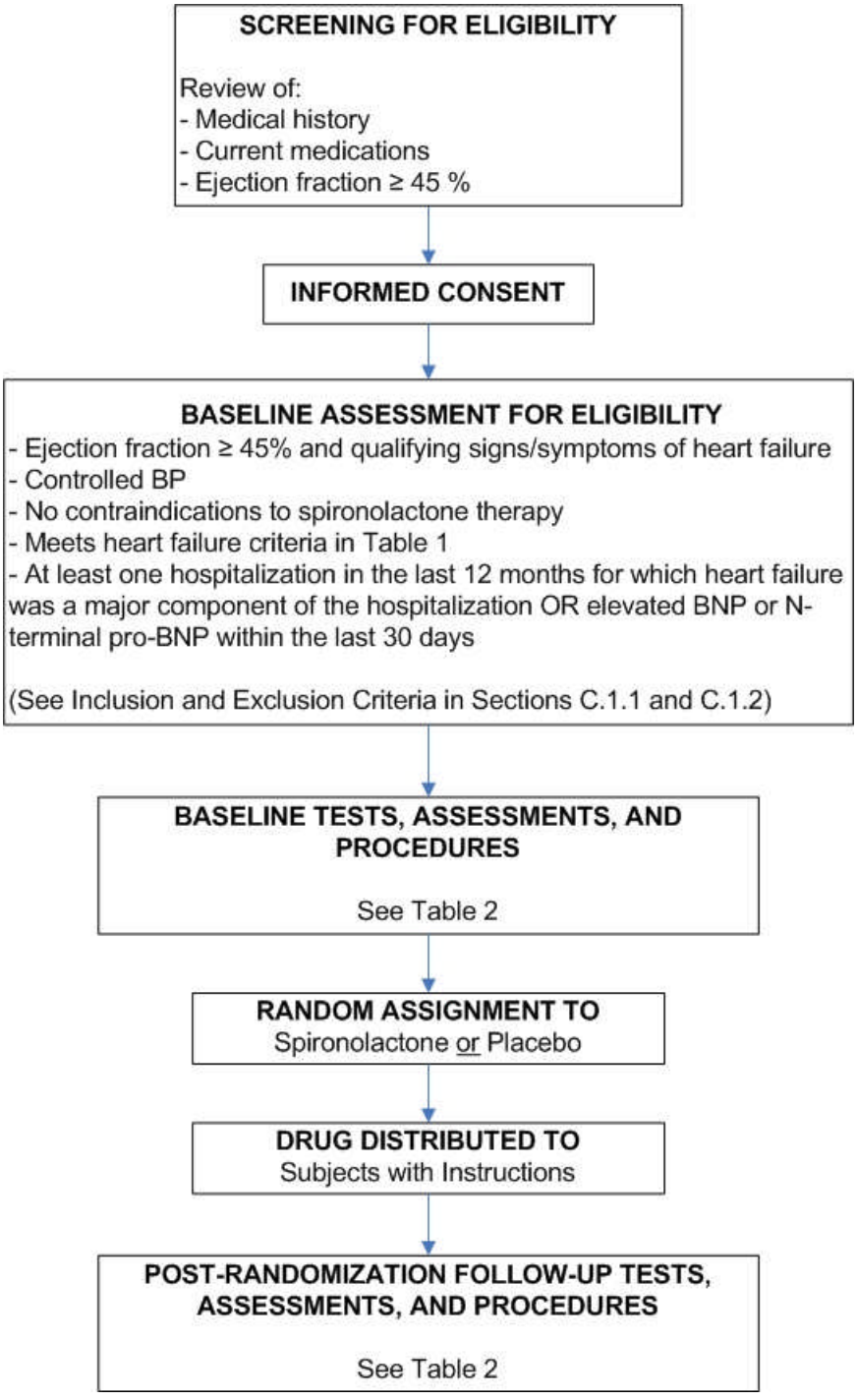
B.2.2 Rationale for Use of Spironolactone

There are two candidates for aldosterone inhibition: the more familiar generic drug spironolactone and the newer eplerenone (owned by Pfizer). The important clinical benefits of these two mineralocorticoid receptor blockers are supported by mechanistic animal studies demonstrating that these agents reduce interstitial fibrosis, ventricular remodeling, vascular oxidative stress, improved endothelial function and have other favorable actions that could be anticipated to translate into clinical benefits in patients with heart failure and PSF. Both drugs have demonstrated improvement in survival in high-risk cardiovascular patients by mechanisms that likely go well beyond the renal effects of aldosterone inhibition. Spironolactone has an associated 10% rate of gynecomastia in males, which is not a side effect of eplerenone. However, from the Randomized Aldactone Evaluation Study (RALES) trial experience, this side effect resulted in negligible discontinuance of the drug. In the TOPCAT trial, gynecomastia is not anticipated to be a major issue as the population recruited for the trial will include a large number of females, many of whom are postmenopausal.

C. STUDY DESIGN AND METHODS

Next page.

Figure 1
SUBJECT FLOW IN TRIAL



C.1 Participants

C.1.1 Inclusion Criteria

In order for a subject to be eligible for inclusion in the trial, all of the following criteria must be met:

1. Male or female; Age 50 years or older;
2. Heart failure as defined in Table 1. One symptom must be present at the time of screening and one sign must be present in the last 12 months. Heart failure eligibility should be carefully monitored and documented in the subject's medical records.
3. Left ventricular ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable) ≥ 45% (per local reading). The ejection fraction must have been obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction;
4. Controlled systolic BP, defined as a target systolic BP < 140 mm Hg. Subjects with BP up to and including 160 mm Hg are eligible for enrollment if on 3 or more medications to control BP.
5. Serum potassium < 5.0 mmol/L prior to randomization;
6. At least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization. Transient heart failure in the context of myocardial infarction (MI) does not qualify.

   OR

   Brain natriuretic peptide (BNP) in the last 30 days ≥ 100 pg/ml or N-terminal pro-BNP ≥ 360 pg/ml and not explained by another disease entity;
7. Women of child-bearing potential must have a negative serum/urine pregnancy test within 72 hours prior to randomization, must not be lactating, and must agree to use an effective method of contraception during the entire course of study participation.
8. Willing to comply with scheduled visits, as outlined in Table 2;
9. Informed consent form signed by the subject.

TABLE 1. Criteria for Diagnosing Heart Failure

SYMPTOMS (at least one must be present at the time of screening)	SIGNS (at least one in last 12 mo.)
• Paroxysmal nocturnal dyspnea • Orthopnea • Dyspnea on mild or moderate exertion	• Any rales post cough • Jugular venous pressure (JVP) ≥ 10 cm H_2O • Lower extremity edema • Chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly

C.1.2 Exclusion Criteria

If a subject meets any one of the following criteria then he/she is ineligible for enrollment in the trial:

1. Severe systemic illness with life expectancy judged less than three years;
2. Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator;
3. Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;

4. Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial;
5. Atrial fibrillation with a resting heart rate > 90 bpm;
6. Myocardial infarction in past 90 days;
7. Coronary artery bypass graft surgery in past 90 days;
8. Percutaneous coronary intervention in past 30 days;
9. Heart transplant recipient;
10. Currently implanted left ventricular assist device;
11. Stroke in past 90 days;
12. Systolic blood pressure (SBP) > 160 mm Hg;
13. Known orthostatic hypotension;
14. Gastrointestinal disorder that could interfere with study drug absorption;
15. Use of any aldosterone antagonist or potassium sparing medication in last 14 days or any known condition that would require the use of an aldosterone antagonist during study participation;
16. Known intolerance to aldosterone antagonists;
17. Current lithium use;
18. Current participation (including prior 30 days) in any other therapeutic trial;
19. Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol;
20. History of hyperkalemia (serum potassium ≥ 5.5 mmol/L) in the past six months or serum potassium ≥ 5.0 mmol/L within the past two weeks;
21. Severe renal dysfunction, defined as an estimated glomerular filtration rate (GFR) < 30 ml/min (per the Modification of Diet in Renal Disease (MDRD) 4-component study equation). Subjects with serum creatinine ≥ 2.5 mg/dl are also excluded even if their GFR is ≥ 30 ml/min;
22. Known chronic hepatic disease, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels > 3.0 times the upper limit of normal as read at the local lab.

C.1.3 Human Subjects Considerations

C.1.3.a Informed Consent

A waiver of consent may be requested from the Institutional Review Board/Ethics Committee (IRB/EC) of each clinical center in order to submit to the Clinical Trial Coordinating Center (CTCC) a completed screening form on non-randomized subjects. Written informed consent will be obtained from all potentially eligible trial subjects. Consent from a surrogate will not be permitted.

The repository will be a side-arm study of the main protocol. All sites participating in the side-arm study will approach all potentially eligible trial subjects for consent. A separate informed consent for each specimen type collected will be obtained prior to randomization. There are two portions to the repository sub-study: (1) DNA portion and (2) blood and urine portion. Random codes will be assigned to the repository samples and subjects may request to have their repository samples withdrawn and destroyed at any time while the trial is ongoing. At the completion of the trial, the repository samples and the clinical database will be double-coded. The clinical dataset will be anonymized such that it could not be linked back to the study subjects. Once the link between the subject ID and the repository sample code has been destroyed, subjects will no longer have the option to withdraw and/or destroy their repository samples. Repository samples with associated clinical data will not be made available for future research studies until the database and samples have been anonymized at the end of the trial.

The repository samples will be stored for future testing in a central repository maintained by NHLBI and may be kept for up to 30 years after the close of the study.

Other than random assignment to either spironolactone or placebo, all subjects will undergo routine care for heart failure with PSF.

Before the first trial-related procedure for a subject is performed, the investigator will obtain informed consent from the study subject by means of a dated and signed consent approved by the local IRB/EC in his/her country.

The informed consent process will be performed in accordance with the ICH guidelines for Good Clinical Practice (GCP), local laws and regulations.

The process will involve two steps. In the first step, potential study subjects will be given an information sheet and adequate time to study the information. The second step, obtaining informed consent, may only take place after the potential study subject has had adequate time to study the information sheet, ask any questions and to decide whether or not to participate in the trial. Both the consent and the patient information sheet will be provided to the subject in the local language.

The informed consent process includes individual discussion with the subject about what study participation will involve. The information to be discussed will include all the information provided in the TOPCAT trial patient information sheet. The discussion process includes informing the study subject both verbally and in writing that:

-if he/she refuses to participate in the study, the quality of medical care he/she receives will not be affected and
-he/she may withdraw at any time without giving reason and without affecting future care and
-without disclosing his/her name, relevant medical and personal data will be disclosed to the sponsor and regional coordinating centers who are obliged to use the information anonymously and solely for scientific purposes and
-his/her medical records may be reviewed during on-site monitoring, and may be inspected by auditors and/or regulatory authorities who are obliged to confidentiality and
-confidentiality will be maintained at all times according to local data protection laws.

Both the date a potential study subject is given the information sheet and the date the study subject gives informed consent must be recorded. The study subject will be given a copy of the signed informed consent form and information sheet.

After informed consent has been provided by the study subject, the declaration of consent will be kept in the patient file at the clinical site and will be made available for audit purposes. If the filing of the original signed consent form in the subject's hospital file is not permitted by the hospital or clinical setting, it must be filed in the investigator files and an indication that consent was obtained (with the date specified) should be noted in the medical files.

C.1.3.b Patient Confidentiality

Patient confidentiality will be maintained according to ICH guidelines for GCP and applicable local and national data protection laws. A study identification number will be assigned to each subject. The link between patient name and I.D. number will be stored only at the clinical center where the subject receives his/her care, thereby ensuring that all data transferred from a

subject's medical records to a study report form and any process derived from the study report form is handled confidentially.

C.1.3.c DNA Confidentiality

Blood samples prepared for DNA extraction will be sent to the repository. The sample will not have the original study I.D. number, the patient's name, or any other information that could identify the subject. The specific procedures will be detailed in the Manual of Procedures (MOP) and the Repository Instruction Manual.

C.1.3.d Potential Risks

Spironolactone has been licensed for the treatment of heart failure in all of the countries participating in the TOPCAT trial for many years. The most common risks of taking spironolactone include hyperkalemia (observed at < 1.0% in the RALES trial with no serious consequences), hyponatremia, headache, drowsiness, lethargy, diarrhea, cramps, bleeding, gastritis, vomiting, anorexia, nausea, rash, pruritis, and urticaria. Gynecomastia, erectile dysfunction, and post-menopausal bleeding are less common. Hirsutism, agranulocytosis, and hyperchloremic metabolic acidosis have also been reported.

Although breast tenderness and gynecomastia have been reported in up to 10% of male patients treated with spironolactone, the risk of this side effect is dose-related and uncommon in patients treated with daily doses of 50 mg or less (as planned in this trial). In the RALES trial, gynecomastia resulted in negligible discontinuance of the drug and the condition is expected to be less of a problem in the TOPCAT trial as the study will be investigating patients with HF-PSF, a large proportion of whom are post-menopausal women.

A potentially serious side effect sometimes seen in patients treated with spironolactone is hyperkalemia. People with impaired renal function are considered to be at higher risk of hyperkalemia - an observation used to define the exclusion criteria of first the RALES trial and now TOPCAT. The investigators in the RALES trial attributed the observed incidence of hyperkalemia (1% in the placebo group and 2% in the spironolactone-treated group) to the exclusion of patients with elevated serum creatinine and potassium at baseline (and also to the relatively low treatment dose of spironolactone: the mean dose was 26 mg). Similar exclusion criteria will be used in the TOPCAT trial; however, the starting dose of spironolactone will be lower and renal function will be more accurately and reliably defined at baseline by estimated GFR. By careful evaluation of the pre-disposing factors for hyperkalemia and use of close monitoring of serum potassium during the study, it is anticipated that the rate of clinically significant hyperkalemia seen in TOPCAT will be similar to or possibly lower than that observed in the RALES trial.

Therapeutic trials investigating heart failure have been performed to date almost exclusively on patients with systolic dysfunction. However, now there is a growing awareness that a large proportion of patients with heart failure have preserved systolic function and that survival of these patients is also adversely affected. While treatment has been shown to be useful in patients with heart failure with systolic dysfunction, this is an area which has been understudied in those heart failure patients with PSF. Consequently much still remains to be learned about HF-PSF and its treatment.

C.1.3.e Potential Benefits

Subjects enrolled in this trial who are receiving active drug may receive a benefit. Also, there may be considerable benefit to future patients with HF-PSF as a result of the medical knowledge obtained from this study.

C.2 Trial Enrollment

C.2.1 Recruitment Protocol

The Principal Investigator at each private practice or clinical center, his or her designee, and the coordinator will have the responsibility for case finding and subject recruitment. The coordinator will conduct a chart review, while complying with local institution Health Insurance Portability and Accountability Act (HIPAA) requirements, to identify potentially eligible subjects. The coordinator will contact the subject per local guidelines to assess interest in the trial and to schedule an office or clinic visit for determination of full eligibility. Subjects may also be approached for participation while in-hospital if the subject is potentially eligible based on chart review. It should be noted that a subject may be screened for trial eligibility more than once during the accrual period.

C.2.2 Stratification

Due to the large number of clinical centers and potentially small number of enrolled subjects at some sites, dynamic balancing (Zelen, 1974) rather than stratified randomization across sites will be utilized to ensure that the distributions of clinical centers are similar in the two treatment groups. This approach will prevent the creation of excessively small stratum sizes. In addition, subjects will be stratified on inclusion criterion #6. Stratum I will include subjects selected based on a hospitalization in the 12 months prior to enrollment with a heart failure diagnosis and stratum II will include those subjects not reporting a hospitalization in the prior 12 months for which heart failure was a major component (for whom elevated BNP is required).

C.2.3 Blinding

Subjects and treating physicians will be blinded to whether subjects are receiving spironolactone or placebo. Because the trial has a double-blind design, safety laboratory tests will be performed for each subject for the duration of the trial, regardless of treatment arm. Similarly, monitoring of potential side effects will be continuous and irrespective of treatment assignment. While unmasking of the drug assignment for an individual subject is not anticipated given the proposed dosing and safety-monitoring regimen described in Section C.3, a procedure for unblinding will be included in the Manual of Procedures (MOP).

C.2.4 Baseline Visit and Randomization

After written informed consent is obtained, a baseline visit will occur, during which confirmation of eligibility will be obtained and baseline labs will be drawn. The maximum allowable timeframe between study baseline visit and the randomization date is 14 days. If baseline laboratory values were collected more then two weeks before the date of randomization, the clinic sites should repeat baseline labs, update any changes in the subject's medical history and concomitant medications, and confirm that the subject still meets all the study inclusion/exclusion criteria prior to randomization. Laboratory values obtained within the two week interval are acceptable as long as there were no inter-current change in medications and/or no borderline laboratory values. Subjects will be randomly assigned in a 1:1 ratio using permuted blocks to receive either spironolactone or placebo. Randomization will be accomplished over the Internet using randomization software accessed via a secure website. After verifying key eligibility criteria and supplying clinical center information, the randomization software will return a Treatment Allocation Code (A thru L) corresponding to either spironolactone or placebo. Labels containing treatment allocation code will be on the drug packet to verify correct assignment.

C.3 Treatment

C.3.1 Description of Study Medication

Study drug supplies will be provided by the Department of Health and Human Services (DHHS) Program Support Center in Perry Point, MD. Shipments will consist of the following:

1. Bottles containing 150 spironolactone 15 mg tablets
2. Bottles containing 150 placebo tablets, identical in size and appearance to the 15 mg spironolactone tablets.

Both the spironolactone 15 mg tablets and matching placebo are manufactured by URL Mutual Pharmaceutical in Philadelphia, PA, USA in accordance with federal regulations and ICH guidelines for Good Manufacturing Practices.

C.3.2 Randomization Procedures

Subjects will be assigned in the order they are enrolled into the study, to receive the allocated treatment according to a computer-generated randomization plan using NERI's Verandi software package. Once a subject has been assigned a Treatment Allocation Code, the subject will remain on the same study drug treatment allocation code for the duration of the study.

C.3.3 Study Drug Administration

Study medication will be dispensed at Randomization, 4 Month visit, 8 Month visit, 12 Month visit, and every 6 months thereafter. Previously dispensed drug supplies are to be brought in at each subsequent visit to verify drug compliance. The volume of unused tablets or number of tablets will be recorded on the appropriate case report form (CRF), and the tablets will be returned to the subject. Site personnel will instruct the subject on the importance of compliance. A guideline for study drug dispensing is in the Manual of Operations.

The first dose of study drug will be administered as soon as possible after written informed consent has been obtained, baseline procedures have been performed, and there is confirmation that laboratory results are within acceptable parameters.

C.3.4 Study Drug Titration and Dosing Regimen

All subjects randomized into the study will begin on an initial dose of 15 mg daily (i.e. one tablet by mouth every day). The titration schedule and safety assessment intervals are illustrated in Figure 2. After 4 weeks, the dose should be increased to 30 mg daily (i.e. two tablets by mouth every day) if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the treating physician has the option to increase the dose to 45 mg daily at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily. Safety labs (i.e., electrolytes and chemistries) will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped). Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. Chemistries will include BUN and creatinine.

Once the subject is appropriately titrated, the dosing regimen (i.e., 15 mg, 30 mg, or 45 mg by mouth every day) should remain stable **unless** scheduled laboratory results exceed the safety parameters, and the potassium value is confirmed by a non-hemolyzed sample (i.e. a sample drawn into a tube with anti-coagulant) The flowchart in Figure 2 illustrates the various pathways for dose titration of the study drug as follows:

1. Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; and if the subject is already on the lowest dose (i.e. 15 mg) and if there no alternative explanations for the elevated potassium level (e.g. subjects are taking potassium supplements), then the study drug should be permanently discontinued if deemed appropriate by the treating physician and/or TOPCAT Medical Monitors. Once a downward dose adjustment has been made, the drug should not be uptitrated beyond this level for the trial duration.

2. Study drug should be permanently discontinued if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen, if there no alternative explanations for the elevated potassium level.

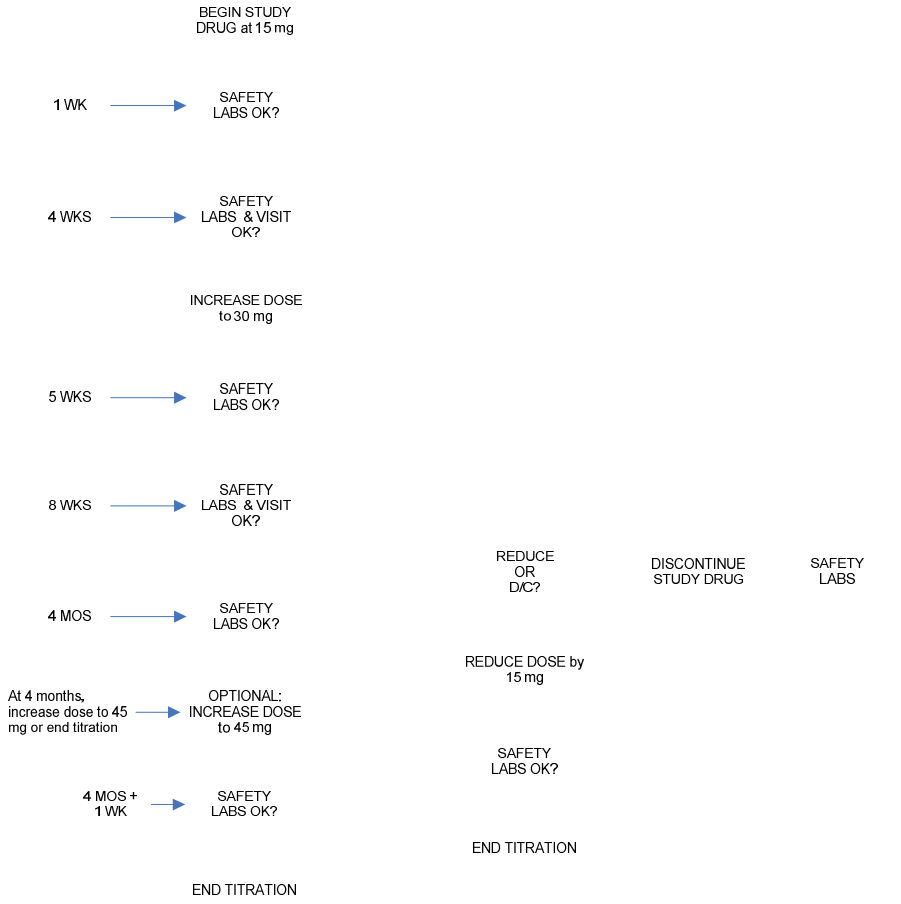
   NOTE: Treating physicians may consult the TOPCAT Medical Monitors prior to discontinuing any subjects on study drug as a result of elevated potassium levels. Since there is some room for clinical judgment, subjects could potentially continue to take study drug as long as they are properly monitored. Treating physicians may opt to control a subject's potassium level by adjusting his/her potassium supplement intake (if deemed appropriate and safe) or by recommending a low potassium diet.

3. Reinitiate study drug, at the discretion of the treating physician, if the dosing regimen is interrupted due to non-compliance. If a subject is eligible for study drug reinitiation, the physician should choose from one the following three options:
   - Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation)
   - Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable.
   - Do not reinitiate study drug

If possible, drug should be reinitiated within one week of drug discontinuation. The number of times that drug can be reinitiated is at the discretion of the treating physician.

Figure 2. Study Drug Titration and Safety Assessment Schedule

The study drug titration and safety assessment schedule is illustrated in this figure.



NOTE: Treating physicians should consult the TOPCAT Medical Monitors prior to permanently discontinuing any subjects on study drug as a result of elevated potassium levels. Since there is some room for clinical judgment, subjects could potentially continue to take study drug as long as they are properly monitored. Treating physicians may opt to control a subject's potassium level by adjusting his/her potassium supplement intake (if deemed appropriate and safe) or by recommending a low potassium diet.

Titration: Initial dose: **15 mg/day.** After 4 weeks, the dose should be increased to **30 mg/day** if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the investigator has the option to increase the dose to **45 mg/day** at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily.

Reduce drug: Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; if the subject is already on the lowest dose (i.e. 15 mg), the study drug should be permanently discontinued. Once a downward dose adjustment has been made, the study drug should not be uptitrated beyond this level for the trial duration.

Discontinue drug: Permanently discontinue study drug if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen.

Safety labs: Collect safety labs (i.e., electrolytes and chemistries) at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped). Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. Chemistries will include BUN and creatinine.

Reinitiation (after non-compliance): If the dosing regimen is interrupted due to non-compliance, study drug may be reinitiated at the discretion of the treating physician. If a subject is eligible for drug reinitiation, the physician should choose from one the following three options:

- Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation); or
- Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable; or
- Do not reinitiate study drug

If possible, study drug should be reinitiated within one week of drug discontinuation. The number of times study drug may be reinitiated after non-compliance is at the discretion of the treating physician.

C.3.5 Concomitant Medication

Subjects will be treated with other medications at the discretion of their cardiologist and/or primary care provider. At study visits, current medications will be recorded on the study forms. If a subject begins open-label use of any aldosterone antagonist or potassium-sparing diuretic at any time during the study, withdrawal from study drug is required.

The following drug interactions have been observed with spironolactone:

- ACE inhibitors or ARB – may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics – may be associated with hypokalemia
- Corticosteroids, ACTH – may be associated with hypokalemia
- Pressor amines (e.g. norepinephrine) – may reduce vascular responsiveness
- Skeletal muscle relaxants – may amplify muscle relaxant responsiveness
- Lithium – may lead to lithium toxicity
- NSAIDs – may be associated with hyperkalemia
- Cardiac glycosides (e.g. digoxin) – may lead to digoxin toxicity
- Anticoagulants (e.g. warfarin, heparin) – may reduce the effects of anticoagulation

C.3.6 Indications for Permanent Discontinuation of Study Drug

- Persistent hyperkalemia (potassium ≥ 6.0 mmol/L, based on a non-hemolyzed sample)
- Potassium ≥ 5.5 mmol/L, based on a non-hemolyzed sample, and subject on lowest dose of study drug (15 mg). Other explanations for the elevated potassium level should be ruled out.
- Anaphylactoid reaction or intolerance
- Serum creatinine $\geq$ 3.0 mg/dl, or at a lower threshold per local physician judgment
- Open label use of any aldosterone antagonist or potassium-sparing diuretic that cannot be discontinued for valid clinical reason
- Other adverse events that require discontinuation of study drug in the judgment of the study investigator, such as a medical course that is incompatible with the concomitant use of spironolactone.

The reason and the circumstances for permanent discontinuation of study drug will be documented. If study drug is permanently discontinued, the subject will continue to be followed until the end of the trial period.

C.3.7 Indications for Withdrawal From the Study

- Subject refusal to continue in the study
- Heart transplantation

All protocol-specified visits and follow-up procedures should be performed for every subject enrolled in the trial, even if the study drug is discontinued. If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. The reason for withdrawal will be documented for all subjects withdrawn from the study. If the withdrawing subject is unwilling to have his/her medical records reviewed until the end of the trial period (to document vital status and cause of death), he/she must submit a written refusal. Subjects may withdraw consent from the repository sub-study but continue participating in the main study. Subjects who withdraw consent from the main study are automatically withdrawn from the sub-study.

C.3.8 Study Completion

A subject will be considered to have completed the study if he/she has completed follow-up until the end of the trial period, undergoes heart transplantation, or dies. All subjects will be followed for a minimum of 2.25 years and a maximum of 4.25 years.

Clinic sites must complete all the necessary "End of Study" CRFs for all study subjects even if the end of study visit falls in-between the study scheduled clinic visits. Please refer to the MOP and ADEPT user guide for additional information.

C.3.9 Subject Compliance

Study drug compliance will be assessed at each study visit by comparing the expected vs. actual consumption of study drug tablets. The subject will bring all remaining study drug to the follow-up visit. The study coordinator will measure and record the volume of remaining tablets, and a new 4 or 6 month supply (depending on the visit schedule) will be dispensed.

C.3.10 Drug Accountability Log

All study drug supplies (i.e. spironolactone 15 mg and corresponding placebo tablets and bottles) provided by the DHHS Program Support Center to the investigator for use in the clinical study must be accounted for in written documentation that must be maintained by the investigator and that will be monitored by the CTCC.

Forms to record dispensing of study medication will be provided with the initial shipment of the study medication. A copy of the complete records of study drug accountability for all supplies received for the study must be provided to the CTCC as part of the close-out procedure for the study. The drug accountability records must be retained by the investigator along with the subjects' study records.

C.3.11 Remote Monitoring for Eligibility

To ensure patient eligibility, the CTCC may perform regular remote monitoring "visits" on all clinic sites by requesting specific source documents from a random group of subjects throughout the study. Source documents for study eligibility monitoring purposes may include ECHO reports, lab data, and hospital discharge summaries.

C.3.12 Code Break

The Treatment Allocation Code may be broken if an emergency situation arises that in the Investigator's opinion requires knowledge of the code.

A request for unblinding should only be made in situations where knowledge of the treatment assignment will actually affect the subsequent care or decision-making process for care of the trial subject. It should be assumed that the trial subject will remain in the trial and will continue adherence to the trial protocol after the event is resolved. Therefore, every effort should be made to maintain trial participation in a blinded nature. It is anticipated that all assignments will remain blinded for the trial duration and that all subjects will be appropriately monitored for safety.

Refer to the Manual of Procedures (MOP) for a description of the process for code break.

C.4 Measurements

C.4.1 Schedule of Measurement

See next page.

Table 2. Schedule of Trial Measurements

	Record Screening	Baseline Screening	Randomization and Drug Distribution	1 Week	4 Weeks	5 Weeks	8 Weeks	4 Months	8 Months	12 Months	18 Months	24, 36, 48 Months	30, 42, 54 Months
Medical History	X	X											
Current Medications	X	X			X		X	X	X	X	X	X	X
Echocardiogram*	X												
Physical Exam, Wt., Vital Signs		X			X		X	X	X	X	X	X	X
Assessment of Study Drug Compliance					X		X	X	X	X	X	X	X
Blood Studies**		X		X***	X	X***	X	X	X	X	X	X	X
ECG		X											
Adverse Event Monitoring					X		X	X	X	X	X	X	X
Urine Microalbuminuria		X								X		X	
QOL****		X						X		X		X	
Repository Specimens													
Urine Specimen		X								X			
Blood Specimen		X								X			
DNA Specimen		X								X			

* Ejection fraction obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction.

** Blood Studies (local lab):

- Baseline blood studies include: CBC, electrolytes, BUN, creatinine, blood glucose, and LFTs and should be done within 2 weeks prior to the randomization date CBC will include WBC count, hematocrit, hemoglobin, and platelet count. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. LFTs will include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, and albumin.
- Follow-up safety blood studies include: electrolytes, BUN and creatinine. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2.

*** Safety labs will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

**** OTE instrument will only be administered at the 4 and 12 month visits; KCCQ and EQ-5D instruments will only be administered at Baseline, 4 and 12 month visits and annually thereafter; Patient Health Questionnaire instrument will only be administered at Baseline and 12 month visits and annually thereafter.

C.4.1.a Record Screening (Table 2)

Record screening will include review of past medical history and current medications. The most recent echocardiogram from the past 6 months will be evaluated to determine if ejection fraction is ≥ 45% (per local reading). It is preferred that the qualifying ejection fraction be obtained by echocardiography. A subset of the echocardiograms (video copy or digital image is acceptable) utilized for screening must be submitted to the Brigham and Women's Hospital Echocardiography Core Laboratory for QC purposes. Each site is required to submit the first 2 echos used to determine eligibility to the Echocardiography Core Laboratory which will read these pre-eligibility echocardiograms for a central QC of ejection fraction. Subjects may withdraw or decline to release their echocardiograms to the Echocardiography Core Laboratory at any time during the study. Clinic sites should notify the CTCC immediately of a subject's request to withdraw his/her echocardiogram from the core lab. Ejection fraction obtained by radionuclide ventriculography or angiography is also acceptable in instances where an echocardiogram suitable for quantification is not available.

C.4.1.b Baseline Screening (Table 2)

At the baseline screening visit, the subject will have a physical examination, including vital signs. Blood will be drawn for CBC, electrolytes, BUN, creatinine, blood glucose, and liver function tests (LFTs). CBC will include WBC count, hematocrit, hemoglobin, and platelet count. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. LFTs will include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, and albumin. A urine test for microalbuminuria will be conducted. Creatinine, potassium, and LFTs, as well as the blood pressure measurements will be used to confirm eligibility. Current medication use will be reviewed to confirm that the subject does not meet exclusion criteria. Age, gender, race, and serum creatinine concentration will be obtained in order to calculate an estimated GFR using the 4-component MDRD Study prediction equation. The GFR estimate will be used to determine whether a subject has acceptable renal function to be enrolled in this study (see exclusion criterion 21). The initial medical history will focus on demographics, cardiac risk factors, and the prior 12 months for recent hospitalizations and procedures. An electrocardiogram (ECG) will be obtained at baseline. The subject will be asked to complete the first quality of life questionnaires. Procedures for the physical examination, blood draw, and urine test will be detailed in the Manual of Procedures (MOP). After randomization, two bottles of study drug will be dispensed with instructions.

All subjects from sites participating in the repository sub-study will be approached for consent to provide blood and urine samples for the repository, including a whole blood sample for DNA extraction.

C.4.1.c Follow-Up Visits (Table 2)

Health status and study drug compliance will be evaluated at scheduled visits throughout the study. Subjects must plan to have blood drawn for safety labs at 1 week post drug initiation/dose change. They will be scheduled to have an office visit and safety labs at 4 weeks post drug initiation. If the study drug is increased at this time, they will have blood work one week after dose change (week 5), and then full evaluation at 8 weeks. Subsequent planned visits will be scheduled every four months for the first year and every six months thereafter. Specifics for study drug titration are described in Section C.3.4 and Figure 2. Unplanned visits will be determined by the treating physician for symptoms, abnormal lab work, or other reasons.

At each office visit, the following will be obtained by short interview: current signs/symptoms consistent with HF and with administration of study drug, and current medications (subjects will be asked to bring these to each visit for accurate inventory). Blood pressure will be taken and

recorded. Every effort should be made to control blood pressure throughout the course of follow-up. Body weight will be recorded. Electrolytes, BUN, and creatinine, will be drawn to assess study drug safety. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. A urine test for microalbuminuria will be conducted annually.

Four quality of life instruments will be administered to trial subjects in the appropriate language according to the Schedule of Measurement (Table 2).

Blood and urine specimens for the repository will be obtained at baseline and 12 months from a subset of subjects.

If drug reduction/discontinuance is indicated by the chemistry panel results, a follow-up visit will be scheduled within one week at which time the subject will be evaluated for change in course of therapy.

Towards the end of the trial follow-up period, the Social Security or National Death Index will be searched for any subjects of unknown vital status in the U.S. Similar procedures will be implemented as feasible in other countries, with the assistance of the Regional Leaders.

C.4.1.d Windows for Visits

The acceptable windows for study visits are shown in Table 3. Safety monitoring during the titration period must be conducted at the study site. If for some reason a subject is unable to complete a study visit in person for a visit at Month 4 or later, the QOL instruments will be mailed to the subject along with a hospital-addressed stamped envelope for return of the completed questionnaires to the clinical site. The QOL instruments will be assigned for analysis to the nearest available window based on completion date.

Table 3. Acceptable Windows for Study Visits

Visit	Window
Week 1, 4, 5, 8	$\pm$ 3 days
Month 4	$\pm$ 2 weeks
Month 8, 12	$\pm$ 2 weeks
Later Visits	$\pm$ 4 weeks

C.4.2 Outcome Variables

Outcome variables have been chosen that will best capture the multi-faceted impact of spironolactone on heart failure with relatively PSF, a disease with significant morbidity, mortality, and associated costs. The primary trial endpoint is **a composite of** cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Table 4 provides a summary of all outcome measures for the trial. In addition, all components of composite endpoints will be reported.

Table 4. Trial Outcome Measures

Primary Outcome

- Cardiovascular (CV) mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite.

Secondary Outcomes

Morbidity and Mortality

- **All-cause mortality**
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

New Clinical Findings

- New onset of diabetes mellitus
- Development of atrial fibrillation
- Myocardial infarction (fatal and non-fatal)
- Stroke (fatal and non-fatal)
- Deterioration of renal function (see Section C.4.2.b)
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

Quality of Life

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol (EQ5D) visual analog scale
- McMaster Overall Treatment Evaluation (OTE)
- Patient Health Questionnaire (depression scale)

Safety Measures

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function

C.4.2.a Morbidity and Mortality

Vital and hospitalization status will be monitored through subject contacts and by interview and medical record review at the clinic site. If a death occurs, the nurse coordinator will complete a death form indicating the date, time, and official cause of death, as well as a description of events leading up to the death.

Selected outcome forms and supporting documentation will be forwarded from the CTCC to the Clinical Endpoints Committee (CEC) for review as described in the TOPCAT Manual of Procedures (MOP).

C.4.2.b New Clinical Findings

New onset of diabetes mellitus will be assessed by physical exam, symptoms, and defined by measurement of blood glucose and introduction of anti-diabetic medication. New diagnosis of atrial fibrillation will be made by reported symptoms and clinically indicated monitoring of heart rhythm. Deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal. Stroke and MI will be centrally adjudicated and defined in the CEC Manual of Procedures (MOP).

C.4.2.c Quality of Life

The primary goals of heart failure management are improving patient function, slowing disease progression, and improving quality of life. The quantification of this latter treatment goal requires the use of a health-related quality of life instrument, typically including a range of domains of health status. Four instruments will be administered to trial subjects in the appropriate language according to the Schedule of Measurement (Table 2). The overall quality of life assessment at each visit typically will not exceed 12-15 minutes per subject.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be used as the primary endpoint for evaluation of functional status and quality of life in this trial. The KCCQ is a self-administered 23-item questionnaire taking approximately 4-6 minutes that measures physical limitation, symptoms (frequency, severity and recent change over time), quality of life, social interference, and self-efficacy. The KCCQ has been used in several recent and ongoing heart failure trials, including the EPHESUS trial.

In addition to the KCCQ, a brief generic health status measure, the "feeling thermometer" from the EuroQOL Health Status Questionnaire (EQ-5D; Brazier et al., 1993), which is a visual analog (0-100) scale, ranging from the worst imaginable health state (0) to the best imaginable health state (100) will be administered, as well as the McMaster Overall Treatment Evaluation (OTE) (Juniper et al. 1994). The OTE has 3 items addressing the overall effect of the treatment according to whether a subject has improved or deteriorated with respect to symptoms related to heart failure since the treatment started (therefore this instrument will not be part of the baseline QOL battery). If subjects indicate an improvement or deterioration, they will be asked to score the magnitude and the importance of the perceived change on a 7-point scale. The items will be combined to form a 15-graded scale, ranging from the worst deterioration (-7) to the highest improvement (+7) with "No change" (0) as the middle score. The OTE will be administered only at the 4 and 12 month follow-up visits.

Finally, the Patient Health Questionnaire, a 9-item health scale derived from the PRIME-MD that includes a measure of depression severity, will be administered.

C.4.3 Event Adjudication

New England Research Institutes, Inc. (NERI) as the CTCC will serve as the primary liaison to the sites for reporting of study endpoints and will be responsible for ensuring the required endpoint-related data and source documents are collected. The Clinical Endpoint Committee at the Brigham and Women's Hospital in Boston will serve as the CEC and will be responsible for reviewing and adjudicating all suspected study endpoints consisting of cardiovascular vs. non-cardiovascular death, hospitalization for congestive heart failure, cardiac arrest, myocardial infarction, stroke, new onset of diabetes mellitus, new onset of atrial fibrillation, and hospitalization for the management of ventricular tachycardia.

The primary objective of the CEC is consistent and unbiased review and adjudication of study endpoints throughout the course of the trial. At the CEC, each event will be assigned and reviewed by a Physician Reviewer. The Physician Reviewer will document key details of the event, make a preliminary decision, and present his/her findings at the CEC meeting. In certain instances, the Chairman will generate a case precedent, an internal consistency measure, for difficult or noteworthy events that set a precedent for how future events should be regarded.

For each endpoint, the Physician Reviewers are responsible for providing a final adjudication for each event along with appropriate chart documentation describing the key details related to the event as well as rationale supporting their adjudication. The CEC maintains strict internal quality assurance measures in order to maintain the high-level quality of adjudicated data and in addition, all operations are conducted under the International Conference on Harmonization Good Clinical Practices (ICH/GCP) and Code of Federal Regulations (21 CFR 312, 21 CFR 50, 21 CFR 56). The CEC maintains Standard Operating Procedures for all functions and procedures and is subject to review and audit by the sponsor, or their representatives, and regulatory authorities. A 10% sample for re-adjudication will be randomly and blindly inserted in the review process by the CTCC and the results will be reported at CEC meetings. Details of CEC procedures will be included in the TOPCAT trial Manual of Procedures (MOP).

C.4.4 Repository

The repository will be a sub-study of the main protocol and subjects will be asked to provide additional informed consent to participate. For those subjects who consent, urine and blood specimens will be collected at baseline and 12 months, spanning an interval when most events and physiological changes are likely to occur. A whole blood sample for DNA extraction will also be collected for those subjects who consent. The proposed collections are summarized in Table 5. SeraCare BioServices currently serves as the long term NHLBI repository. All pre-barcode labeled collection and shipping containers will be provided to the clinical centers. The repository specimens will be stored for later use in ancillary studies yet to be approved and funded. Details of sample handling, storage, and shipping procedures are included in the TOPCAT MOP.

TABLE 5. Specimen Collection

Serum	• Up to three 10 ml tubes whole blood, collected and processed for storage of plasma and serum r as detailed in the Manual of Procedures (MOP) • Aliquot into pre-labeled cryovials and store at -20^{o}C • Shipment to repository when shipping rack filled
Urine	• 20 ml urine (mid-stream, time of day recorded but unrestricted)Aliquot into pre labeled cryovials and stored at -20 ^{o}C • Shipment to repository as above
DNA	• Packed cells from whole blood collected in EDTA tubes will be used for the DNA extraction.

C.5 Adverse Events

C.5.1 Definition

For purposes of this study, an adverse event (AE) is any untoward medical occurrence in a subject which is unrelated, possibly, probably or definitely related to study drug (spironolactone or placebo). In addition, all events included in trial outcomes are considered AEs, whether or not they are attributed to the study drug. Clinic sites must report all AEs (related or not related

to study drug) to the CTCC in a timely manner. AEs are automatically reported to the CTCC when the sites complete the AE CRFs in ADEPT.

C.5.2 Classification of Adverse Events

C.5.2.a Severity

The severity (intensity) of each AE will be assessed according to the following definitions:

Mild: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity/intensity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

Severe: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the drug. Treatment for symptom(s) may be given.

Life-threatening: Symptom(s) of a sufficient severity/intensity to cause the subject to be at immediate risk of death. Treatment for symptom(s) may be given.

C.5.2.b Relationship

The temporal/causal relationship between the study drug (spironolactone or placebo) will be determined by the investigator according to the following definitions:

Definite: Clearly related to the study drug.

Probable: Likely (high suspicion) related to the study drug.

Possible: May be related to the study drug.

Unrelated: Clearly not related to the study drug.

C.5.3 Data Collection Procedures for Adverse Events

Adverse events will be recorded according to the date and time of first occurrence, severity, and duration, as well as any treatment prescribed. Following initiation of study drug dosing, all new or continuing adverse events that were not present at enrollment will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, worsening of a medical condition that was present at the initial visit will be considered a new adverse event and reported if there is suspicion of causal relationship with study drug. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE Form and assessed in terms of severity and relationship to study drug. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded on the AE Form.

C.5.4 Serious Adverse Events (SAEs)

The term “Serious Adverse Event” is defined to serve as a guide for regulatory reporting requirements and should not be confused with the severity (intensity) of an event. An AE is considered serious for this trial if it meets one or more of the following criteria:

- Fatal
- Life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- Congenital anomaly/ birth defect
- Results in permanent impairment/damage of a body function/structure
- Requires intervention to prevent permanent impairment of a body function/structure

Clinic sites must report all SAEs to the CTCC within 48 hours. SAEs are automatically reported to the CTCC when the sites complete the SAE CRFs in ADEPT. The subject must be monitored carefully until the condition disappears and/or the etiology is defined.

C.5.5 Unanticipated Adverse Drug Effects (UADEs)

An Unanticipated Adverse Drug Effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with the study drug, if that effect, problem, or death was:

- Not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or
- Any other unanticipated serious problem that relates to the rights, safety, or welfare of subjects.

We anticipate UADEs to be rare events as this study drug is well-documented.

C.5.6 Reporting Procedures

All SAEs and UADEs will be considered time-sensitive events reportable to the TOPCAT CTCC within 48 hours in order to meet FDA reporting guidelines as specified by regulations. A summary of all other adverse events will be reported to the FDA at the time of the annual report and semi-annually to the DSMB.

Sponsor reporting of UADEs and other safety information requiring reporting to regulatory authorities and ethics committees in other participating countries will occur according to the local requirements of that country.

The sponsor will also inform all investigators concerned of relevant information about UADEs that could adversely affect the safety of study subjects.

C.6 Statistical Methods

C.6.1 Sample Size and Power

The primary composite endpoint of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure will be analyzed as the time to first occurrence of any such event, utilizing all follow-up data (censored at trial end) and a two-sided log rank test (.05 Type I error). The sample size calculation also assumes an average of 3.0 years follow-up (minimum 2.25 years and maximum of 4.25 years), with quarterly enrollment ratios of 1.1% in the first quarter, 4.4% in the second quarter, 8.9% in the third quarter, 17.8% in quarters four through seven, and 14.4% in the eighth quarter of enrollment. It should also be noted that the CHARM-Preserved trial data suggest that the 3.5 year rate of CV deaths combined with heart failure hospitalization is approximately 27%. We expect that few patients will have aborted cardiac arrest as their first event for the composite endpoint, so placebo event rates in this study are expected to be only slightly higher than those in CHARM. A rate of 24.09% for an average of 3.0. years of follow-up corresponds to an event rate of 27.5% for an average of 3.5 years of follow-up. A 20% reduction in the number of such events can be observed with 90% power using 3,208 subjects (Shih, 1995). After 3% inflation of the sample size to account for interim looks at the data, 3,304 subjects would be necessary for this scenario. The target sample size

for this trial is 4,500 subjects, to maintain power in the possible setting of a Placebo combined event rate slightly lower than 24.09%, resulting in a slightly lower absolute difference between groups. In case enrollment is lower than anticipated, power has also been calculated assuming quarterly enrollments of 50, 150, 300, 600, 600, 700, 700, and 400, for a total of 3,500 subjects with average follow-up of 3.0 years. Table 6 shows the available power for both the expected enrollment scenario and this more conservative enrollment scenario, calculated using Shih's macro (Shih, 1995), and taking into account a sample size inflation of 3% to account for interim monitoring.

Because quality of life is a continuous measure, there will be high power to detect moderate to small differences in the change scores of the two treatment groups using a sample size of 4,500.

Table 6. Achievable statistical power, assuming 17.41% to 30.87% event rate in the placebo group over 3. 0 years average follow-up, equal number of subjects in each treatment arm, Type I error = .05, two-sided test, 10% loss to follow-up, and 3% inflation for interim monitoring. Shading indicates inadequate power in the study.

3.25-YEAR Event Rate		Relative Reduction	4500 subjects	3500 subjects
Placebo*	**Treatment**			
17.41	13.93	20.0%	87.2%	78.0%
19.63	15.70	20.0%	91.4%	83.6%
21.85	17.48	20.0%	94.5%	88.1%
24.09	19.27	20.0%	96.6%	91.6%
26.34	21.07	20.0%	98.0%	94.3%
28.60	22.88	20.0%	98.9%	96.2%
30.87	24.70	20.0%	99.4%	97.6%

*These placebo event rates correspond to event rates of 20.0%, 22.5%, 25.0%, 27.5%, 30.0%, 32.5%, and 35.0% over 3.5 years average follow-up.

C.6.2 Primary Endpoint Analysis Plan

C.6.2.a Primary Analysis of the Primary Endpoint

The primary analysis of all study endpoints will be conducted according to intention-to-treat (with no covariate adjustment). The primary endpoint, a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, at the end of the 4.25 year subject accrual and follow-up period, will be compared by trial arm (spironolactone vs. placebo) using a logrank test of time to first event from the time of randomization. For this composite endpoint the time to event will be the time at which the first observed event component of the composite endpoint is observed. This method will utilize all available follow-up (ranging from 2.25 to 4.25 years for subjects who complete the trial) to provide the most powerful treatment comparison.

For all time-to-event analyses, subjects will be censored at the time of their last contact, unless they undergo a heart transplant. If a patient undergoes a heart transplant, their time-to-event measurement for any trial outcome will be censored at the date of heart transplant or last contact, whichever occurs earlier. Every effort will be made to obtain vital status on all trial subjects whose last contact was earlier than planned (dropouts), initially through telephone tracking by site staff, and at the end of the trial using National Death Index and/or Social Security Death Index search (for U.S. subjects).

C.6.2.b Secondary Analysis of the Primary Endpoint

Secondary analyses of the primary study endpoint will be of three types:

1) Comparison of spironolactone vs. placebo will be made as a function of treatment compliance (randomized treatment taken at correct current dose on at least 80% of study days vs. less than 80% of study days). This method attempts to better estimate the magnitude of the true treatment effect although parameter estimates are at risk due to subject selection bias created by evaluation of treatment outside of the original randomization structure.

2) Cox proportional hazards regression (Cox, 1972) will be used to most efficiently estimate the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure (Pocock, 2002). For this analysis, age, diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes), and hospitalization for the management of heart failure in the 6 months prior to enrollment will be used for covariate adjustment, based on risk factor analyses of CHARM-Preserved trial data.

3) A descriptive dose response analysis, using currently prescribed mg/kg as a time-varying covariate in a Cox proportional hazards model, will be performed for subjects randomized to the active treatment. (Subjects randomized to the active treatment but currently taken off study drug will be assigned a current dose of 0 mg/kg.) The dose per kilogram may be confounded with how well a patient's CHF responds to the drug, and also confounded with how a patient's safety markers respond to the drug. Therefore, descriptive analyses of safety markers by currently prescribed mg/kg will also be performed.

C.6.2.c Interim Analyses

A group sequential analysis plan is proposed, with four looks at the data including the final analysis, and with the interim looks conducted at roughly equal intervals in terms of statistical information (number of observed events). However, the DSMB may decide to increase the number of interim looks. Conditional power will be calculated at each look. Asymmetric stopping boundaries are proposed in Table 7a, using an alpha-spending approach (DeMets et al., 1994). These boundaries are designed to accommodate a possible increase in the number of looks that the DSMB chooses to have, and to accommodate any reasonable spacing of looks. The proposed boundaries will facilitate early stopping of the trial if there are safety concerns, i.e. if the event rate is much higher in the spironolactone treatment arm than in the placebo treatment arm. Early halting for efficacy, if the event rate is much higher in the placebo arm than the spironolactone arm, may also occur. However, stronger statistical evidence will be required to halt early for efficacy than for safety. The p-value boundaries shown in Table 7b are based on the assumption that there are 4 looks (3 interim, 1 final) that take place at exactly equal intervals in terms of statistical information. Note that if the study continues to its planned sample size, a more extreme p-value will be needed to declare spironolactone to be worse that placebo, than to declare spironolactone to be better than placebo. This is because more of the "safety alpha" than the "efficacy alpha" will have been spent during the interim looks. If the actual number of looks is different, or if the looks take place at different information times, the p-values for the final look will be adjusted accordingly. For example, Table 7c shows the boundaries if there are 7 looks (6 interim, 1 final) at equally spaced information times. The final group sequential stopping rule will be determined by the DSMB.

Table 7a. Proposed interim monitoring boundaries for safety and efficacy.		
	P-value boundaries for early stopping (two-sided p-values based on log-rank test)	
Look	For safety (observed spironolactone event rate higher than observed placebo event rate)	For efficacy (observed placebo event rate higher than observed spironolactone event rate)
Any interim look with ≤ half the expected events observed	.001	.0001
Any interim look with > half the expected events observed	.01	.001
Final look	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0

Table 7b. Proposed interim monitoring boundaries for safety and efficacy: Example with 4 looks, equally spaced in terms of number of expected events		
	P-value boundaries for early stopping (two-sided p-values based on log-rank test)	
Look	For safety (observed spironolactone event rate higher than observed placebo event rate)	For efficacy (observed placebo event rate higher than observed spironolactone event rate)
Interim look when 25% of the expected events have been observed	.001	.0001
Interim look when 50% of the expected events have been observed	.001	.0001
Interim look when 75% of the expected events have been observed	.01	.001
Final look	.0476	.0498

Table 7c. Proposed interim monitoring boundaries for safety and efficacy: Example with 7 looks, equally spaced in terms of number of expected events		
	P-value boundaries for early stopping (two-sided p-values based on log-rank test)	
Look	For safety (observed spironolactone event rate higher than observed placebo event rate)	For efficacy (observed placebo event rate higher than observed spironolactone event rate)
Interim look when 1/7 of the expected events have	.001	.0001

been observed		
Interim look when 2/7 of the expected events have been observed	.001	.0001
Interim look when 3/7 of the expected events have been observed	.001	.0001
Interim look when 4/7 of the expected events have been observed	.01	.001

The stopping boundaries for analysis of the primary endpoint, in conjunction with secondary endpoint comparisons and evaluation of safety (adverse event rates, including abnormal laboratory findings, all-cause mortality, and hospitalization for any reason) will all be considered by the DSMB to determine whether to stop the trial early. The TOPCAT trial will actively recruit subjects for 2.0 years. Maximum length of time on study will be 4.25 years, minimum 2.25 years.

C.6.2.d Subgroup Analyses

In order to identify the subject subgroups for whom spironolactone may be most or least beneficial, several pre-specified subgroup analyses will be conducted based on the subject's status at the time of randomization, namely:

- Ejection fraction based on local reading, above vs. below the median
- Age 50-64 vs. 65-74 vs. $\geq$ 75 years
- Male vs. female
- History of hypertension vs. no history of hypertension
- Diabetes mellitus (insulin-treated) vs. diabetes mellitus (non-insulin-treated) vs. no diabetes mellitus
- New York Heart Association congestive heart failure class II vs. (III or IV)
- Systolic blood pressure below vs. above median
- Systolic blood pressure < 140 mm Hg vs. systolic blood pressure $\geq$ 140 mm Hg (entry into trial with controlled vs. uncontrolled blood pressure)
- Use vs. no use of cardiac medications, specifically beta-blockers, ACE inhibitors, aspirin, angiotensin receptor blockers, and lipid-lowering agents, diuretics
- Use vs. no use of blood pressure lowering medication
- Pulse pressure above and below median
- Estimated GFR above and below median
- BMI above and below median
- Analysis by region: Americas and E. Europe
- Prior MI vs. no prior MI

Covariate by treatment group interaction tests will be performed to test whether the treatment effect is homogenous across subgroups. Statistical testing within subgroups will not be conducted unless the interaction test p-value is < 0.05.

C.6.3 Secondary Endpoints Analysis Plan

Secondary endpoints further characterizing the morbidity and disease-specific mortality of this patient population will also be analyzed using time-to-event methods as described in Section C.6.2.a for the primary trial endpoint. These secondary endpoints include: all-cause mortality, CV mortality and CV hospitalization composite, all components of composite endpoints,

hospitalization for any reason, new onset of diabetes mellitus, development of atrial fibrillation, deterioration of renal function (twofold increase in baseline serum creatinine), myocardial infarction, stroke, sudden death and/or aborted cardiac arrest. To account for multiple hospitalizations per subject, an incidence rate for hospitalization for heart failure in the two groups will be compared using a two-sample test based on the binomial distribution.

An interim monitoring plan for all-cause mortality is proposed, using the same approach and p-value boundaries as described in Section C.6.2.c for interim monitoring of the primary endpoint.

Laboratory indices of renal and metabolic function to assess drug safety will be analyzed using longitudinal linear regression methods, with normalizing transformations as appropriate.

Two general approaches to the analysis of quality of life and health status data will be taken. Analyses examining the influence of treatment on quality of life outcomes at specific follow up time points will be carried out through the use of analysis of covariance, adjusting for baseline status and other covariates. In order to utilize all available data describing the trajectory of subjects' functioning during the follow-up period, statistical models developed specifically for the analysis of longitudinal repeated measures data will also be used in secondary analyses to analyze the repeated quality of life measurements.

In addition to the general linear model described above, a generalized estimating equation model for ordinal multinomial data will be used to analyze repeated NYHA functional status measurements.

A challenge in the analysis of quality of life data relates to the unavoidable problem of missing data (due to death, incapacity, subject refusal, or loss to follow up). The proposed analytic strategy assumes that measurements are missing at random (Rubin, 1976), however it is possible that subjects with impaired quality of life may be less likely to complete the interviews. We will examine the sensitivity of our results to a variety of alternative assumptions regarding the relationship between quality of life and the likelihood of completing the instruments. Potential approaches will include imputing missing values with the natural "worst case" score for each of the quality of life endpoints and application of multiple imputation techniques (Schafer, 1997).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be the primary measure of quality of life (QOL). However, each QOL measure captures somewhat different aspects of QOL. Each QOL measure will be analyzed in a similar fashion. Qualitative agreement or disagreement in the direction of spironolactone's effect on each QOL measure will be described.

C.6.4 Site and Cohort Differences

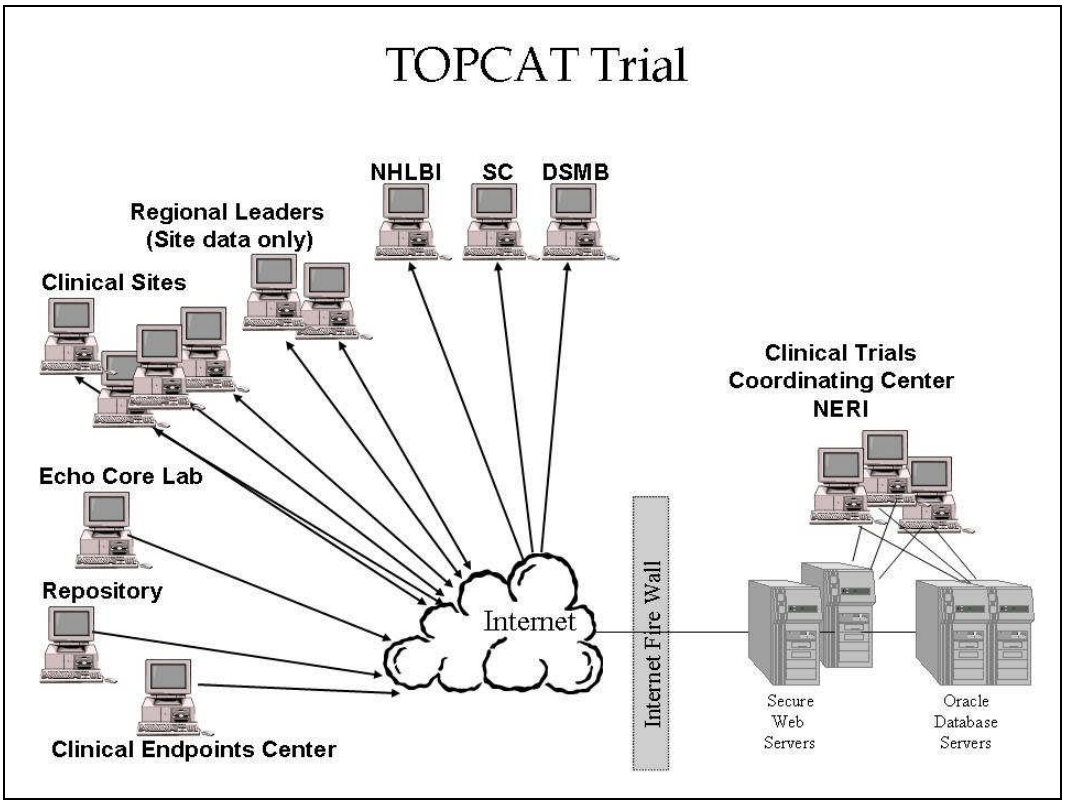
During the ongoing trial, analyses will be conducted on a periodic basis to assess geographic and site differences in protocol violation rates, enrollment rates, subject characteristics and adverse event rates. Differences identified may lead to a site visit to review subject data. The characteristics of subjects who are screened for but do not participate in the trial will also be compared with enrolled subjects. This analysis will allow assessment of the generalizability of trial findings and whether the enrolled subject cohort is representative of the entire patient population.

C.7 Data Management

C.7.1 Information Flow

Data will be sent to and received from several sources, including the clinical sites, the repository, the CEC, and the Echocardiography Core Laboratory. The flow of data among the units in this trial is illustrated in Figure 3. Clinical sites will enter data over the Internet using the Advanced Data Entry and Protocol Tracking (ADEPT) software, a customized and secure Web application. Sites will send blood and urine specimens directly to the repository for central processing, and records of receipt of such samples and final volumes stored will be electronically transmitted to the CTCC and stored in the ADEPT Data Management System (DMS). Echocardiograms stored on videotape or CD-ROM will be submitted to the Echocardiography Core Laboratory by FedEx. Results of interpretations/analyses performed by the Echocardiography Core Laboratory will be entered electronically using the ADEPT DMS.

Figure 3. Information Flow



C.7.2 Overview of Data Management System

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at the CTCC, and then stores these data centrally at the CTCC. Information entered into the data entry system will be by study I.D. number; names will not be linked with subject data in the database. Clinical sites will maintain records linking the patient name with the I.D. assigned for the study in locked files. Sites will have full access to their own data and be able to view this data remotely, over the Internet.

All study data will be stored on NERI's Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. Oracle archiving and backup system ensures minimal data loss.

C.7.3 Protocol Management and Reporting

In addition to providing robust data entry capabilities, ADEPT includes numerous features to streamline field operations and facilitate protocol adherence. Specifically, information regarding the study protocol and relative order of study events (e.g., medical exams, questionnaires) are programmed into ADEPT. Web-based, real time reports in both graphical and tabular format are available to the funding agency, Executive Committee, DSMB, and site management staff to track participant accrual and data quality. Standard ADEPT reports include:

- Upcoming appointments;
- Study Instruments pending entry;
- Study Instruments pending edit resolution;
- Missing data rates;
- Time (minimum, maximum, and average) to data enter each study CRF;
- Audit logs for all edits to study data;
- Subjects with overdue visits;
- Protocol violations

In addition to these standard reports, custom reports can be readily developed within the ADEPT system. The CTCC will provide sites, laboratories and the sponsor on-line access to a variety of reports designed to summarize recruitment, retention and compliance with the study protocol.

C.8 Quality Assurance

C.8.1 Site Certification

C.8.1.a Regulatory Documentation:

The investigator(s) who are responsible for the conduct of this study, in compliance with this protocol, are identified on the FDA Form 1572 Statement of Investigator. The following regulatory documentation will be collected from each site prior to study initiation:

- IRB or EC approval of the protocol and informed consent form
- FDA Form 1572 Statement of Investigator ensuring compliance with 21 CFR 312 Investigational New Drug Application (or country equivalent)
- Curriculum vitae and current medical licenses from all investigators (PI and Sub-investigators)
- IRB/EC membership list and Federal Wide Assurance (FWA) certification ensuring compliance with 21 CFR 50 Protection of Human Subjects and 21 CFR 56 Institutional Review Boards

- Laboratory certification(s) as appropriate, and list of normal ranges
- Financial Disclosure and Conflict of Interest forms for all investigators (PI and Sub-investigators)
- Protocol Signature Page

C.8.1.b Site Contracts: Two contracts are required per site. One is legally binding and includes references to any insurance policy. This is signed by a Clinical Center Administrator or by the Regional Leader. The second is the Investigator contract, signed by all Clinical Investigators. This contract obligates the Investigator to follow trial protocol and protocol related documents, adhere to GCPs, properly store and control study drug, accommodate and assist with site monitoring visits, complete any required reporting and make the best effort to recruit a minimum number of subjects at the site. All contracts will be translated as required.

C.8.1.c Training: Training will be completed on-line via a website established by the CTCC, or via a CD-ROM from the CTCC. Each training module will be followed by exercises to be completed by each individual to be certified for that module.

C.8.2 Site Monitoring

All sites will be visited at least once during the trial by representatives from the CTCC, Regional leader teams, and/or the sponsor. For monitoring purposes, "All sites" refers to all sites meeting their minimum contractual enrollment requirement. Sites not meeting this criterion may not have an in-person visit; however a for-cause visit may be warranted. Additional visits will generally be reserved for sites with problems (audits for cause). The monitoring visit consists of reviewing and evaluating three separate components: conformance to IRB/EC and consent form requirements, compliance with trial protocol, and source document data verification. Any site found to be Unacceptable or Acceptable/Needs Follow-up on any monitoring visit is required to submit a written response and/or corrective action plan to the CTCC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension. Procedures for the termination/closure of a clinical site will be provided in the Manual of Procedures (MOP).

C.9 Close Out Procedures

C.9.1 Site Close Out Procedures

The CTCC will be responsible for notifying the regulatory authorities and ethics committees in the participating countries that the clinical trial has ended according to the laws and regulations of those countries. The trial may terminate at the planned target of 4.25 years after recruitment begins or at an earlier date if circumstances warrant. All visits must be scheduled and completed by December 31, 2010 and details regarding the study closeout period will be provided in the Manual of Procedures (MOP). The objectives of the closeout phase are to:

1) Evaluate the data as fully as possible to permit assessment of the effect of spironolactone on the primary endpoint.
2) Fulfill ethical obligations to trial participants.
3) Exploit the scientific value of study data as fully as possible.

C.9.2 Study Related Closeout Procedures

Closeout procedures will be developed by the Steering Committee and disseminated by the CTCC. Regardless of the timing and circumstances of the end of the study, closeout will proceed in two stages: An interim period for analysis and documentation of study results, and a final reporting of the main study results:

1) Interim - About 3-4 months will be needed to complete data collection and to prepare a manuscript for submission to an appropriate journal, reporting on the trial's main results.
2) Reporting of study results - The study results will be released to participating physicians, referring physicians, subjects, and the general community.

D. STUDY ORGANIZATION & POLICIES

D.1 Organization

The trial is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI is responsible for the overall direction of the trial. Day-to-day management of the study will be the responsibility of the NHLBI Project Office, the CTCC, and the Executive Committee. The Executive Committee (EC) consists of the Steering Committee Chair, the NHLBI, and the CTCC Principal Investigators. In addition to day-to-day management of the trial, their role is to make recommendations to the Steering Committee regarding study conduct. The Steering Committee (SC) has as its voting members the SC Chair, the NHLBI project officer, the CTCC PI, and other investigators appointed by NHLBI. The SC oversees all aspects of the study, including monitoring trial progress and review of trial results. The SC may also establish subcommittees to facilitate the conduct of the trial. The SC will meet at least twice a year.

The Clinical Trial Coordinating Center has responsibility for contracting clinical centers for the trial, developing the Manual of Procedures (MOP), data collection forms, and all related systems. The CTCC is responsible for all reports needed for Committee meetings, and for interim and final statistical analyses.

The Data and Safety Monitoring Board (DSMB) is composed of independent experts in cardiology, biostatistics, and ethics who are appointed by the Director of the NHLBI to monitor the conduct of the trial including enrollment, safety, and efficacy outcomes. The DSMB will meet regularly, at least twice a year. Between these meetings, the DSMB chair will be notified of any events considered probably or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required.

The Drug Distribution Center is based in the U.S. and provides tablets of spironolactone and placebo. They are responsible for the packaging and distribution of study drug in collaboration with the CTCC.

The Regional Leaders for the trial are based in Boston, Montreal, Russia, and South America (see Table 8). The leaders will coordinate up to 110, 50, 60, and 60 trial sites, respectively.

TABLE 8. Regional Leaders/Drug Distributors

Region	Leader	Drug Distributor
A. NorthAmerica	CTCC/MHI, Canada	DHHS, Perry Point, MD
B. South America	ECLA, Argentina	ECLA, Argentina
C. E. Europe	Evidence, Inc., Russia	Evidence Inc., Russia

Each Leader organization will be responsible within its Region for:

- Identification of country leaders (HF specialists) as required;
- Site recruitment and support of site certification (the CTCC will provide the materials and database access);
- Support and triage of site queries – especially clinical;
- Disbursement of site payments (funds and instructions provided by the CTCC);
- Site monitoring as requested by the CTCC;
- Region C: All data entry and editing.

D.2 Publications Policy

The Steering Committee will review all publications following the guidelines given below.

D.2.1 Data Analysis and Release of Results

The scientific integrity of the project requires that data from all of the sites be analyzed study-wide and reported as such. An individual center is expected not to separately report its data. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee. Additionally, all presentations and publications are expected to protect the integrity of the major study objectives. With the exception of interim analyses for the DSMB, endpoint data will not be presented prior to the release of the main study results. Recommendations as to the timing of presentation of endpoint data and the meetings at which they are presented will be provided by the Steering Committee.

D.2.2 Review Process

Each manuscript or abstract must be submitted to the Steering Committee for review of its scientific merit and appropriateness for submission. The Steering Committee may recommend changes to the authors and will make a final decision about submission. Each manuscript or abstract should also be sent to the NHLBI for review prior to submission.

D.2.3 Primary Outcome Papers, Abstracts and Presentations

The primary outcome papers are defined as those that present outcome data for the entire trial cohort. The determination of whether or not a particular analysis represents a primary outcome report will be made by the Steering Committee. Authorship on the baseline and primary outcome papers will be "The TOPCAT TRIAL Investigators." For such manuscripts, there will be an appendix containing the names of all participating site investigators and their organizational affiliation. Papers and abstracts that are not primary outcome papers will have named authors based upon involvement and ending with the phrase "for the TOPCAT TRIAL Investigators." The same appendix will be appended to non-primary outcome manuscripts as for primary outcome papers. All manuscripts for submission must be approved by the Steering Committee.

D.3 Substudies

D.3.1 Introduction

Two types of substudies will be considered: ancillary studies and databank studies. Ancillary studies are those that require data collection beyond the primary protocol and/or propose using specimens in the trial repository, while Databank studies are based solely upon data collected as part of the main study. Participation in the substudies is open to all study investigators. In order to assure that all substudies are of high scientific merit, the DSMB will review applications for ancillary studies and make recommendations regarding merit to the Steering Committee. Databank studies will be considered directly by the Steering Committee or a designated subcommittee.

D.3.2 Ancillary Studies

An ancillary study uses trial participants in an investigation that is not described in the trial protocol and involves collecting new data that are not part of the trial data set or that use repository samples. Such studies must be carried out by applicant investigators or in conjunction with trial investigators. In general, any such study will require an independent consent form, IRB/EC approval, and an independent funding source. Ancillary studies must be approved by the Steering Committee and any external review committees. All applications for ancillary studies must be submitted in writing to the Steering Committee. The scientific merit of the application, and any possible impact of the sub-study on the parent TOPCAT study, will be reviewed and assurance provided that the timing of the resulting publication(s) will not interfere with the main publications of the study.

D.3.3 Databank Studies

A databank study utilizes data that have been collected as part of the main trial in order to answer a question different from that posed by the main protocol. It usually involves only data analysis and generally does not require supplemental funding because it uses the resources of the CTCC. Such studies require the approval of the Steering Committee, are based on scientific merit of the application, assurance that reporting of the databank study will not interfere with the main publications of the study, and availability of CTCC resources.

D.3.4 Application Review Process

The Steering Committee (or designated subcommittee) will review applications for substudies in a timely fashion. If several applications for similar substudies are received, collaboration and joint resubmission will be encouraged. Applications from non-trial investigators will be entertained but will be assigned lower priority than similar applications from trial investigators.

D.3.5 Other Competing Studies

Simultaneous participation by trial subjects in other prospective investigations requires the prior approval of the Steering Committee and is generally to be discouraged. It is recognized that the exigencies of patient care may require that the subject be entered into a compassionate use protocol. If this occurs, the CTCC should be notified within 10 days.

D.3.6 Data Storage and Analysis

All data collection forms for ancillary studies will be stored at the sites and the final dataset will be copied to the CTCC for merging into the primary dataset.

E. REFERENCES

Ahmed A, Roseman JM, Duxbury AS, Allman RM, DeLong JF. Correlates and outcomes of preserved left ventricular systolic function among older adults hospitalized with heart failure. *Am Heart J* 2002;144:365-72.

Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169-80

Cox DR. Regression and life tables (with discussion). *J Roy Stat Soc Series B* 1972; 34, 187-202.

DeMets DL and Lan KKG. Interim analysis: the alpha spending function approach. *Statistics in Medicine* 1994; 13:1341-1352.

Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc* 1987;82:171-200.

Efron B. Bootstrap methods: another look at the Jackknife. *Ann Stat* 1979;7:1-26.

Heart Disease and Stroke Statistics--2003 Update. Dallas: American Heart Association.

Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; 22:6A-13A.

Hsiao WC, Braun P, Dunn D, et al. Results and policy implications of the resource-based relative value scale. *N Engl J Med* 1988;319:881-888.

Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796-802.

Jeunemaitre X, Chatellier G, Kreft-Jais C et al. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol 1987; 60:820-825

Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.

Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144-50.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-70.

McDermott MM, Feinglass J, Lee PI, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997;134:728-36.

McMurray J et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Programme. *Eur J Heart Failure* 2003; 5:261-70.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341(10):709-17.

Pitt B, Remme W, Zannad F, et al, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-1321.

Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment, and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in Medicine* 2002; 21: 2917-30.

Rubin DB. Inference and missing data. *Biometrika* 1976;63:581-592.

Schafer JL. *Analysis of incomplete multivariate data.* London, Chapman and Hall, 1997.

Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-9.

Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Controlled Clinical Trials* 1995;16:395-407.

Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol* 2003;41:1510-8.

Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.

Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.

Yusuf S, Pfeffer M, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* September 2003, 362(9386):777-81.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis* 1974; 27:365-375

Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist

TOPCAT

IND Number: 71,883

Version 1.7 – June 04, 2009

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New England Research Institutes, Inc.
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PROTOCOL SIGNATURE PAGE

I have read the following protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drug and the conduct of the study.

I will use the current informed consent form version approved by the National Heart, Lung and Blood Institute and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and as specified in the Manual of Procedures (MOP) and, in particular, I agree to report any adverse events, serious adverse events, and unanticipated adverse drug effects (UADEs) as defined in Sections C.5.4 – C.5.6 of this protocol.

I further agree that the National Heart, Lung and Blood Institute, the appropriate regulatory authorities and staff from the regional coordinating centers have access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including study drug) provided by the National Heart, Lung and Blood Institute and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this trial protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance with the protocol and Good Clinical Practice guidelines, as well as local regulations; and to accept respective revisions conducted by authorized personnel of National Heart, Lung and Blood Institute and by competent authorities.

PRINTED OR TYPED NAME(S)	SIGNATURE	DATE
Principal Investigator(s)		
Principal Investigator(s)		

TRIAL OF ALDOSTERONE ANTAGONIST THERAPY IN ADULTS WITH PRESERVED EJECTION FRACTION CONGESTIVE HEART FAILURE

TABLE OF CONTENTS

PROTOCOL OVERVIEW (ABSTRACT)

This Phase III trial is a multicenter, international, randomized, double blind placebo-controlled trial of the aldosterone antagonist, spironolactone, in 3515 adults with heart failure and left ventricular ejection fraction of at least 45%, recruited from over 200 clinical centers. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Secondary endpoints include all-cause mortality, new onset of diabetes mellitus, atrial fibrillation, and quality of life. The trial duration is approximately 6 years, with approximately 4 years for subject enrollment and an additional 2 years of follow-up, with an average subject follow-up of 3.45 years. Dynamic balancing by clinical center at the time of randomization will be used to ensure that the distribution of clinical centers is similar in the two treatment groups. The study population will include those who meet the inclusion criteria, some of which are:

- Male or female age 50 years or older;
- Heart failure defined as one symptom at screening and one sign present in the last 12 months (described in protocol);
- Left ventricular ejection fraction $\geq$ 45% (per local reading);
- Controlled systolic blood pressure (SBP), defined as: SBP < 140 mm Hg or SBP from 140-160 mm Hg if subject is being treated with 3 or more medications to control BP;
- Serum potassium < 5.0 mmol/L prior to randomization;
- At least one hospitalization in the last 12 months for which heart failure was a major component of the hospitalization OR elevated BNP or N-terminal pro-BNP within the last 60 days;
- Willing to comply with scheduled visits, as outlined in the protocol;
- Signed informed consent form.

Exclusion criteria can be found in Section C.1.2.

Study drug dosing will start at 15 mg/day and may be titrated up to 45 mg according to subject tolerance, safety parameters, and symptoms, and will be continued throughout the trial. Following each change in the dosing regimen, subjects will have blood drawn for safety labs 1 week later. Subjects will take study medication every day according to specific instructions provided by the study staff at the clinical site. All other treatments will follow accepted local standards for medical care for specific morbidities as described by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) Practice Guidelines, as appropriate. Such treatments may also be adjusted by the local medical practitioner, if necessary. All randomized subjects will be followed even if study drug is discontinued ahead of schedule, except in the case that the subject refuses to participate further in the study.

Follow-up study visits to monitor symptoms, medications, and events and to dispense study drug will occur every 4 months during the first year and every 6 months thereafter. Quality of life will be assessed three times in the first year of the trial and annually thereafter. An electrocardiogram (ECG) will be performed at baseline only. Blood, DNA, and urine samples will be collected from a subset of subjects and stored in a repository for later use in ancillary studies. Clinical endpoints of pre-specified types will be adjudicated by a clinical events committee in a blinded fashion. Continual safety surveillance has been built into the study by means of the proposed dosing and safety assessment regimen described in the protocol. The 15 mg dose of spironolactone was formulated to reduce the risks and side-effects associated with this drug. The Data and Safety Monitoring Board (DSMB) will meet regularly, at least twice

a year. The DSMB chair will be notified of any events considered probably or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required. The study will be conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and applicable national and local regulations.

A. SPECIFIC AIMS

A.1 Primary Aim

To determine if treatment with spironolactone can produce a clinically meaningful reduction in cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Primary Outcome Measure: Cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite. Treatment arms will be compared using time-to-event analysis.

Secondary Outcome Measures:

- All-cause mortality
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- CV-related hospitalization
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

A.2 Secondary Aim #1

To determine if treatment with spironolactone can produce a clinically meaningful reduction in new clinical diagnoses compared with placebo, in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- New onset of diabetes mellitus
- Development of atrial fibrillation
- Myocardial infarction (fatal and non-fatal)
- Stroke (fatal and non-fatal)
- Deterioration of renal function
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

A.3 Secondary Aim #2

To evaluate the relative impact of spironolactone versus placebo on functional status and quality of life in adults with heart failure and left ventricular ejection fraction of at least 45%.

Secondary Outcome Measures:

- Quality of life, as measured by the:
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) – Primary quality of life outcome measure
  - EuroQOL (EQ5D) visual analog scale

- McMaster Overall Treatment Evaluation (OTE)
- Patient Health Questionnaire (depression scale)

A.4 Secondary Aim #3

To determine if treatment with spironolactone is safe, compared with placebo, in adults with heart failure and left ventricular ejection of at least 45%.

Safety Outcome Measures:

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function.

B. BACKGROUND

B.1 Prior Literature/Studies

Chronic heart failure (CHF) is a broad syndrome characterized by the relative inability of the heart to adequately meet metabolic demands of tissues without an abnormal elevation in filling pressure, which contributes to the clinically recognizable constellation of signs and symptoms. Although the etiologies of CHF are diverse, the premature mortality, incumbent morbidity, and associated healthcare burdens are not cause specific. Regardless of the etiology, CHF represents a progressive disorder that afflicts approximately 10% of the elderly and is the most common reason for hospitalization of patients over 65 years old (Hunt et al., 2001), with a prevalence of 4.9 million people in the United States, and 550,000 new cases diagnosed annually (American Heart Association, 2003). Epidemiologic and hospital-based studies have demonstrated that among patients with newly diagnosed CHF in the community, 43% to 54% of patients have preserved systolic function (PSF) (Senni et al., 1998; Vasan et al., 1999; Ahmed et al., 2002; McDermott et al., 1997). CHF patients without low ejection fractions have been variably described as having HF-PSF, heart failure with preserved ejection fraction, or diastolic heart failure. Although each term has relative merits, they do not completely characterize the complex interactions between systolic and diastolic function, vascular-ventricular coupling, neuroendocrine activation, and cardiorenal adaptations that result in the syndrome of heart failure. Pragmatically, since a quantitative left ventricular ejection fraction (LVEF) is used to define the well-studied systolic dysfunction (LVEF<40%) component of the heart failure population, an LVEF ≥40% can be used to identify the remaining proportion of heart failure patients with relatively PSF.

Relative to systolic dysfunction CHF, HF-PSF has a higher proportion of women and the elderly. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Trials, with concurrent screening for both systolic dysfunction and HF-PSF, found a similar incidence of atrial fibrillation and diabetes mellitus across ejection fraction groups but a lower frequency of prior myocardial infarction in those with HF-PSF (McMurray et al., 2003). In the Cardiovascular Health Study, approximately 67% of women older than 65 years of age had PSF compared with 42% of men (Kitzman et al., 2001). The estimate of the prevalence of this syndrome varies dramatically based upon the study design with a range from 13 to 74% reported among those with heart failure (Ahmed et al., 2002). The annual mortality rate has been estimated to be between 1.3 and 17.5% (Vasan et al., 1995). In the recently completed CHARM-Preserved trial, involving 3025 patients with symptomatic heart failure and an LVEF greater than 40% (median 54%), the mortality rate was 5.5 per 100 person-years, which though less than the approximately 10 per 100 person-years for heart failure with depressed LVEF, was still threefold higher than age-matched subjects without heart failure (Yusuf et al., 2003). These

patients also have significant morbidity. CHF patients with PSF (HF-PSF) have a high risk of re-hospitalization for HF and functional decline, reduced exercise performance, and worse quality of life than non-HF patients (Hundley et al., 2001; Kitzman et al., 2002; Smith et al., 2003).

B.2 Rationale for This Trial

B.2.1 Rationale for Investigation of New Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors in CHF Patients with PSF

This randomized double-blind placebo-controlled trial is designed to test the hypothesis that the addition of a mineralocorticoid receptor blocker to conventional therapy would improve clinical outcomes as assessed by reduced risk of death and hospitalizations for major cardiovascular events in patients with symptomatic heart failure and a quantitative LVEF at or above 45%. Despite the persistent advances over the past two decades in the treatment and prevention of cardiovascular diseases, the incidence of heart failure continues to increase. In some respects, this increase is a consequence of successes in the management of other life-threatening cardiovascular disorders, producing a larger reservoir of older individuals surviving with coexisting major cardiovascular comorbidities. Moreover, patients with heart failure and PSF have a particularly high rate of recurrent hospitalizations for a variety of major cardiovascular complications. The efficacy demonstrated with two separate mineralocorticoid receptor blockers, reducing the risk of death and hospitalizations for heart failure in patients with symptomatic heart failure and reduced ejection fraction, and acute MI complicated by heart failure, (spironolactone and eplerenone, respectively), provides a strong rationale for testing a mineralocorticoid receptor blocker in patients with heart failure and relatively preserved systolic ejection fraction. In addition to the potential reductions of individual risks of cardiovascular morbidity and mortality, the benefits achieved in this understudied population that utilizes considerable health care resources, would have major public health implications – reductions in both mortality and in costly hospitalizations.

B.2.2 Rationale for Use of Spironolactone

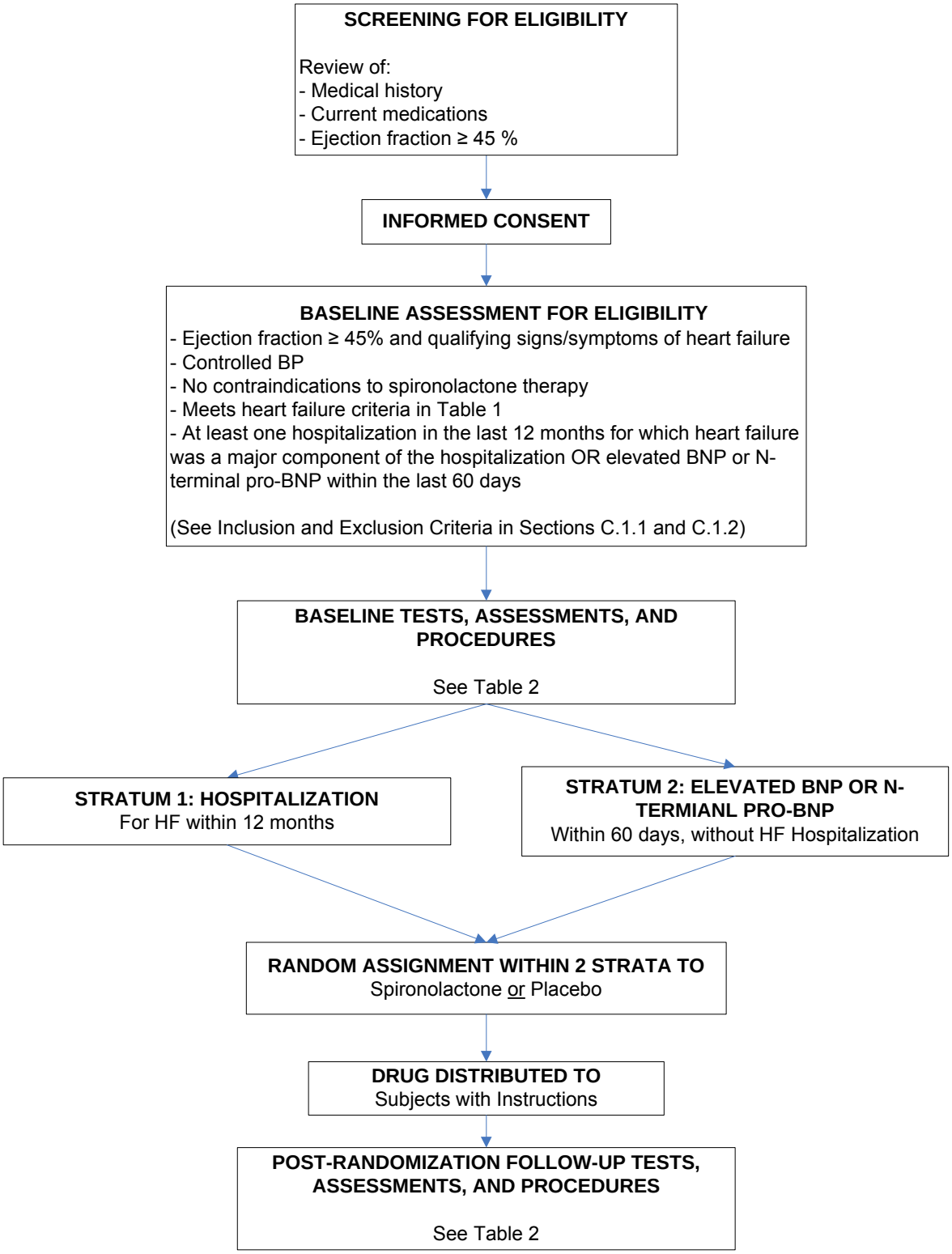
There are two candidates for aldosterone inhibition: the more familiar generic drug spironolactone and the newer eplerenone (owned by Pfizer). The important clinical benefits of these two mineralocorticoid receptor blockers are supported by mechanistic animal studies demonstrating that these agents reduce interstitial fibrosis, ventricular remodeling, vascular oxidative stress, improved endothelial function and have other favorable actions that could be anticipated to translate into clinical benefits in patients with heart failure and PSF. Both drugs have demonstrated improvement in survival in high-risk cardiovascular patients by mechanisms that likely go well beyond the renal effects of aldosterone inhibition. Spironolactone has an associated 10% rate of gynecomastia in males, which is not a side effect of eplerenone. However, from the Randomized Aldactone Evaluation Study (RALES) trial experience, this side effect resulted in negligible discontinuance of the drug. In the TOPCAT trial, gynecomastia is not anticipated to be a major issue as the population recruited for the trial will include a large number of females, many of whom are postmenopausal.

C. STUDY DESIGN AND METHODS

Next page.

Figure 1

SUBJECT FLOW IN TRIAL



C.1 Participants

C.1.1 Inclusion Criteria

In order for a subject to be eligible for inclusion in the trial, all of the following criteria must be met:

1. Male or female; Age 50 years or older;
2. Heart failure as defined in Table 1. One symptom must be present at the time of screening and one sign must be present in the last 12 months. Heart failure eligibility should be carefully monitored and documented in the subject's medical records.
3. Left ventricular ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable) ≥ 45% (per local reading). The ejection fraction must have been obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction;
4. Controlled systolic BP, defined as a target systolic BP < 140 mm Hg. Subjects with BP up to and including 160 mm Hg are eligible for enrollment if on 3 or more medications to control BP.
5. Serum potassium < 5.0 mmol/L prior to randomization;
6. At least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization. Transient heart failure in the context of myocardial infarction (MI) does not qualify.

   OR

   Brain natriuretic peptide (BNP) in the last 60 days ≥ 100 pg/ml or N-terminal pro-BNP ≥ 360 pg/ml and not explained by another disease entity;
7. Women of child-bearing potential must have a negative serum/urine pregnancy test within 72 hours prior to randomization, must not be lactating, and must agree to use an effective method of contraception during the entire course of study participation.
8. Willing to comply with scheduled visits, as outlined in Table 2;
9. Informed consent form signed by the subject prior to participation in the trial.

TABLE 1. Criteria for Diagnosing Heart Failure

SYMPTOMS (at least one must be present at the time of screening)	SIGNS (at least one in last 12 mos.)
• Paroxysmal nocturnal dyspnea • Orthopnea • Dyspnea on mild or moderate exertion	• Any rales post cough • Jugular venous pressure (JVP) ≥ 10 cm H_2O • Lower extremity edema • Chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly

C.1.2 Exclusion Criteria

If a subject meets any one of the following criteria then he/she is ineligible for enrollment in the trial:

1. Severe systemic illness with life expectancy judged less than three years;
2. Chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator;
3. Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;

4. Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant, or any valvular disease expected to lead to surgery during the trial;
5. Atrial fibrillation with a resting heart rate > 90 bpm;
6. Myocardial infarction in past 90 days;
7. Coronary artery bypass graft surgery in past 90 days;
8. Percutaneous coronary intervention in past 30 days;
9. Heart transplant recipient;
10. Currently implanted left ventricular assist device;
11. Stroke in past 90 days;
12. Systolic blood pressure (SBP) > 160 mm Hg;
13. Known orthostatic hypotension;
14. Gastrointestinal disorder that could interfere with study drug absorption;
15. Use of any aldosterone antagonist or potassium sparing medication in last 14 days or any known condition that would require the use of an aldosterone antagonist during study participation;
16. Known intolerance to aldosterone antagonists;
17. Current lithium use;
18. Current participation (including prior 30 days) in any other therapeutic trial;
19. Any condition that, in the opinion of the investigator, may prevent the subject from adhering to the trial protocol;
20. History of hyperkalemia (serum potassium ≥ 5.5 mmol/L) in the past six months or serum potassium ≥ 5.0 mmol/L within the past two weeks;
21. Severe renal dysfunction, defined as an estimated glomerular filtration rate (GFR) < 30 ml/min (per the Modification of Diet in Renal Disease (MDRD) 4-component study equation). Subjects with serum creatinine ≥ 2.5 mg/dl are also excluded even if their GFR is ≥ 30 ml/min;
22. Known chronic hepatic disease, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels > 3.0 times the upper limit of normal as read at the local lab.

C.1.3 Human Subjects Considerations

C.1.3.a Informed Consent

A waiver of consent may be requested from the Institutional Review Board/Ethics Committee (IRB/EC) of each clinical center in order to submit to the Clinical Trial Coordinating Center (CTCC) a completed screening form on non-randomized subjects. Written informed consent will be obtained from all potentially eligible trial subjects. Consent from a surrogate will not be permitted.

The repository will be a side-arm study of the main protocol. All sites participating in the side-arm study will approach all potentially eligible trial subjects for consent. A separate informed consent for each specimen type collected will be obtained prior to randomization. There are two portions to the repository sub-study: (1) DNA portion and (2) blood and urine portion. Random codes will be assigned to the repository samples and subjects may request to have their repository samples withdrawn and destroyed at any time while the trial is ongoing. At the completion of the trial, the repository samples and the clinical database will be double-coded. The clinical dataset will be anonymized such that it could not be linked back to the study subjects. Once the link between the subject ID and the repository sample code has been destroyed, subjects will no longer have the option to withdraw and/or destroy their repository samples. Repository samples with associated clinical data will not be made available for future research studies until the database and samples have been anonymized at the end of the trial.

The repository samples will be stored for future testing in a central repository maintained by NHLBI and may be kept for up to 30 years after the close of the study.

Other than random assignment to either spironolactone or placebo, all subjects will undergo routine care for heart failure with PSF.

Before the first trial-related procedure for a subject is performed, the investigator will obtain informed consent from the study subject by means of a dated and signed consent approved by the local IRB/EC in his/her country.

The informed consent process will be performed in accordance with the ICH guidelines for Good Clinical Practice (GCP), local laws and regulations.

Potential study subjects will be provided the current informed consent form and be given adequate time to study the information. The informed consent form will be provided to the subject in the local language. Informed consent may only take place after the potential study subject has had adequate time to study the informed consent form, ask any questions and decide whether or not to participate in the trial.

The informed consent process includes individual discussion with the subject about what study participation will involve. The information to be discussed will include all the information provided in the TOPCAT trial informed consent form. The discussion process includes informing the study subject both verbally and in writing that:

-if he/she refuses to participate in the study, the quality of medical care he/she receives will not be affected and
-he/she may withdraw at any time without giving reason and without affecting future care and
-without disclosing his/her name, relevant medical and personal data will be disclosed to the sponsor and regional coordinating centers who are obliged to use the information anonymously and solely for scientific purposes and
-his/her medical records may be reviewed during on-site monitoring, and may be inspected by auditors and/or regulatory authorities who are obliged to confidentiality and
-confidentiality will be maintained at all times according to local data protection laws.

Both the date a potential study subject is given the informed consent form and the date the study subject gives informed consent must be recorded. The study subject will be given a copy of the signed informed consent form.

After informed consent has been provided by the study subject, the original informed consent form will be kept in the patient file at the clinical site and will be made available for audit purposes. If the filing of the original signed consent form in the subject's hospital file is not permitted by the hospital or clinical setting, it must be filed in the investigator files and an indication that consent was obtained (with the date specified) should be noted in the medical files.

C.1.3.b Patient Confidentiality

Patient confidentiality will be maintained according to ICH guidelines for GCP and applicable local and national data protection laws. A study identification number will be assigned to each subject. The link between patient name and I.D. number will be stored only at the clinical center where the subject receives his/her care, thereby ensuring that all data transferred from a

subject's medical records to a study report form and any process derived from the study report form is handled confidentially.

C.1.3.c DNA Confidentiality

Blood samples prepared for DNA extraction will be sent to the repository. The sample will not have the original study I.D. number, the patient's name, or any other information that could identify the subject. The specific procedures are detailed in the Manual of Procedures (MOP) and the Repository Instruction Manual.

C.1.3.d Potential Risks

Spironolactone has been licensed for the treatment of heart failure in all of the countries participating in the TOPCAT trial for many years. The most common risks of taking spironolactone include hyperkalemia (observed at < 1.0% in the RALES trial with no serious consequences), hyponatremia, headache, drowsiness, lethargy, diarrhea, cramps, bleeding, gastritis, vomiting, anorexia, nausea, rash, pruritis, and urticaria. Gynecomastia, erectile dysfunction, and post-menopausal bleeding are less common. Hirsutism, agranulocytosis, and hyperchloremic metabolic acidosis have also been reported.

Although breast tenderness and gynecomastia have been reported in up to 10% of male patients treated with spironolactone, the risk of this side effect is dose-related and uncommon in patients treated with daily doses of 50 mg or less (as planned in this trial). In the RALES trial, gynecomastia resulted in negligible discontinuance of the drug and the condition is expected to be less of a problem in the TOPCAT trial as the study will be investigating patients with HF-PSF, a large proportion of whom are post-menopausal women.

A potentially serious side effect sometimes seen in patients treated with spironolactone is hyperkalemia. People with impaired renal function are considered to be at higher risk of hyperkalemia - an observation used to define the exclusion criteria of first the RALES trial and now TOPCAT. The investigators in the RALES trial attributed the observed incidence of hyperkalemia (1% in the placebo group and 2% in the spironolactone-treated group) to the exclusion of patients with elevated serum creatinine and potassium at baseline (and also to the relatively low treatment dose of spironolactone: the mean dose was 26 mg). Similar exclusion criteria will be used in the TOPCAT trial; however, the starting dose of spironolactone will be lower and renal function will be more accurately and reliably defined at baseline by estimated GFR. By careful evaluation of the pre-disposing factors for hyperkalemia and use of close monitoring of serum potassium during the study, it is anticipated that the rate of clinically significant hyperkalemia seen in TOPCAT will be similar to or possibly lower than that observed in the RALES trial.

Therapeutic trials investigating heart failure have been performed to date almost exclusively on patients with systolic dysfunction. However, now there is a growing awareness that a large proportion of patients with heart failure have preserved systolic function and that survival of these patients is also adversely affected. While treatment has been shown to be useful in patients with heart failure with systolic dysfunction, this is an area which has been understudied in those heart failure patients with PSF. Consequently much still remains to be learned about HF-PSF and its treatment.

C.1.3.e Potential Benefits

Subjects enrolled in this trial who are receiving active drug may receive a benefit. Also, there may be considerable benefit to future patients with HF-PSF as a result of the medical knowledge obtained from this study.

C.2 Trial Enrollment

C.2.1 Recruitment Protocol

The Principal Investigator at each private practice or clinical center, his or her designee, and the coordinator will have the responsibility for case finding and subject recruitment. The coordinator will conduct a chart review, while complying with local institution Health Insurance Portability and Accountability Act (HIPAA) requirements, to identify potentially eligible subjects. The coordinator will contact the subject per local guidelines to assess interest in the trial and to schedule an office or clinic visit for determination of full eligibility. Subjects may also be approached for participation while in-hospital if the subject is potentially eligible based on chart review. It should be noted that a subject may be screened for trial eligibility more than once during the accrual period.

C.2.2 Stratification

Due to the large number of clinical centers and potentially small number of enrolled subjects at some sites, dynamic balancing (Zelen, 1974) rather than stratified randomization across sites will be utilized to ensure that the distributions of clinical centers are similar in the two treatment groups. This approach will prevent the creation of excessively small stratum sizes. In addition, subjects will be stratified on inclusion criterion #6. Stratum I will include subjects selected based on a hospitalization in the 12 months prior to enrollment with a heart failure diagnosis and stratum II will include those subjects not reporting a hospitalization in the prior 12 months for which heart failure was a major component (for whom elevated BNP or Pro-BNP is required).

C.2.3 Blinding

Subjects and treating physicians will be blinded to whether subjects are receiving spironolactone or placebo. Because the trial has a double-blind design, safety laboratory tests will be performed for each subject for the duration of the trial, regardless of treatment arm. Similarly, monitoring of potential side effects will be continuous and irrespective of treatment assignment. While unmasking of the drug assignment for an individual subject is expected to be very rare, given the proposed dosing and safety-monitoring regimen described in Section C.3, a procedure for unblinding is included in the Manual of Procedures (MOP).

C.2.4 Baseline Visit and Randomization

After written informed consent is obtained, a baseline visit will occur, during which confirmation of eligibility will be obtained and baseline labs will be drawn. The maximum allowable timeframe between study baseline visit and the randomization date is 14 days. The baseline visit and randomization may occur on the same day. If baseline laboratory values were collected more than 14 days before the date of randomization, the clinic sites should repeat baseline labs, update any changes in the subject's medical history and concomitant medications, and confirm that the subject still meets all the study inclusion/exclusion criteria prior to randomization. Laboratory values obtained within the 14 day interval are acceptable as long as there were no inter-current change in medications and no borderline laboratory values. Subjects will be randomly assigned in a 1:1 ratio using permuted blocks to receive either spironolactone or placebo. Randomization will be accomplished over the Internet using randomization software accessed via a secure website. After verifying key eligibility criteria and supplying clinical center information, the randomization software will return a Treatment Allocation Code (A thru L) corresponding to either spironolactone or placebo. Labels containing treatment allocation code will be on the drug packet to verify correct assignment.

C.3 Treatment

C.3.1 Description of Study Medication

Study drug supplies will be provided by the Department of Health and Human Services (DHHS) Program Support Center in Perry Point, MD. Shipments will consist of the following:

1. Bottles containing 150 spironolactone 15 mg tablets
2. Bottles containing 150 placebo tablets, identical in size and appearance to the 15 mg spironolactone tablets.

Both the spironolactone 15 mg tablets and matching placebo are manufactured by URL Mutual Pharmaceutical in Philadelphia, PA, USA in accordance with federal regulations and ICH guidelines for Good Manufacturing Practices.

C.3.2 Randomization Procedures

Subjects will be assigned in the order they are enrolled into the study, to receive the allocated treatment according to a computer-generated randomization plan using NERI's Verandi software package. Once a subject has been assigned a Treatment Allocation Code, the subject will remain on the same study drug treatment allocation code for the duration of the study.

C.3.3 Study Drug Administration

Study medication will be dispensed at Randomization, 4 Month visit, 8 Month visit, 12 Month visit, and every 6 months thereafter. Previously dispensed study drug supplies are to be brought in at each subsequent visit to verify drug compliance. The volume of unused tablets or number of tablets will be recorded on the appropriate case report form (CRF), and the tablets will be returned to the subject. Site personnel will instruct the subject on the importance of compliance. A guideline for study drug dispensing is in the Manual of Operations.

The first dose of study drug will be administered as soon as possible after written informed consent has been obtained, baseline procedures have been performed, there is confirmation that laboratory results are within acceptable parameters, and randomization has occurred. Initial dosing should occur on the same date as randomization.

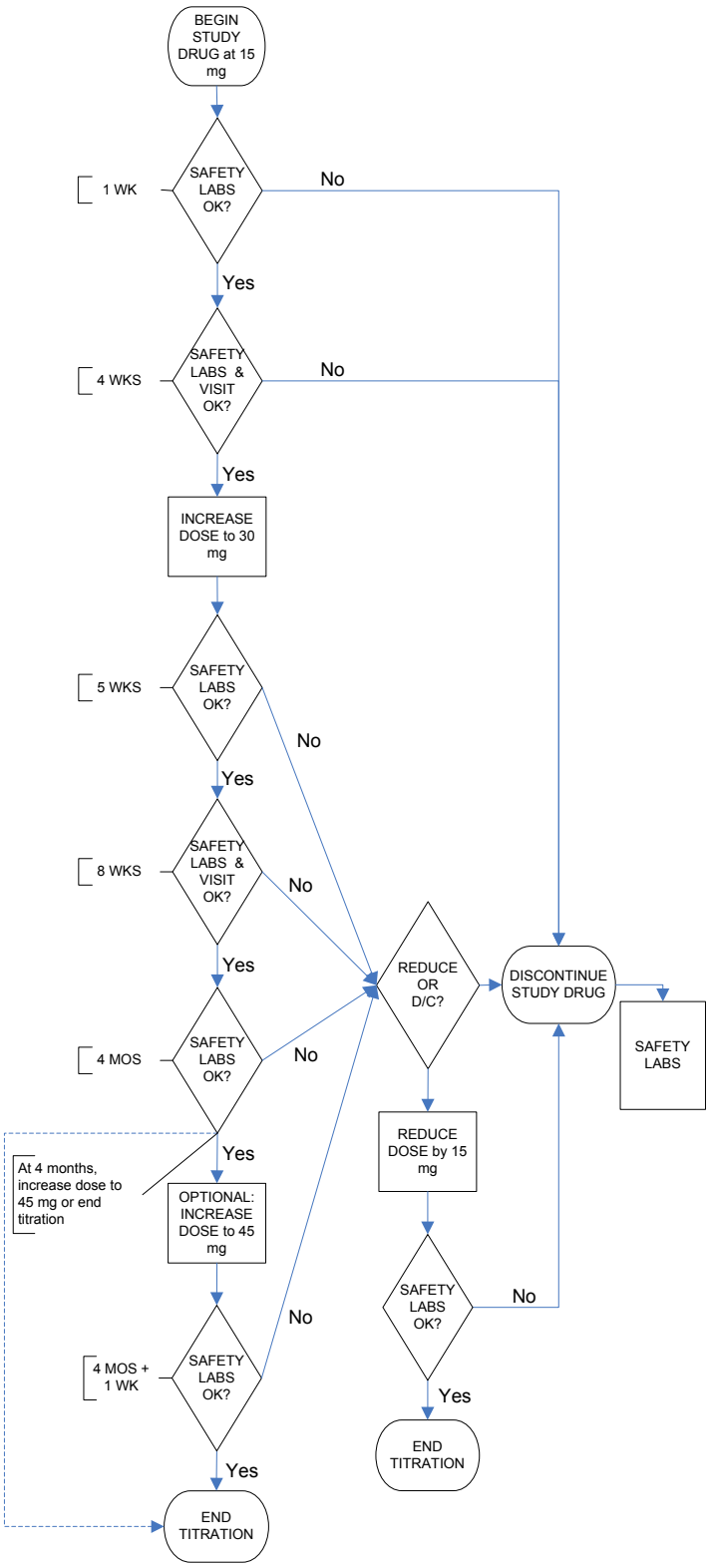
C.3.4 Study Drug Titration and Dosing Regimen

All subjects randomized into the study will begin on an initial dose of 15 mg daily (i.e. one tablet by mouth every day). The titration schedule and safety assessment intervals are illustrated in Figure 2. After 4 weeks, the dose should be increased to 30 mg daily (i.e. two tablets by mouth every day) if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the treating physician has the option to increase the dose to 45 mg daily at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily. Safety labs (i.e., electrolytes and chemistries) will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped). Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. Chemistries will include BUN and creatinine.

Once the subject is appropriately titrated, the dosing regimen (i.e., 15 mg, 30 mg, or 45 mg by mouth every day) should remain stable **unless** scheduled laboratory results exceed the safety parameters, and the potassium value is confirmed by a non-hemolyzed sample. The flowchart in Figure 2 illustrates the various pathways for dose titration of the study drug. Also included in Figure 2 are descriptions of when to reduce, discontinue and/or reinitiate study drug. :

Figure 2. Study Drug Titration and Safety Assessment Schedule

The study drug titration and safety assessment schedule is illustrated in this figure.



Titration: Initial dose: **15 mg/day.** After 4 weeks, the dose should be increased to **30 mg/day** if all safety parameters are acceptable. In the event that the subject continues to have ongoing heart failure symptoms, the investigator has the option to increase the dose to **45 mg/day** at 4 months. Study drug may only be increased after a subject has remained at a constant dose level for 4 weeks. Study drug may not be titrated to less than 15 mg daily or greater than 45 mg daily.

Reduce drug: Reduce the dosing regimen if potassium ≥ 5.5 mmol/L. If the subject is on 45 mg, the dose should be reduced to 30 mg; if the subject is on 30 mg, the dose should be reduced to 15 mg; if the subject is already on the lowest dose (i.e. 15 mg), and if there no alternative explanations for the elevated potassium level (e.g. subjects are taking potassium supplements), the study drug should be permanently discontinued if deemed appropriate by the treating physician and/or TOPCAT Medical Monitors. Once a downward dose adjustment has been made, the study drug should not be uptitrated beyond this level for the trial duration.

Discontinue drug: Permanently discontinue study drug if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample, regardless of the dosing regimen, if there no alternative explanations for the elevated potassium level.

NOTE: Treating physicians may consult the TOPCAT Medical Monitors prior to discontinuing any subjects on study drug as a result of elevated potassium levels. Since there is some room for clinical judgment, subjects could potentially continue to take study drug as long as they are properly monitored. Treating physicians may opt to control a subject's potassium level by adjusting his/her potassium supplement intake (if deemed appropriate and safe) or by recommending a low potassium diet.

Safety labs: Collect safety labs (i.e., electrolytes and chemistries) at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

Reinitiation (after non-compliance): If the dosing regimen is interrupted due to non-compliance, study drug may be reinitiated at the discretion of the treating physician. If a subject is eligible for drug reinitiation, the physician should choose from one the following three options:

- Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation); or
- Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits if lab work is acceptable; or
- Do not reinitiate study drug

If possible, study drug should be reinitiated within one week of drug discontinuation. The number of times study drug may be reinitiated after non-compliance is at the discretion of the treating physician.

C.3.5 Concomitant Medication

Subjects will be treated with other medications at the discretion of their cardiologist and/or primary care provider. At study visits, current medications will be recorded on the study forms. If a subject begins open-label use of any aldosterone antagonist or potassium-sparing diuretic at any time during the study, withdrawal from study drug is required.

The following drug interactions have been observed with spironolactone:

- ACE inhibitors or ARB – may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics – may be associated with hypokalemia
- Corticosteroids, ACTH – may be associated with hypokalemia
- Pressor amines (e.g. norepinephrine) – may reduce vascular responsiveness
- Skeletal muscle relaxants – may amplify muscle relaxant responsiveness
- Lithium – may lead to lithium toxicity
- NSAIDs – may be associated with hyperkalemia
- Cardiac glycosides (e.g. digoxin) – may lead to digoxin toxicity
- Anticoagulants (e.g. warfarin, heparin) – may reduce the effects of anticoagulation

C.3.6 Indications for Permanent Discontinuation of Study Drug

- Persistent hyperkalemia (potassium ≥ 6.0 mmol/L, based on a non-hemolyzed sample)
- Potassium ≥ 5.5 mmol/L, based on a non-hemolyzed sample, and subject on lowest dose of study drug (15 mg). Other explanations for the elevated potassium level should be ruled out.
- Anaphylactoid reaction or intolerance
- Serum creatinine ≥ 3.0 mg/dl, or at a lower threshold per local physician judgment
- Open label use of any aldosterone antagonist or potassium-sparing diuretic that cannot be discontinued for valid clinical reason
- Other adverse events that require discontinuation of study drug in the judgment of the study investigator, such as a medical course that is incompatible with the concomitant use of spironolactone.

The reason and the circumstances for permanent discontinuation of study drug will be documented. If study drug is permanently discontinued, the subject will continue to be followed until the end of the trial period.

C.3.7 Indications for Withdrawal From the Study

- Subject refusal to continue in the study
- Heart transplantation

All protocol-specified visits and follow-up procedures should be performed for every subject enrolled in the trial, even if the study drug is discontinued. If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. The reason for withdrawal will be documented for all subjects withdrawn from the study. If the withdrawing subject is unwilling to have his/her medical records reviewed until the end of the trial period (to document vital status and cause of death), he/she must submit a written refusal. Subjects may withdraw consent from the repository sub-study but continue participating in the main study. Subjects who withdraw consent from the main study are automatically withdrawn from the sub-study.

C.3.8 Study Completion

A subject will be considered to have completed the study if he/she has completed follow-up until the end of the trial period, undergoes heart transplantation, or dies. All subjects will be followed for a minimum of 2 years and a maximum of 6 years.

Clinic sites must complete all the necessary "End of Study" CRFs for all study subjects even if the end of study visit falls in-between the study scheduled clinic visits. Please refer to the MOP and ADEPT user guide for additional information.

C.3.9 Subject Compliance

Study drug compliance will be assessed at each study visit by comparing the expected vs. actual consumption of study drug tablets. The subject will bring all remaining study drug to the follow-up visit. The study coordinator will measure and record the volume or count and record number of remaining tablets, and a new 4 or 6 month supply (depending on the visit schedule) will be dispensed.

C.3.10 Drug Accountability Log

All study drug supplies (i.e. spironolactone 15 mg and corresponding placebo tablets and bottles) provided by the DHHS Program Support Center to the investigator for use in the clinical study must be accounted for in written documentation that must be maintained by the investigator and that will be monitored by the CTCC.

Forms to record dispensing of study medication will be provided with the initial shipment of the study medication. A copy of the complete records of study drug accountability for all supplies received for the study must be provided to the CTCC as part of the close-out procedure for the study. The drug accountability records must be retained by the investigator along with the subjects' study records.

C.3.11 Remote Monitoring for Eligibility

To ensure patient eligibility, the CTCC may perform regular remote monitoring "visits" on all clinic sites by requesting specific source documents from a random group of subjects throughout the study. Source documents for study eligibility monitoring purposes may include ECHO reports, lab data, and hospital discharge summaries.

C.3.12 Code Break

The Treatment Allocation Code may be broken if an emergency situation arises that in the Investigator's opinion requires knowledge of the code.

A request for unblinding should only be made in situations where knowledge of the treatment assignment will actually affect the subsequent care or decision-making process for care of the trial subject. It should be assumed that the trial subject will remain in the trial and will continue adherence to the trial protocol after the event is resolved. Therefore, every effort should be made to maintain trial participation in a blinded nature. It is anticipated that code breaks will be very rare and that all subjects will be appropriately monitored for safety.

Refer to the Manual of Procedures (MOP) for a description of the process for code break.

C.4 Measurements

C.4.1 Schedule of Measurement

See next page.

Table 2. Schedule of Trial Measurements

	Record Screening	Baseline Screening	Randomization and Drug Distribution	1 Week	4 Weeks	5 Weeks	8 Weeks	4 Months	8 Months	12 Months	18 Months	24, 36, 48, 60, 72 Months	30, 42, 54, 66 Months
Medical History	X	X											
Current Medications	X	X			X		X	X	X	X	X	X	X
Echocardiogram*	X												
Physical Exam, Wt., Vital Signs		X			X		X	X	X	X	X	X	X
Assessment of Study Drug Compliance					X		X	X	X	X	X	X	X
Blood Studies**		X		X***	X	X***	X	X	X	X	X	X	X
ECG		X											
Adverse Event and Study Outcome Monitoring					X		X	X	X	X	X	X	X
Urine Microalbuminuria		X								X		X	
QOL****		X						X		X		X	
Repository Specimens													
Urine Specimen		X								X			
Blood Specimen		X								X			
DNA Specimen		X								X			

* Ejection fraction obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction.

** Blood Studies (local lab):

- Baseline blood studies include: CBC, electrolytes, BUN, creatinine, blood glucose, and LFTs and should be done within 14 days prior to the randomization date CBC will include WBC count, hematocrit, hemoglobin, and platelet count. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. LFTs will include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, and albumin.
- Follow-up safety blood studies include: electrolytes, BUN and creatinine. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2.

*** Safety labs will be collected at 1 week after each change in the dosing regimen (i.e., either increased, decreased, or stopped).

**** OTE instrument will only be administered at the 4 and 12 month visits; KCCQ and EQ-5D instruments will only be administered at Baseline, 4 and 12 month visits and annually thereafter; Patient Health Questionnaire instrument will only be administered at Baseline and 12 month visits and annually thereafter.

C.4.1.a Record Screening (Table 2)
Record screening will include review of past medical history and current medications. The most recent echocardiogram from the past 6 months will be evaluated to determine if ejection fraction is ≥ 45% (per local reading). It is preferred that the qualifying ejection fraction be obtained by echocardiography. Ejection fraction obtained by radionuclide ventriculography or angiography is also acceptable in instances where an echocardiogram suitable for quantification is not available. A subset of the echocardiograms (video copy or digital image is acceptable) utilized for screening must be submitted to the Brigham and Women's Hospital Echocardiography Core Laboratory for QC purposes. Each site is required to submit the first 2 echos used to determine eligibility to the Echocardiography Core Laboratory which will read these pre-eligibility echocardiograms for a central QC of ejection fraction. Subjects may withdraw or decline to release their echocardiograms to the Echocardiography Core Laboratory at any time during the study. Clinic sites should notify the CTCC immediately of a subject's request to withdraw his/her echocardiogram from the core lab.

C.4.1.b Baseline Screening (Table 2)
At the baseline screening visit, the subject will have a physical examination, including vital signs. Blood will be drawn for CBC, electrolytes, BUN, creatinine, blood glucose, and liver function tests (LFTs). CBC will include WBC count, hematocrit, hemoglobin, and platelet count. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. LFTs will include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, and albumin. A urine test for microalbuminuria will be conducted. Creatinine, potassium, and LFTs, as well as the blood pressure measurements will be used to confirm eligibility. Current medication use will be reviewed to confirm that the subject does not meet exclusion criteria. Age, gender, race, and serum creatinine concentration will be obtained in order to calculate an estimated GFR using the 4-component MDRD Study prediction equation. The GFR estimate will be used to determine whether a subject has acceptable renal function to be enrolled in this study (see exclusion criterion 21). The initial medical history will focus on demographics, cardiac risk factors, and the prior 12 months for recent hospitalizations and procedures. An electrocardiogram (ECG) will be obtained at baseline. The subject will be asked to complete the first quality of life questionnaires. Procedures for the physical examination, blood draw, and urine test will be detailed in the Manual of Procedures (MOP). After randomization, two bottles of study drug will be dispensed with instructions.

All subjects from sites participating in the repository sub-study will be approached for consent to provide blood and urine samples for the repository, including a whole blood sample for DNA extraction.

C.4.1.c Follow-Up Visits (Table 2)
Health status and study drug compliance will be evaluated at scheduled visits throughout the study. Subjects must plan to have blood drawn for safety labs at 1 week post drug initiation/dose change. They will be scheduled to have an office visit and safety labs at 4 weeks post drug initiation. If the study drug is increased at this time, they will have blood work one week after dose change (week 5), and then full evaluation at 8 weeks. Subsequent planned visits will be scheduled every four months for the first year and every six months thereafter. Specifics for study drug titration are described in Section C.3.4 and Figure 2. Unplanned visits will be determined by the treating physician for symptoms, abnormal lab work, or other reasons.

At each office visit, the following will be obtained by short interview: current signs/symptoms consistent with HF and with administration of study drug, and current medications (subjects will be asked to bring these to each visit for accurate inventory). Blood pressure will be taken and

recorded. Every effort should be made to control blood pressure throughout the course of follow-up. Body weight will be recorded. Electrolytes, BUN, and creatinine, will be drawn to assess study drug safety. Electrolytes will include sodium, potassium, chloride, and bicarbonate/total CO_2. A urine test for microalbuminuria will be conducted annually.

Four quality of life instruments will be administered to trial subjects in the appropriate language according to the Schedule of Measurement (Table 2).

Blood and urine specimens for the repository will be obtained at baseline and 12 months from a subset of subjects.

If drug reduction/discontinuance is indicated by the chemistry panel results, a follow-up visit will be scheduled within one week at which time the subject will be evaluated for change in course of therapy.

Towards the end of the trial follow-up period, the Social Security or National Death Index will be searched for any subjects of unknown vital status in the U.S. Similar procedures will be implemented as feasible in other countries, with the assistance of the Regional Leaders.

C.4.1.d Windows for Visits

The acceptable windows for study visits are shown in Table 3. Safety monitoring during the titration period must be conducted at the study site. If for some reason a subject is unable to complete a study visit in person for a visit at Month 4 or later, the QOL instruments will be mailed to the subject along with a hospital-addressed stamped envelope for return of the completed questionnaires to the clinical site. The QOL instruments will be assigned for analysis to the nearest available window based on completion date.

Table 3. Acceptable Windows for Study Visits

Visit	Window
Week 1, 4, 5, 8	$\pm$ 3 days
Month 4	$\pm$ 2 weeks
Month 8, 12	$\pm$ 2 weeks
Later Visits	$\pm$ 4 weeks

C.4.2 Outcome Variables

Outcome variables have been chosen that will best capture the multi-faceted impact of spironolactone on heart failure with relatively PSF, a disease with significant morbidity, mortality, and associated costs. The primary trial endpoint is **a composite of** cardiovascular mortality, aborted cardiac arrest or hospitalization for the management of heart failure. Table 4 provides a summary of all outcome measures for the trial. In addition, all components of composite endpoints will be reported.

Table 4. Trial Outcome Measures

Primary Outcome

- Cardiovascular (CV) mortality, aborted cardiac arrest or hospitalization for the management of heart failure, as a composite.

Secondary Outcomes

Morbidity and Mortality

- All-cause mortality
- CV mortality or CV-related hospitalization (i.e. hospitalization for non-fatal MI, non-fatal stroke, or the management of heart failure) composite
- CV-related hospitalization
- Hospitalization for the management of heart failure incidence rate (to account for multiple hospitalizations per subject)
- Sudden death or aborted cardiac arrest

New Clinical Findings

- New onset of diabetes mellitus
- Development of atrial fibrillation
- Myocardial infarction (fatal and non-fatal)
- Stroke (fatal and non-fatal)
- Deterioration of renal function (see Section C.4.2.b)
- Sudden death, aborted cardiac arrest, or hospitalization for management of ventricular tachycardia

Quality of Life

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol (EQ5D) visual analog scale
- McMaster Overall Treatment Evaluation (OTE)
- Patient Health Questionnaire (depression scale)

Safety Measures

- All-cause mortality
- Hospitalization for any reason
- Laboratory indices of renal and metabolic function

C.4.2.a Morbidity and Mortality

Vital and hospitalization status will be monitored through subject contacts and by interview and medical record review at the clinic site. If a death occurs, the nurse coordinator will complete a death form indicating the date, time, and official cause of death, as well as a description of events leading up to the death.

Selected outcome forms and supporting documentation will be forwarded from the CTCC to the Clinical Endpoints Committee (CEC) for review as described in the TOPCAT Manual of Procedures (MOP).

C.4.2.b New Clinical Findings

New onset of diabetes mellitus will be assessed by physical exam, symptoms, and defined by measurement of blood glucose and introduction of anti-diabetic medication. New diagnosis of atrial fibrillation will be made by reported symptoms and clinically indicated monitoring of heart rhythm. Deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal. Stroke and MI are centrally adjudicated and defined in the CEC Manual of Procedures (MOP).

C.4.2.c Quality of Life

The primary goals of heart failure management are improving patient function, slowing disease progression, and improving quality of life. The quantification of this latter treatment goal requires the use of a health-related quality of life instrument, typically including a range of domains of health status. Four instruments will be administered to trial subjects in the appropriate language, if a validated version is available, according to the Schedule of Measurement (Table 2). The overall quality of life assessment at each visit typically will not exceed 12-15 minutes per subject.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be used as the primary endpoint for evaluation of functional status and quality of life in this trial. The KCCQ is a self-administered 23-item questionnaire taking approximately 4-6 minutes that measures physical limitation, symptoms (frequency, severity and recent change over time), quality of life, social interference, and self-efficacy. The KCCQ has been used in several recent and ongoing heart failure trials, including the EPHESUS trial.

In addition to the KCCQ, a brief generic health status measure, the “feeling thermometer” from the EuroQOL Health Status Questionnaire (EQ-5D; Brazier et al., 1993), which is a visual analog (0-100) scale, ranging from the worst imaginable health state (0) to the best imaginable health state (100) will be administered, as well as the McMaster Overall Treatment Evaluation (OTE) (Juniper et al. 1994). The OTE has 3 items addressing the overall effect of the treatment according to whether a subject has improved or deteriorated with respect to symptoms related to heart failure since the treatment started (therefore this instrument will not be part of the baseline QOL battery). If subjects indicate an improvement or deterioration, they will be asked to score the magnitude and the importance of the perceived change on a 7-point scale. The items will be combined to form a 15-graded scale, ranging from the worst deterioration (-7) to the highest improvement (+7) with “No change” (0) as the middle score. The OTE will be administered only at the 4 and 12 month follow-up visits.

Finally, the Patient Health Questionnaire, a 9-item health scale derived from the PRIME-MD that includes a measure of depression severity, will be administered.

C.4.3 Event Adjudication

New England Research Institutes, Inc. (NERI) as the CTCC will serve as the primary liaison to the sites for reporting of study endpoints and will be responsible for ensuring the required endpoint-related data and source documents are collected. The Clinical Endpoint Committee at the Brigham and Women’s Hospital in Boston will serve as the CEC and will be responsible for reviewing and adjudicating all suspected study endpoints consisting of cardiovascular vs. non-cardiovascular death, hospitalization for congestive heart failure, cardiac arrest, myocardial infarction, stroke, new onset of diabetes mellitus, new onset of atrial fibrillation, and hospitalization for the management of ventricular tachycardia.

The primary objective of the CEC is consistent and unbiased review and adjudication of study endpoints throughout the course of the trial. At the CEC, each event will be assigned and reviewed by a Physician Reviewer. The Physician Reviewer will document key details of the event, make a preliminary decision, and present his/her findings at the CEC meeting. In certain instances, the Chairman will generate a case precedent, an internal consistency measure, for difficult or noteworthy events that set a precedent for how future events should be regarded.

For each endpoint, the Physician Reviewers are responsible for providing a final adjudication for each event along with appropriate chart documentation describing the key details related to the event as well as rationale supporting their adjudication. The CEC maintains strict internal quality assurance measures in order to maintain the high-level quality of adjudicated data and in addition, all operations are conducted under the International Conference on Harmonization Good Clinical Practices (ICH/GCP) and Code of Federal Regulations (21 CFR 312, 21 CFR 50, 21 CFR 56). The CEC maintains Standard Operating Procedures for all functions and procedures and is subject to review and audit by the sponsor, or their representatives, and regulatory authorities. A 10% sample for re-adjudication will be randomly and blindly inserted in the review process by the CTCC and the results will be reported at CEC meetings. Details of CEC procedures will be included in the TOPCAT trial Manual of Procedures (MOP).

C.4.4 Repository

The repository will be a sub-study of the main protocol and subjects will be asked to provide additional informed consent to participate. For those subjects who consent, urine and blood specimens will be collected at baseline and 12 months, spanning an interval when most events and physiological changes are likely to occur. A whole blood sample for DNA extraction will also be collected for those subjects who consent. The proposed collections are summarized in Table 5. SeraCare BioServices currently serves as the long term NHLBI repository. All pre-barcode labeled collection and shipping containers will be provided to the clinical centers. The repository specimens will be stored for later use in ancillary studies yet to be approved and funded. Details of sample handling, storage, and shipping procedures are included in the TOPCAT MOP.

TABLE 5. Specimen Collection

Serum	• Up to three 10 ml tubes whole blood, collected and processed for storage of plasma and serum r as detailed in the Manual of Procedures (MOP) • Aliquot into pre-labeled cryovials and store at -20^{o}C • Shipment to repository when shipping rack filled
Urine	• 20 ml urine (mid-stream, time of day recorded but unrestricted)Aliquot into pre labeled cryovials and stored at -20 ^{o}C • Shipment to repository as above
DNA	• Packed cells from whole blood collected in EDTA tubes will be used for the DNA extraction.

C.5 Adverse Events

C.5.1 Definition

For purposes of this study, an adverse event (AE) is any untoward medical occurrence in a subject which occurs after the subject signs the informed consent form for the trial and no later than 30 days after a subject has permanently discontinued the study medication. Except for the study outcomes (see Table 4 Trial Outcome Measures) any untoward medical occurrences beginning more than 30 days after a subject has permanently discontinued study drug will not

be collected. Clinic sites must report all AEs (related and not related to study drug) to the CTCC in a timely manner. AEs are automatically reported to the CTCC when the sites complete the AE CRFs in ADEPT.

C.5.2 Classification of Adverse Events

C.5.2.a Severity

The severity (intensity) of each AE will be assessed according to the following definitions:

Mild: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity/intensity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

Severe: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the drug. Treatment for symptom(s) may be given.

Life-threatening: Symptom(s) of a sufficient severity/intensity to cause the subject to be at immediate risk of death. Treatment for symptom(s) may be given.

C.5.2.b Relationship

The temporal/causal relationship between the study drug (spironolactone or placebo) will be determined by the investigator according to the following definitions:

Definite: Clearly related to the study drug.

Probable: Likely (high suspicion) related to the study drug.

Possible: May be related to the study drug.

Unrelated: Clearly not related to the study drug.

C.5.3 Data Collection Procedures for Adverse Events

Adverse events will be recorded according to the date and time of first occurrence, severity, and duration, as well as any treatment prescribed. Following the subject's signing of the informed consent form, all adverse events that were not present at enrollment will be recorded. Any medical condition present at the signing of the informed consent form, which remains unchanged or improves, will not be recorded as an adverse event. However, worsening of a medical condition that was present at the time of the informed consent form signing will be considered a new adverse event and reported. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE Form and assessed in terms of severity and relationship to study drug. Laboratory values that are abnormal prior the signing of the informed consent form and that do not worsen will not be recorded on the AE Form. AEs will not be collected after a subject has been permanently discontinued from the study drug for 30 days.

C.5.4 Serious Adverse Events (SAEs)

The term "Serious Adverse Event" is defined to serve as a guide for regulatory reporting requirements and should not be confused with the severity (intensity) of an event. An AE is considered serious for this trial if it meets one or more of the following criteria:

- Fatal
- Life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/ birth defect
- Results in permanent impairment/damage of a body function/structure
- Requires intervention to prevent permanent impairment of a body function/structure

Clinic sites must report all SAEs to the CTCC within 48 hours of learning of the event. SAEs are automatically reported to the CTCC when the sites complete the SAE CRFs in ADEPT. The subject must be monitored carefully until the condition disappears and/or the etiology is defined. SAEs will not be collected after a subject has been permanently discontinued from study drug for 30 days.

C.5.5 Unanticipated Adverse Drug Effects (UADEs)

An Unanticipated Adverse Drug Effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with the study drug, if that effect, problem, or death was:

- Not previously identified in nature, severity, or degree of incidence in the protocol, informed consent template, investigator brochure, or package insert (including any revisions to these materials)
- Any other unanticipated serious problem that relates to the rights, safety, or welfare of subjects.

We anticipate UADEs to be rare events as this study drug is well-documented.

C.5.6 Reporting Procedures

All study outcome events should be reported to the TOPCAT CTCC within 48 hours. All SAEs and UADEs will be considered time-sensitive events reportable to the TOPCAT CTCC within 48 hours of learning of the event to meet regulatory (e.g. FDA) reporting guidelines as specified by regulations. A summary of all other adverse events will be reported to regulatory agencies (e.g. FDA) at the time of the annual report and semi-annually to the DSMB.

Sponsor reporting of UADEs and other safety information requiring reporting to regulatory authorities and ethics committees in other participating countries will occur according to the local requirements of that country.

The sponsor will also inform all investigators concerned of relevant information about UADEs that could adversely affect the safety of study subjects.

C.6 Statistical Methods

C.6.1 Sample Size and Power

The primary composite endpoint of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure will be analyzed as the time to first occurrence of any such event, utilizing all follow-up data (censored at trial end) and a two-sided log rank test (.05 Type I error). At least 80% power is desired to detect a 20% relative decrease in the 3-year event rate.

The power calculations assume 3515 subjects with an average of 3.45 years follow-up (minimum 2 years and maximum of 6 years). After a 24-month ramp-up period, enrollment rates are assumed to average 88 subjects per month, with 2 additional years of follow-up.

The CHARM-Preserved trial data suggested that the 3.0 year rate of CV deaths combined with heart failure hospitalization would be approximately 24% in the TOPCAT placebo group. Few patients are expected to have aborted cardiac arrest as their first event for the composite endpoint, so placebo event rates in the TOPCAT study were initially expected to be very similar to those in CHARM. A range of 3-year event rates were initially considered for the TOPCAT placebo group, ranging from 17.41% to 30.87%.

The I-PRESERVE study results were published in December 2008 (Massie et. Al, 2008). Mean follow-up in I-PRESERVE was 49.5 months. The primary outcome for I-PRESERVE was a composite of all-cause mortality and cardiovascular hospitalization, which is somewhat broader than the TOPCAT primary outcome because it includes all mortality, not just cardiovascular mortality, and it includes all cardiovascular hospitalizations, not just heart-failure-related hospitalizations. Of the 2061 subjects in the I-PRESERVE placebo group, 763 experienced the I-PRESERVE primary outcome, which corresponds to a 3-year event rate of approximately 28.6%. One of the secondary outcomes for I-PRESERVE was a composite of mortality due to heart failure and hospitalization due to heart failure. This is somewhat narrower than the TOPCAT primary outcome, because it only includes heart-failure related mortality rather than all cardiovascular mortality. In the I-PRESERVE placebo group, 438 of 2061 subjects experienced this secondary outcome. This corresponds to a 3-year event rate of approximately 15.8%. The eligibility criteria for TOPCAT are expected to produce a study population with somewhat higher event rates than I-PRESERVE, which did not require that all subjects have either a recent heart-failure hospitalization or elevated BNP or pro-BNP.

Therefore, the 3-year event rate in the TOPCAT placebo group is expected to be at least 17.41%.

The 3-year loss-to-follow-up rate is expected to be between 15% and 20%.

Table 6 shows the statistical power available to detect a 20% relative decrease in the 3-year event rate, for a range of placebo event rates, assuming 3515 subjects with an average of 3.45 years follow-up. The power was calculated using Shih's macro (Shih, 1995), after taking into account a sample size inflation of 3% to account for interim monitoring.

Table 6. Achievable statistical power for N=3515, assuming equal number of subjects in each treatment arm, Type I error = .05, two-sided test, 2.0 additional years of follow-up, 15.00% to 26.34% event rate in the placebo group over 3.0 years follow-up, 15% to 20% loss rate over 3.0 years follow-up, and 3% sample size inflation for interim monitoring.

Event rates						Power	
At 3 years follow-up			At 3.45 years follow-up			15% loss rate	20% loss rate
Placebo	Treatment	Relative Reduction	Placebo	Treatment	Relative Reduction		
15.00%	12.00%	20.0%	17.05%	13.67%	19.8%	73.8%	72.4%
16.00%	12.80%	20.0%	18.17%	14.57%	19.8%	76.9%	75.5%
17.41%	13.93%	20.0%	19.75%	15.85%	19.8%	80.9%	79.5%
19.63%	15.70%	20.0%	22.22%	17.83%	19.8%	86.0%	84.9%
21.85%	17.48%	20.0%	24.69%	19.82%	19.7%	90.1%	89.1%
24.09%	19.27%	20.0%	27.16%	21.82%	19.7%	93.2%	92.4%
26.34%	21.07%	20.0%	29.64%	23.82%	19.6%	95.5%	94.9%

Because quality of life is a continuous measure, there will be high power to detect moderate to small differences in the change scores of the two treatment groups using a sample size of 3515.

C.6.2 Primary Endpoint Analysis Plan

C.6.2.a Primary Analysis of the Primary Endpoint

The primary analysis of all study endpoints will be conducted according to intention-to-treat (with no covariate adjustment). The primary endpoint, a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, at the end of the 6 year subject accrual and follow-up period, will be compared by trial arm (spironolactone vs. placebo) using a logrank test of time to first event from the time of randomization. For this composite endpoint the time to event will be the time at which the first observed event component of the composite endpoint is observed. This method will utilize all available follow-up (ranging from 2 to 6 years for subjects who complete the trial) to provide the most powerful treatment comparison.

For all time-to-event analyses, subjects will be censored at the time of their last contact, unless they undergo a heart transplant. If a patient undergoes a heart transplant, their time-to-event measurement for any trial outcome will be censored at the date of heart transplant or last contact, whichever occurs earlier. Every effort will be made to obtain vital status on all trial subjects whose last contact was earlier than planned (dropouts), initially through telephone tracking by site staff, and at the end of the trial using National Death Index and/or Social Security Death Index search (for U.S. subjects).

C.6.2.b Secondary Analysis of the Primary Endpoint

Secondary analyses of the primary study endpoint will be of three types:

1) Comparison of spironolactone vs. placebo will be made as a function of treatment compliance (randomized treatment taken at correct current dose on at least 80% of study days vs. less than 80% of study days). This method attempts to better estimate the magnitude of the true treatment effect although parameter estimates are at risk due to subject selection bias created by evaluation of treatment outside of the original randomization structure.

2) Cox proportional hazards regression (Cox, 1972) will be used to most efficiently estimate the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure (Pocock, 2002). For this analysis, age, diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes), and hospitalization for the management of heart failure in the 6 months prior to enrollment will be used for covariate adjustment, based on risk factor analyses of CHARM-Preserved trial data.
3) A descriptive dose response analysis, using currently prescribed mg/kg as a time-varying covariate in a Cox proportional hazards model, will be performed for subjects randomized to the active treatment. (Subjects randomized to the active treatment but currently taken off study drug will be assigned a current dose of 0 mg/kg.) The dose per kilogram may be confounded with how well a patient's CHF responds to the drug, and also confounded with how a patient's safety markers respond to the drug. Therefore, descriptive analyses of safety markers by currently prescribed mg/kg will also be performed.

C.6.2.c Interim Analyses

A group sequential analysis plan is proposed, with four looks at the data including the final analysis. However, the DSMB may decide to change the number or timing of interim looks. Conditional power will be calculated at each look. Asymmetric stopping boundaries are proposed in Table 7, using an alpha-spending approach (DeMets et al., 1994). These boundaries are designed to accommodate a possible change in the number of looks that the DSMB chooses to have, and to accommodate any reasonable spacing of looks. The proposed boundaries will facilitate early stopping of the trial if there are safety concerns, i.e. if the event rate is much higher in the spironolactone treatment arm than in the placebo treatment arm. Early halting for efficacy, if the event rate is much higher in the placebo arm than the spironolactone arm, may also occur. However, stronger statistical evidence will be required to halt early for efficacy than for safety.. Note that if the study continues to its planned sample size, a more extreme p-value will be needed to declare spironolactone to be worse than placebo, compared to the p-value needed to declare spironolactone to be better than placebo. This is because more of the "safety alpha" than the "efficacy alpha" will have been spent during the interim looks.

Table 7 Proposed interim monitoring boundaries for safety and efficacy.

	P-value boundaries for early stopping (two-sided p-values based on log-rank test)	
Look	For safety (observed spironolactone event rate higher than observed placebo event rate)	For efficacy (observed placebo event rate higher than observed spironolactone event rate)
Any interim look with ≤ half the expected events observed	.001	.0001
Any interim look with > half the expected events observed	.01	.001
Final look	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0

The stopping boundaries for analysis of the primary endpoint, in conjunction with secondary endpoint comparisons and evaluation of safety (adverse event rates, including abnormal laboratory findings, all-cause mortality, and hospitalization for any reason) will all be considered by the DSMB to determine whether to recommend stopping the trial early. The TOPCAT trial will actively recruit subjects for 4 years. Maximum length of time on study will be 6 years, minimum 2 years.

C.6.2.d Subgroup Analyses

In order to identify the subject subgroups for whom spironolactone may be most or least beneficial, several pre-specified subgroup analyses will be conducted based on the subject's status at the time of randomization, namely:

- Randomization stratum: Hospitalized for heart failure in the year prior to study enrollment, vs. not hospitalized for heart failure during that time period
- Ejection fraction based on local reading, above vs. below the median
- Age 50-64 vs. 65-74 vs. $\geq$ 75 years
- Male vs. female
- Racial category: Black vs. White vs. All Others
- Ethnicity: Hispanic vs. Non-Hispanic
- History of hypertension vs. no history of hypertension
- Diabetes mellitus (insulin-treated) vs. diabetes mellitus (non-insulin-treated) vs. no diabetes mellitus
- New York Heart Association congestive heart failure class II vs. (III or IV)
- Systolic blood pressure below vs. above median
- Systolic blood pressure < 140 mm Hg vs. systolic blood pressure $\geq$ 140 mm Hg (entry into trial with controlled vs. uncontrolled blood pressure)
- Use vs. no use of cardiac medications, specifically beta-blockers, ACE inhibitors, aspirin, angiotensin receptor blockers, lipid-lowering agents, and diuretics
- Use vs. no use of blood pressure lowering medication
- Pulse pressure above and below median
- Estimated GFR above and below median
- BMI above and below median
- Analysis by region: Americas and E. Europe
- Prior MI vs. no prior MI

Covariate by treatment group interaction tests will be performed to test whether the treatment effect is homogenous across subgroups. Statistical testing within subgroups will not be conducted unless the interaction test p-value is < 0.05.

C.6.3 Secondary Endpoints Analysis Plan

Secondary endpoints further characterizing the morbidity and disease-specific mortality of this patient population will also be analyzed using time-to-event methods as described in Section C.6.2.a for the primary trial endpoint. These secondary endpoints include: all-cause mortality, CV mortality and CV hospitalization composite, CV hospitalization, all components of composite endpoints, hospitalization for any reason, new onset of diabetes mellitus, development of atrial fibrillation, deterioration of renal function (twofold increase in baseline serum creatinine to a value above the upper limit of normal), myocardial infarction, stroke, sudden death and/or aborted cardiac arrest. To account for multiple hospitalizations per subject, an incidence rate for hospitalization for heart failure in the two groups will be compared using a two-sample test based on the binomial distribution.

An interim monitoring plan for all-cause mortality is proposed, using the same approach and p-value boundaries as described in Section C.6.2.c for interim monitoring of the primary endpoint.

Laboratory indices of renal and metabolic function to assess drug safety will be analyzed using longitudinal linear regression methods, with normalizing transformations as appropriate.

Two general approaches to the analysis of quality of life and health status data will be taken. Analyses examining the influence of treatment on quality of life outcomes at specific follow up time points will be carried out through the use of analysis of covariance, adjusting for baseline status and other covariates. In order to utilize all available data describing the trajectory of subjects' functioning during the follow-up period, statistical models developed specifically for the analysis of longitudinal repeated measures data will also be used in secondary analyses to analyze the repeated quality of life measurements.

In addition to the general linear model described above, a generalized estimating equation model for ordinal multinomial data will be used to analyze repeated NYHA functional status measurements.

A challenge in the analysis of quality of life data relates to the unavoidable problem of missing data (due to death, incapacity, subject refusal, or loss to follow up). The proposed analytic strategy assumes that measurements are missing at random (Rubin, 1976); however, it is possible that subjects with impaired quality of life may be less likely to complete the interviews. We will examine the sensitivity of our results to a variety of alternative assumptions regarding the relationship between quality of life and the likelihood of completing the instruments. Potential approaches will include imputing missing values with the natural "worst case" score for each of the quality of life endpoints and application of multiple imputation techniques (Schafer, 1997).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be the primary measure of quality of life (QOL). However, each QOL measure captures somewhat different aspects of QOL. Each QOL measure will be analyzed in a similar fashion. Qualitative agreement or disagreement in the direction of spironolactone's effect on each QOL measure will be described.

C.6.4 Site and Cohort Differences

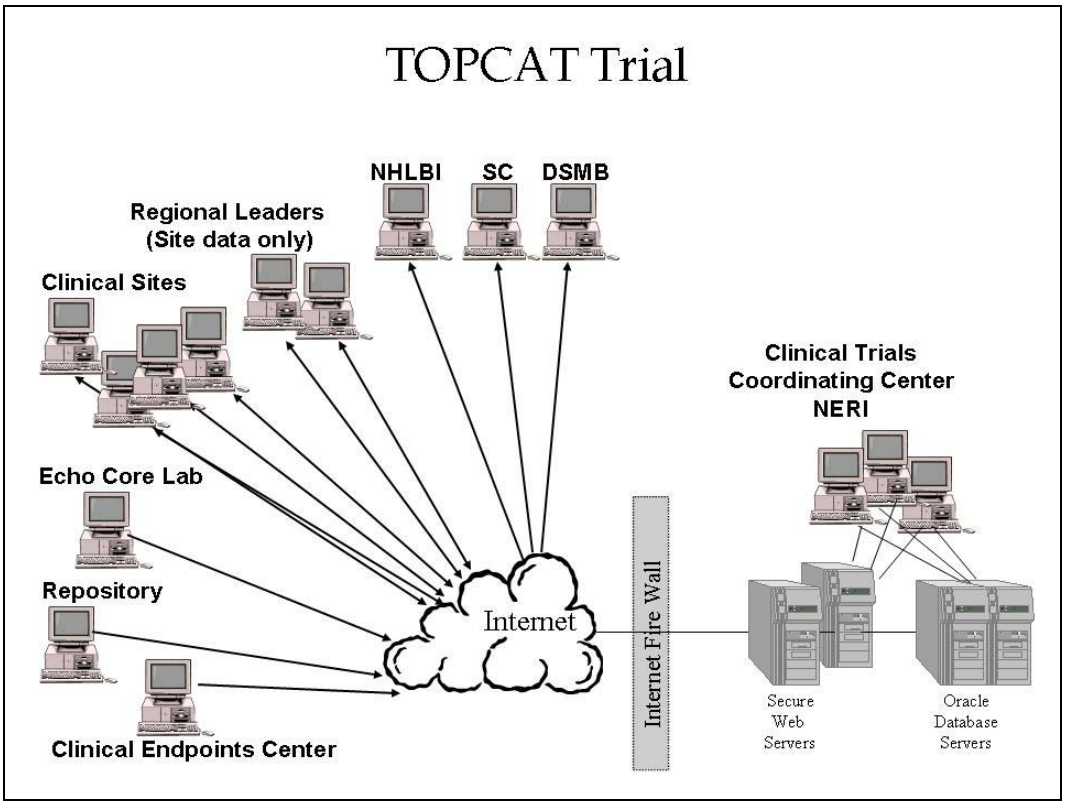
During the ongoing trial, analyses will be conducted on a periodic basis to assess geographic and site differences in protocol violation rates, enrollment rates, subject characteristics and adverse event rates. Differences identified may lead to a site visit to review subject data. The characteristics of subjects who are screened for but do not participate in the trial will also be compared with enrolled subjects. This analysis will allow assessment of the generalizability of trial findings and whether the enrolled subject cohort is representative of the entire patient population.

C.7 Data Management

C.7.1 Information Flow

Data will be sent to and received from several sources, including the clinical sites, the repository, the CEC, and the Echocardiography Core Laboratory. The flow of data among the units in this trial is illustrated in Figure 3. Clinical sites will enter data over the Internet using the Advanced Data Entry and Protocol Tracking (ADEPT) software, a customized and secure Web application. Sites will send blood and urine specimens directly to the repository for central processing, and records of receipt of such samples and final volumes stored will be electronically transmitted to the CTCC and stored in the ADEPT Data Management System (DMS). Echocardiograms stored on videotape or CD-ROM will be submitted to the Echocardiography Core Laboratory by FedEx. Results of interpretations/analyses performed by the Echocardiography Core Laboratory will be entered electronically using the ADEPT DMS.

Figure 3. Information Flow



C.7.2 Overview of Data Management System

ADEPT uses a "browser-based" user interface together with an Oracle relational database engine which allows direct data entry from multiple study sites or at the CTCC, and then stores these data centrally at the CTCC. Information entered into the data entry system will be by study I.D. number; names will not be linked with subject data in the database. Clinical sites will maintain records linking the patient name with the I.D. assigned for the study in locked files. Sites will have full access to their own data and be able to view this data remotely, over the Internet.

All study data will be stored on NERI's Oracle server. Access to data on this server (from both inside and outside the data center) is controlled by Oracle's extensive security features. Oracle archiving and backup system ensures minimal data loss.

C.7.3 Protocol Management and Reporting

In addition to providing robust data entry capabilities, ADEPT includes numerous features to streamline field operations and facilitate protocol adherence. Specifically, information regarding the study protocol and relative order of study events (e.g., medical exams, questionnaires) are programmed into ADEPT. Web-based, real time reports in both graphical and tabular format are available to the funding agency, Executive Committee, DSMB, and site management staff to track participant accrual and data quality. Standard ADEPT reports include:

- Upcoming appointments;
- Study Instruments pending entry;
- Study Instruments pending edit resolution;
- Missing data rates;
- Time (minimum, maximum, and average) to data enter each study CRF;
- Audit logs for all edits to study data;
- Subjects with overdue visits;
- Protocol violations

In addition to these standard reports, custom reports can be readily developed within the ADEPT system. The CTCC will provide sites, laboratories and the sponsor on-line access to a variety of reports designed to summarize recruitment, retention and compliance with the study protocol.

C.8 Quality Assurance

C.8.1 Site Certification

C.8.1.a Regulatory Documentation

The investigator(s) who are responsible for the conduct of this study, in compliance with this protocol, are identified on the FDA Form 1572 Statement of Investigator. The following regulatory documentation will be collected from each site prior to study initiation:

- IRB or EC approval of the protocol and informed consent form
- FDA Form 1572 Statement of Investigator ensuring compliance with 21 CFR 312 Investigational New Drug Application (or country equivalent)
- Curriculum vitae and current medical licenses from all investigators (PI and Sub-investigators)
- IRB/EC membership list and Federal Wide Assurance (FWA) certification ensuring compliance with 21 CFR 50 Protection of Human Subjects and 21 CFR 56 Institutional Review Boards
- Laboratory certification(s) as appropriate, and list of normal ranges
- Financial Disclosure and Conflict of Interest forms for all investigators (PI and Sub-investigators)
- Protocol Signature Page

C.8.1.b Site Contracts

Two contracts are required per site. One is legally binding and includes references to any insurance policy. This is signed by a Clinical Center Administrator or by the Regional Leader. The second is the Investigator contract, signed by all Clinical Investigators. This contract obligates the Investigator to follow trial protocol and protocol related documents, adhere to GCPs, properly store and control study drug, accommodate and assist with site monitoring

visits, complete any required reporting and make the best effort to recruit a minimum number of subjects at the site. All contracts will be translated as required.

C.8.1.c Training
Training will be completed on-line via a website established by the CTCC, or via a CD-ROM from the CTCC. Each training module will be followed by exercises to be completed by each individual to be certified for that module.

C.8.2 Site Monitoring
All sites will be visited at least once during the trial by representatives from the CTCC, Regional leader teams, and/or the sponsor. For monitoring purposes, "All sites" refers to all sites that enroll three or more subjects in the trial. Sites not meeting this criterion may not have an in-person visit; however a for-cause visit may be warranted. Additional visits will generally be reserved for sites with problems (audits for cause). The monitoring visit consists of reviewing and evaluating three separate components: conformance to IRB/EC and consent form requirements, compliance with trial protocol, and source document data verification. Any site found to be Unacceptable or Acceptable/Needs Follow-up on any monitoring visit is required to submit a written response and/or corrective action plan to the CTCC within 21 days of the receipt of the final monitor findings. Sites that fail to meet the standards for acceptable performance will undergo follow-up action, which will be determined by the severity of the discrepancies and may include repeat on-site monitoring, probation, or suspension. Procedures for the termination/closure of a clinical site are provided in the Manual of Procedures (MOP).

C.9 Close Out Procedures

C.9.1 Site Close Out Procedures
The CTCC will be responsible for notifying the regulatory authorities and ethics committees in the participating countries that the clinical trial has ended according to the laws and regulations of those countries. The trial may terminate at the planned target of 6 years after recruitment begins or at an earlier date if circumstances warrant. Details regarding the study closeout period will be provided in the Manual of Procedures (MOP). The objectives of the closeout phase are to:

1) Resolve all missing and inconsistent data to the extent possible
2) Evaluate the data as fully as possible to permit assessment of the effect of spironolactone on the primary endpoint.
3) Fulfill ethical obligations to trial participants.
4) Exploit the scientific value of study data as fully as possible.

C.9.2 Study Related Closeout Procedures
Closeout procedures will be developed by the Steering Committee and disseminated by the CTCC. Regardless of the timing and circumstances of the end of the study, closeout will proceed in two stages: An interim period for analysis and documentation of study results, and a final reporting of the main study results:

1) Interim - About 3-4 months will be needed to complete data collection and to prepare a manuscript for submission to an appropriate journal, reporting on the trial's main results.
2) Reporting of study results - The study results will be released to participating physicians, referring physicians, subjects, and the general community.

D. STUDY ORGANIZATION & POLICIES

D.1 Organization

The trial is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI is responsible for the overall direction of the trial. Day-to-day management of the study will be the responsibility of the NHLBI Project Office, the CTCC, and the Executive Committee. The Executive Committee (EC) consists of the Steering Committee Chair, the NHLBI, and the CTCC Principal Investigators. In addition to day-to-day management of the trial, their role is to make recommendations to the Steering Committee regarding study conduct. The Steering Committee (SC) has as its voting members the SC Chair, the NHLBI project officer, the CTCC PI, and other investigators appointed by NHLBI. The SC oversees all aspects of the study, including monitoring trial progress and review of trial results. The SC may also establish subcommittees to facilitate the conduct of the trial. The SC will meet at least twice a year.

The Clinical Trial Coordinating Center has responsibility for contracting clinical centers for the trial, developing the Manual of Procedures (MOP), data collection forms, and all related systems. The CTCC is responsible for all reports needed for Committee meetings, and for interim and final statistical analyses.

The Data and Safety Monitoring Board (DSMB) is composed of independent experts in cardiology, biostatistics, and ethics who are appointed by the Director of the NHLBI to monitor the conduct of the trial including enrollment, safety, and efficacy outcomes. The DSMB will meet regularly, at least twice a year. Between these meetings, the DSMB chair will be notified of any events considered probably or definitely related to study drug. At the time of notification, he/she will determine if an additional DSMB meeting is required.

The Drug Distribution Center is based in the U.S. and provides tablets of spironolactone and placebo. They are responsible for the packaging and distribution of study drug in collaboration with the CTCC.

The Regional Leaders for the trial are based in Boston, Montreal, Russia, Republic of Georgia, Argentina, and Brazil. The leaders will coordinate approximately 100 trial sites in the US, 50 sites in Canada, 60 sites in Russia and Republic of Georgia, and 60 sites in South America.

Each Leader organization will be responsible within its Region for:

- Identification of country leaders (HF specialists) as required;
- Site recruitment and support of site certification (the CTCC will provide the materials and database access);
- Support and triage of site queries – especially clinical;
- Disbursement of site payments (funds and instructions provided by the CTCC);
- Site monitoring as requested by the CTCC;
- Region C: All data entry and editing.

D.2. Conflict of Interest Policy

A Financial Conflict of Interest form will be filled out by each investigator at least annually, and also at any time that a new significant financial conflict of interest is identified.

The Investigators include the Executive Committee Members, the Steering Committee Members, the Principal Investigator at each site, and any other person who is responsible for the design, conduct, or reporting of TOPCAT research, including sub-grantees, contractors, or collaborators. For purposes relating to conflict of interest, the definition of Investigator also includes the Investigator's spouse and dependent children.

D.3 Publications Policy

The Steering Committee will review all publications following the guidelines given below.

D.3.1 Data Analysis and Release of Results

The scientific integrity of the project requires that data from all of the sites be analyzed study-wide and reported as such. An individual center is expected not to separately report its data. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee. Additionally, all presentations and publications are expected to protect the integrity of the major study objectives. With the exception of interim analyses for the DSMB, endpoint data will not be presented prior to the release of the main study results. Recommendations as to the timing of presentation of endpoint data and the meetings at which they are presented will be provided by the Steering Committee.

D.3.2 Review Process

Each manuscript or abstract must be submitted to the Steering Committee for review of its scientific merit and appropriateness for submission. The Steering Committee may recommend changes to the authors and will make a final decision about submission. Each manuscript or abstract should also be sent to the NHLBI for review prior to submission.

D.3.3 Primary Outcome Papers, Abstracts and Presentations

The primary outcome papers are defined as those that present outcome data for the entire trial cohort. The determination of whether or not a particular analysis represents a primary outcome report will be made by the Steering Committee. Authorship on the baseline and primary outcome papers will be "The TOPCAT TRIAL Investigators." For such manuscripts, there will be an appendix containing the names of all participating site investigators and their organizational affiliation. Papers and abstracts that are not primary outcome papers will have named authors based upon involvement and ending with the phrase "for the TOPCAT TRIAL Investigators." The same appendix will be appended to non-primary outcome manuscripts as for primary outcome papers. All manuscripts for submission must be approved by the Steering Committee.

D.4 Substudies

D.4.1 Introduction

Two types of substudies will be considered: ancillary studies and databank studies. Ancillary studies are those that require data collection beyond the primary protocol and/or propose using specimens in the trial repository, while Databank studies are based solely upon data collected as part of the main study. Participation in the substudies is open to all study investigators. In order to assure that all substudies are of high scientific merit, the DSMB will review applications for ancillary studies and make recommendations regarding merit to the Steering Committee. Databank studies will be considered directly by the Steering Committee or a designated subcommittee.

D.4.2 Ancillary Studies

An ancillary study uses trial participants in an investigation that is not described in the trial protocol and involves collecting new data that are not part of the trial data set or that use repository samples. Such studies must be carried out by applicant investigators or in conjunction with trial investigators. In general, any such study will require an independent consent form, IRB/EC approval, and an independent funding source. Ancillary studies must be

approved by the Steering Committee and any external review committees. All applications for ancillary studies must be submitted in writing to the Steering Committee. The scientific merit of the application, and any possible impact of the sub-study on the parent TOPCAT study, will be reviewed and assurance provided that the timing of the resulting publication(s) will not interfere with the main publications of the study.

D.4.3 Databank Studies

A databank study utilizes data that have been collected as part of the main trial in order to answer a question different from that posed by the main protocol. It usually involves only data analysis and generally does not require supplemental funding because it uses the resources of the CTCC. Such studies require the approval of the Steering Committee, are based on scientific merit of the application, assurance that reporting of the databank study will not interfere with the main publications of the study, and availability of CTCC resources.

D.4.4 Application Review Process

The Steering Committee (or designated subcommittee) will review applications for substudies in a timely fashion. If several applications for similar substudies are received, collaboration and joint resubmission will be encouraged. Applications from non-trial investigators will be entertained but will be assigned lower priority than similar applications from trial investigators.

D.4.5 Other Competing Studies

Simultaneous participation by trial subjects in other prospective investigations requires the prior approval of the Steering Committee and is generally to be discouraged. It is recognized that the exigencies of patient care may require that the subject be entered into a compassionate use protocol. If this occurs, the CTCC should be notified within 10 days.

D.4.6 Data Storage and Analysis

Data collection forms for ancillary studies will be stored at the sites and the final dataset will be copied to the CTCC for merging into the primary dataset.

E. REFERENCES

Ahmed A, Roseman JM, Duxbury AS, Allman RM, DeLong JF. Correlates and outcomes of preserved left ventricular systolic function among older adults hospitalized with heart failure. *Am Heart J* 2002;144:365-72.

Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169-80

Cox DR. Regression and life tables (with discussion). *J Roy Stat Soc Series B* 1972; 34, 187-202.

DeMets DL and Lan KKG. Interim analysis: the alpha spending function approach. *Statistics in Medicine* 1994; 13:1341-1352.

Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc* 1987;82:171-200.

Efron B. Bootstrap methods: another look at the Jackknife. *Ann Stat* 1979;7:1-26.

Heart Disease and Stroke Statistics--2003 Update. Dallas: American Heart Association.

Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; 22:6A-13A.

Hsiao WC, Braun P, Dunn D, Becker ER, DeNicola M, and Ketcham TR. Results and policy implications of the resource-based relative value scale. *N Engl J Med* 1988;319:881-888.

Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796-802.

Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, Devries C, Plouin PF, Corvo P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol 1987; 60:820-825

Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL; Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.

Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP, RT, RDMS. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144-50.

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-70.

Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G. Irbesartan in patients with heart failure and preserved ejection fraction. *NEJM* 2008; 359:2456-67.

McDermott, MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, Gheorghiade M.Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997;134:728-36.

O'Meara E, Solomon S, McMurray J, Pfeffer M, Yusuf S, Michelson E, Granger C, Olofsson B, Young JB, Swedberg K. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Programme. *Eur J Heart Failure* 2003; 5:261-70.Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and

mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341(10):709-17.

Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M , for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309-1321.

Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment, and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in Medicine* 2002; 21: 2917-30.

Rubin DB. Inference and missing data. *Biometrika* 1976;63:581-592.

Schafer JL. *Analysis of incomplete multivariate data.* London, Chapman and Hall, 1997.

Senni, M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-9.

Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Controlled Clinical Trials* 1995;16:395-407.

Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol* 2003;41:1510-8.

Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.

Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.

Yusuf S, Pfeffer M, Swedberg K, Granger C, Held P, McMurray J, Michelson E, Olofsson B, Östergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* September 2003, 362(9386):777-81.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis* 1974; 27:365-375

Analysis Plan: TOPCAT Main Results Paper

Complete Name of Proposed Manuscript: To be determined

DCC Statisticians: Susan Assmann, Brian Harty, possibly others to be determined

A. Aims

AIM 1) Describe baseline characteristics, overall and by treatment arm, with emphasis on treatment group equivalence.

AIM 2) Describe treatment compliance (pills taken compared to assigned dose), study retention (ending study before last expected study visit or death), and dilution of treatment effects (early discontinuation of study drug, use of open-label spironolactone).

AIM 3) Primary analysis of the primary endpoint (time to a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure), according to intention-to-treat (with no covariate adjustment) compared by trial arm (spironolactone vs. placebo)

AIM 4) Secondary analyses of the primary study endpoint will be of three types.

1) Comparison of spironolactone vs. placebo as a function of treatment compliance
2) Estimation of the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure
3) A descriptive dose response analysis

AIM 5) Equivalent analyses for time to each component of the primary end-point.

AIM 6) Safety analyses.

AIM 7) Pre-specified subgroup analyses (18) listed in protocol Section C.6.2.d), using the primary composite endpoint and an interaction test (Assmann et al Lancet 2000).

B. Subjects (describe inclusion/exclusion criteria, comparison groups, etc):

All randomized patients of TOPCAT study

C. List of variables to be included in analyses:

- Efficacy Outcomes
  - The primary outcome (a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure)
    - CV mortality
    - Aborted cardiac arrest
    - Hospitalization for the management of heart failure
- Safety Outcomes
  - All-cause mortality

- Hospitalization for any reason
- Laboratory indices of renal and metabolic function (potassium, creatinine, sodium, and chloride)
- Time to renal deterioration (deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal)
- Time to renal failure (renal failure is defined as a serum creatinine value ≥ 3.0 mg/dL.)

- Covariates for Efficacy Outcome Analyses
  - Treatment Arms
  - For AIM 1
    - Baseline variables used for the TOPCAT baseline paper
  - For AIM 4.1
    - Percent of prescribed study pills taken. This will be calculated based on data from CRFs T012, T015, T030, T080, and T081 regarding number of bottles dispensed, dose changes and discontinuations, and number of bottles and pills returned to the study site.
    - As a hypothetical example, suppose that a subject had the following data.
      - Treatment was started on 1 pill per day on June 1, 2007. The dose was up-titrated to 2 pills per day starting on June 29, 2007. The study medication was temporarily discontinued on February 1, 2008 and was resumed at 1 pill per day starting on February 10, 2008. The subject withdrew from the study on June 1, 2008.
      - With perfect compliance, the subject would have taken 1 pill per day for 28 days, 2 pills per day for 228 days, 0 pills per day for 9 days, and 1 pill per day for 113 days, for a total of 28+456+0+113 = 597 pills.
      - Over the course of the study, the subject had 6 bottles of 150 pills dispensed, for a total of 900 pills.
      - Based on bottles and pills returned to the site, the subject actually took a total of 500 pills.
      - This subject's percent of prescribed pills taken would be 100*500/597 = 83.8%
  - For AIM 4.2 (as specified in protocol Section C.6.2.b)
    - Age
    - Diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes)
    - Hospitalization for the management of heart failure in the 6 months prior to enrollment
  - For AIM 4.3
    - Prescribed dose (mg/kg) as a time-varying covariate
    - As a hypothetical example, suppose the subject in the above example weighed 75 kg throughout the study. His prescribed dose in mg/kg would be 0.20 for the first 28 days, 0.40 for the next 228 days, and so on.
  - For AIM 7

- Randomization stratum: Hospitalized for heart failure in the year prior to study enrollment, vs. not hospitalized for heart failure during that time period
- Ejection fraction based on local reading, below the median vs. at or above the median
- Age 50-64 vs. 65-74 vs. ≥ 75 years
- Male vs. female
- Racial category: Black vs. White vs. All Others
- Ethnicity: Hispanic vs. Non-Hispanic
- History of hypertension vs. no history of hypertension
- Diabetes mellitus (insulin-treated) vs. diabetes mellitus (non-insulin-treated) vs. no diabetes mellitus
- New York Heart Association congestive heart failure class II vs. class III or IV
- Systolic blood pressure below the median vs. at or above the median
- Systolic blood pressure < 140 mm Hg vs. systolic blood pressure ≥ 140 mm Hg (entry into trial with controlled vs. uncontrolled blood pressure)
- Use vs. no use of cardiac medications, specifically beta-blockers, ACE inhibitors, aspirin, angiotensin receptor blockers, lipid-lowering agents, and diuretics
- Use vs. no use of blood pressure lowering medication
- Pulse pressure below the median vs. at or above the median
- Estimated GFR below the median vs. at or above the median
- BMI below the median vs. at or above the median
- Analysis by region: Americas and E. Europe
- Prior MI vs. no prior MI

D. Statistical Methods

AIM 1)

- Descriptive statistics will be reported as the number and percent for categorical and ordinal variables, or the mean and standard deviation or the median and IQR for continuous variables. Continuous variables will be analyzed using T-test or Wilcoxon two-sample test. Categorical variables will be analyzed by chi-squared test or Fisher's exact test.

Table 1. Baseline characteristics of randomized patients

Variable	Spironolactone % or Mean (SD) or Median (IQR)	Placebo % or Mean (SD) or Median (IQR)	p-value

AIM 2)

- The median and quartiles for each subject's percentage of pills taken vs. prescribed will be calculated overall and by treatment arm.
- The number of subjects who discontinued all study follow-up (not just discontinued study drug) before their last expected study visit or death will be given, overall and by treatment arm, along with the reasons for prematurely leaving the study.
- The number of subjects in each arm who permanently discontinued study medication will be calculated, overall and by treatment arm. The major reasons for discontinuation will be listed. (Note that more than one reason can be indicated for the same subject.) (We would do a table similar to the table in the monthly DSMB report as part of the statistical report for TOPCAT, but we are so limited on tables and figures that we do not propose to include such a table in the NEJM manuscript.) The number of subjects who met protocol criteria requiring permanent discontinuation of study drug will be calculated. The median time from randomization to permanent discontinuation will be calculated for subjects with permanent discontinuation. A time-to-event analysis will also be used to calculate the median time to permanent discontinuation in each treatment arm, with censoring for subjects with no permanent discontinuation. A log-rank test will be carried out.
- Time from randomization to use of open-label spironolactone will be analyzed using methods similar to those for permanent discontinuation of study drug (except that we will not have data on reasons).

AIM 3)

- Time to the primary outcome will be measured as the number of months from randomization to the date of the first event of the primary outcome. Subjects will be censored at the time of their last contact, unless they undergo a heart transplant. If a patient undergoes a heart transplant, their time-to-event measurement for the

primary outcome will be censored at the date of heart transplant or last contact, whichever occurs earlier.

- For comparison of time to the primary outcome between spironolactone and placebo groups, Kaplan-Meier life-table analysis will be performed and the log-rank test will be used.

Table XXX: Time-to-event analyses for primary composite outcome and its components, and for safety outcomes

Outcome	# and % of Subjects with Event		Unadjusted Model HR vs. Placebo 95% CI p-value	Adjusted Model HR vs. Placebo 95% CI p-value	Effect of Currently Prescribed Dose(in mg/kg) for Spironolactone Group Only HR per 0.20 increase in dose 95% CI p-value
	Spironolactone (N = XXX)	Placebo (N = XXX)			
Primary Outcome	XX (XX%)	XX (XX%)	XX (XX – XX) XX	XX (XX – XX) XX	XX (XX – XX) XX
CV Mortality					
Aborted Cardiac Arrest					
Hospitalization for Heart Failure					
All-Cause Mortality					
All-Cause Hospitalizaiton					
Renal Deterioration					
Renal Failure					

Example of Kaplan-Meier Plot
FAKE DATA

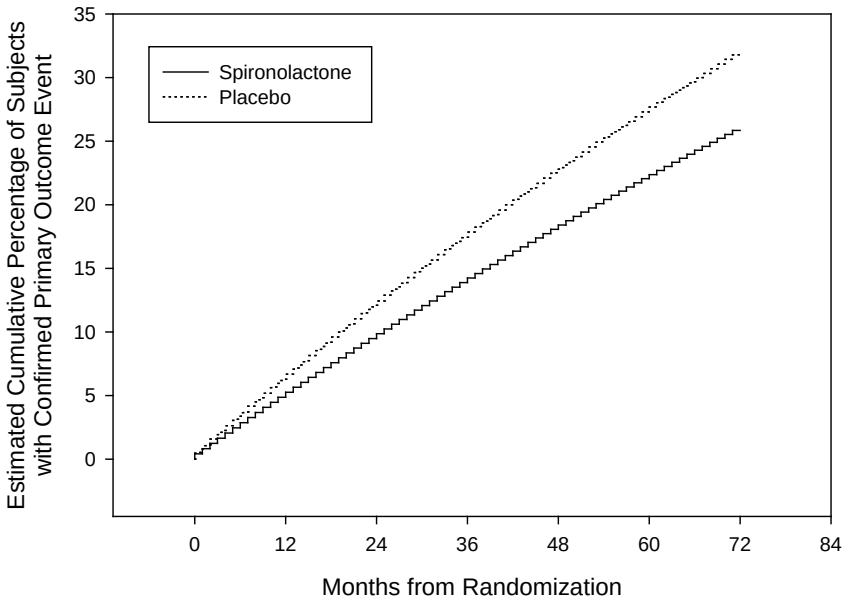


Figure XXX: K-M plot for the Primary Outcome

AIM 4)

1) Comparison of spironolactone vs. placebo as a function of treatment compliance
   - Use >=80% compliance vs. < 80% compliance vs. missing?
   - Fit a Cox model with treatment group, compliance category, and their interaction.
   - If the interaction is significant at the 0.05 level, calculate hazard ratios for spironolactone vs. placebo separately for each compliance category, with confidence intervals and p-values.
   - If the interaction is not significant at the 0.05 level, drop the interaction from the Cox model, and calculate a hazard ratio for spironolactone vs. placebo, with confidence interval and p-value, adjusting for compliance category.

2) Estimation of the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure.
   - Cox proportional hazards regression will be used to estimate the treatment effect after adjustment for important covariates. For this analysis, age at baseline, diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes), and hospitalization for the management of heart failure in the 6 months prior to enrollment will be used for covariate adjustment, as specified in protocol Section C.6.2.b.

3) A descriptive dose response analysis
   - Currently prescribed mg/kg will be used as a time-varying covariate in a Cox model, for subjects randomized to the active treatment only.

Subjects may have had more than one dose value and each dose (mg/kg) value prior to the primary outcome, or censoring time will be used. Time-dependent Cox hazards regression models will be used to assess the relationship between currently prescribed dose (mg/kg) and the primary outcome. The hazard ratio (HR) and 95% confidence interval (CI) will be used to quantify associations. Dose (mg/kg) will be modeled as a time-dependent covariate, using the counting process style of input. Using this approach, multiple records will be created for each subject, one record for each distinct pattern of the time-dependent measurements. Each record will contain a *T1* value and a *T2* value representing the time interval (*T1*,*T2*] at which each subject is considered at risk and during which the value of the dose variable remains unchanged. Each record will also contain the censoring status at *T2*.

AIM 5)

- Repeat time-to-event methods described in the analysis plan for AIM 3 (KM plots and log-rank tests) for each of the components below.
  - CV mortality
  - Aborted cardiac arrest
  - Hospitalization for the management of heart failure
- Compute the time variable for each of components listed above. If a patient undergoes a heart transplant, their time-to-event measurement for any trial outcome will be censored at the date of heart transplant or last contact, whichever occurs earlier.

AIM 6)

- Report SAEs by treatment arms.

Table XXX: Number of subjects experiencing one or more Serious Adverse Events, overall and by body system

Event	Spironolactone (N=XXX)	Placebo (N=XXX)	Total (N=XXX)
Any SAE	XX (XX%)	XX (XX%)	XX (XX%)
Auditory/Ocular			
Cancer			
Cardiovascular			
Endocrine and Metabolic			
Gastrointestinal			
Hematological			
Hepatobiliary/Pancreas			
Infection			
Musculoskeletal/Skin			
Neurological/Psychiatric			
Pulmonary/Upper Respiratory			
Renal/Genitourinary			
Sexual/Reproductive Function			
Vascular (non-cardiac)			
Other			

- Analyses for each safety outcome. For each, the primary analysis will be by intention-to-treat, comparing the two treatment arms with no covariate adjustment, and a secondary analysis will analyze the currently prescribed dose in mg/kg as a time-varying covariate, only in the spironolactone group.
    1) All-cause mortality
        - Time-to-event methods described in the analysis plan for AIM 3.
    2) Hospitalization for any reason
        - Time-to-event methods described in the analysis plan for AIM 3.
    3) Laboratory indices of renal and metabolic function (potassium, creatinine, sodium, and chloride)
        - Longitudinal linear regression methods will be used, with normalizing transformations as appropriate.
    4) Time to renal deterioration (deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal)
        - Time-to-event methods described in the analysis plan for AIM 3.
    5) Time to renal failure (renal failure is defined as a serum creatinine value ≥ 3.0 mg/dL.)
        - Time-to-event methods described in the analysis plan for AIM 3.

AIM 7)

- Subgroup analyses will be conducted only for the primary outcome.
- Interaction effect with treatment group and each covariate listed in Section C will be tested whether the treatment effect is homogenous across subgroups.
- Subgroup analyses will be performed using the Cox proportional hazard model, with treatment group, the subgroup variable, and their interaction as predictor variables.
- The results (HRs and 95% CIs) using subgroup will be reported in the figure only for covariates with the interaction test p-value < 0.05.
- However, the subgroup analyses carried out that have p >= 0.05 will be listed.

List of Tables and Figures (so we can keep track of how close we are to the total of 5 tables and/or figures allowed by NEJM).

Tables:

1. Table of measurements
2. Baseline characteristics
3. N and % with outcome, and hazard ratios and confidence intervals (both unadjusted, and adjusted for pre-specified covariates) for primary outcome, components of primary outcome, all-cause mortality, first hospitalization, renal deterioration, renal failure
4. Perhaps table with hazard ratios and confidence intervals (and linear regression coefficient and confidence intervals) for the "current dose in mg/kg)" time-varying covariate.
5. # and % of subjects with one or more SAEs, overall and for each organ system [I think NEJM will insist on this… They did for PLADO.]

Figures:

1. CONSORT-type patient flow diagram
2. Kaplan-Meier plots for primary outcome and its composites (panels A through D)
3. Kaplan-Meier plots for time-to-event safety outcomes (panels A through D)
4. Possibly also graphs of median labs over time by treatment (panels A through D)

NOTE: Maybe we could combine Figures 2 and 3 (all KM plots), or Figures 3 and 4 (all safety outcomes with graphs)

Detailed Statistical Analysis Plan: TOPCAT Main Results Paper

Complete Name of Proposed Manuscript: To be determined

DCC Statisticians: Susan Assmann, Brian Harty, possibly others to be determined

A. Aims

AIM 1) Describe baseline characteristics, overall and by treatment arm, with emphasis on treatment group equivalence.

AIM 2) Describe treatment compliance (pills taken compared to assigned dose), study retention (ending study before last expected study visit or death), and dilution of treatment effects (early discontinuation of study drug, use of open-label spironolactone).

AIM 3) Primary analysis of the primary endpoint (time to a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure), according to intention-to-treat (with no covariate adjustment) compared by trial arm (spironolactone vs. placebo)

AIM 4) Secondary analyses of the primary study endpoint will be of three types.

1) Comparison of spironolactone vs. placebo as a function of treatment compliance
2) Estimation of the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure
3) A descriptive dose response analysis

AIM 5) Equivalent analyses for time to each component of the primary end-point.

AIM 6) Safety analyses.

AIM 7) Pre-specified subgroup analyses (18) listed in protocol Section C.6.2.d), using the primary composite endpoint and an interaction test (Assmann et al Lancet 2000). Also, additional subgroup analyses pre-specified on March 18, 2013 conference call and August 12, 2013 meeting.

B. Subjects (describe inclusion/exclusion criteria, comparison groups, etc):

All randomized patients of TOPCAT study

C. List of variables to be included in analyses:

- Variables for baseline characteristics comparisons in Aim 1
    - Variables listed in TOPCAT baseline characteristics manuscript
    - Age < 75 vs. at least 75 years at baseline
    - Number of medications subject is taking, stratified by treatment group and by those with baseline SBP below 140 mm Hg versus above 140 mm Hg..

- Efficacy Outcomes
    - The primary outcome (a composite of CV mortality, aborted cardiac arrest, or hospitalization for the management of heart failure)
    - Each component of the primary outcome
        - CV mortality
        - Aborted cardiac arrest
        - Hospitalization for the management of heart failure

- Safety Outcomes
    - All-cause mortality
    - Hospitalization for any reason
    - Laboratory indices of renal and metabolic function (potassium, creatinine, sodium, chloride, and estimated GFR)
    - Time to renal deterioration (deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal)
    - Time to renal failure (renal failure is defined as a serum creatinine value ≥ 3.0 mg/dL.)

- Covariates for Efficacy Outcome Analyses
    - Treatment Arms
    - For AIM 1
        - Baseline variables used for the TOPCAT baseline paper
    - For AIM 4.1
        - Percent of prescribed study pills taken. This will be calculated based on data from CRFs T012, T015, T030, T080, and T081 regarding number of bottles dispensed, dose changes and discontinuations, and number of bottles and pills returned to the study site.
        - As a <u>hypothetical</u> example, suppose that a subject had the following data.
            - Treatment was started on 1 pill per day on June 1, 2007. The dose was up-titrated to 2 pills per day starting on June 29, 2007. The study medication was temporarily discontinued on February 1, 2008 and was resumed at 1 pill per day starting on February 10, 2008. The subject withdrew from the study on June 1, 2008.
            - With perfect compliance, the subject would have taken 1 pill per day for 28 days, 2 pills per day for 217 days, 0 pills per day for 9 days, and 1 pill per day for 112 days, for a total of 28+434+0+112 = 574 pills.
            - Over the course of the study, the subject had 6 bottles of 150 pills dispensed, for a total of 900 pills.
            - Based on bottles and pills returned to the site, the subject actually took a total of 500 pills.
            - This subject's percent of prescribed pills taken would be 100*500/574 = 87.1%
    - For AIM 4.2 (as specified in protocol Section C.6.2.b)
        - Age
        - Diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes)
        - Hospitalization for the management of heart failure in the 6 months prior to enrollment
    - For AIM 4.3
        - Prescribed dose (mg/kg) as a time-varying covariate (also used for Aim 6)
        - As a hypothetical example, suppose the subject in the above example weighed 75 kg. His prescribed dose in mg/kg would be 0.20 for the first 28 days, 0.40 for the next 217 days, and so on.

- For AIM 5
  - Incidence rate for heart failure hospitalization

- For AIM 6
  - Mean change in SBP and mean change in DBP from baseline to Month 8 visit. (Negative values indicate a decrease in blood pressure. Positive values indicate an increase in blood pressure.)
  - Occurrence of symptomatic hypertension. This will require the same hand-searching of SAE reports that we do for the semi-annual DSMB meetings with regard to this type of SAE.
  - Category of highest serum potassium while on study (< 5.5, at least 5.5 but < 6.0, 6.0 and higher)
  - Category of lowest serum potassium while on study (< 3.5, at least 3.5 but < 4.0, 4.0 and higher).
  - Incidence rate of all-cause hospitalization
- For AIM 7
  - Randomization stratum: Hospitalized for heart failure in the year prior to study enrollment, vs. not hospitalized for heart failure during that time period
  - Ejection fraction based on local reading, below the median vs. at or above the median
  - Age 50-64 vs. 65-74 vs. ≥ 75 years
  - Male vs. female
  - Racial category: Black vs. White vs. All Others
  - Ethnicity: Hispanic vs. Non-Hispanic
  - History of hypertension vs. no history of hypertension
  - Diabetes mellitus (insulin-treated) vs. diabetes mellitus (non-insulin-treated) vs. no diabetes mellitus
  - New York Heart Association congestive heart failure class II vs. class III or IV
  - Systolic blood pressure below the median vs. at or above the median
  - Systolic blood pressure < 140 mm Hg vs. systolic blood pressure ≥ 140 mm Hg (entry into trial with controlled vs. uncontrolled blood pressure)
  - Use vs. no use of cardiac medications, specifically beta-blockers, ACE inhibitors, aspirin, angiotensin receptor blockers, lipid-lowering agents, and diuretics
  - Use vs. no use of blood pressure lowering medicationPulse pressure below the median vs. at or above the median
  - Estimated GFR below the median vs. at or above the median
  - BMI below the median vs. at or above the median
  - Analysis by region: Americas and E. Europe
  - Prior MI vs. no prior MI
  - Use vs. no use of statin
  - Heart rate below the median vs. at or above the median
  - Ejection fraction below 50 vs. at or above 50
  - Estimated GFR below 60 vs. at or above 60

D. Statistical Methods

The TOPCAT protocol specified asymmetric stopping boundaries for the primary outcome and for all-cause mortality, using an alpha-spending approach approximating O'Brien-Fleming boundaries, as shown in the following table. The DSMB took 3 interim looks at efficacy and safety outcomes by treatment arm. For calculating the final p-value needed to declare placebo superior to spironolactone, and the final p-value needed to declare spironolactone superior to placebo, the information fraction at each interim look will be defined as the total number of subjects with a confirmed primary TOPCAT outcome event as of the data freeze for that interim look, divided by the total number of subjects with a confirmed primary TOPCAT outcome event after all adjudications had been completed at the end of the trial.

Interim monitoring boundaries for safety and efficacy.		
	P-value boundaries for early stopping (two-sided p-values)	
Look	For safety (observed spironolactone event rate higher than observed placebo event rate)	For efficacy (observed placebo event rate higher than observed spironolactone event rate)
Any interim look with ≤ half the eventual number of subjects with the primary outcome confirmed	.001	.0001
Any interim look with > half the eventual number of subjects with the primary outcome confirmed	.01	.001
Final look	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0	2-sided p-value such that the overall Type I error is 5%, evenly split between declaring placebo better and declaring spironolactone better, when the true difference is 0

AIM 1)

- Descriptive statistics will be reported as the number and percent for categorical and ordinal variables, and the median and IQR for continuous variables.
- Include a row dichotomizing age at < 75 vs. at least 75 years old at baseline
- The number of medications the subject is taking will be calculated.

AIM 2)

- The median and quartiles for each subject's percentage of pills taken vs. prescribed will be calculated overall and by treatment arm.
- Analyses of early discontinuation of study participation (not just discontinuation of study medication) will be presented by treatment arm. These will include

    - The number and percent of subjects who discontinued all study follow-up (not just discontinued study drug) before their last expected study visit or death or heart transplant, along with the reasons for prematurely leaving the study.
    - The median follow-up time from randomization to ending of study participation will be calculated and compared for subjects who ended the study early vs. those who ended study participation as expected (through death, heart transplant, or completing the study).
    - A time to event analysis will also be used to calculate the median time from randomization to early ending of study participation, including both subjects who ended study participation early and those who ended study participation as expected (through death, heart transplant, or completing the study). The latter group will be considered censored in this analysis.
- Analyses of permanent discontinuation of study medication on a date before the subject's end-of-study date will be presented by treatment arm. These will include:
    - The number and percent of subjects who permanently discontinued study medication on a date before the subject's end-of-study date
    - The major reasons for early discontinuation. (Note that more than one reason can be indicated for the same subject.) Where it is possible to determine from other study data, the "anaphyloid reaction or intolerance" reason from the CRF will be separated into "anaphyloid reaction" and "other intolerance". A specific reason "discontinued in-person study visits" will be added to the table of reasons.
    - The number and percent of male subjects who permanently discontinued study medication due to breast side effects.
    - The number of subjects who met protocol criteria requiring permanent discontinuation of study drug.
    - The median time from randomization to study drug discontinuation will be calculated for subjects with permanent discontinuation before their end-of-study date versus subjects who did not permanently discontinue study medication until their end-of-study date.
    - A time-to-event analysis will also be used to calculate the median time to early permanent discontinuation in each treatment arm, with censoring for subjects with no permanent discontinuation before their end-of-study date. A log-rank test will be carried out.
- Time from randomization to use of open-label spironolactone will be analyzed using methods similar to those for permanent discontinuation of study drug (except that we will not have data on reasons).

AIM 3)

- Time to the primary outcome will be measured as the number of months from randomization to the date of the first event of the primary outcome. Subjects will be censored at the time of their last follow-up for clinical outcomes, unless they undergo a heart transplant. If a patient undergoes a heart transplant, their time-to-event measurement for the primary outcome will be censored at the date of heart transplant or last follow-up for clinical outcomes, whichever occurs earlier. In this primary analysis, only events adjudicated by the CEC as meeting their standardized criteria will be included as events in the analysis.

- An annualized event rate will be calculated for each of the randomized groups. The placebo event rate will be discussed in comparison with annualized placebo event rates in other heart failure trials.
- For comparison of time to the primary outcome between spironolactone and placebo groups, Kaplan-Meier life-table analysis will be performed and the log-rank test will be used. An unadjusted Cox regression will also be performed, to obtain an unadjusted hazard ratio and confidence interval for spironolactone vs. placebo.
- If the log-rank test shows a statistically significant difference in favor of spironolactone (i.e. if subjects in the spironolactone group had lower risk of the primary outcome), a number-needed-to-treat (NNT) analysis will be carried out. Note that the NNT will be different for various time periods from randomization. As an artificial example, suppose the spironolactone group is observed to have a constant risk of 10% per year, and the placebo group is observed to have a constant risk of 20% per year, and there was no censoring. At the end of one year the event rates would be 10% and 20%, with an NNT of 10 subjects treated to prevent one primary outcome by one year. At the end of two years, the event rates would be 19% and 36%, with an NNT of approximately 5.9 subjects treated to prevent one primary outcome by two years. The NNT would gradually decrease to about 3.7 at years 6 and 7, and then start increasing again. By year 25, the event rates would be approximately 92.8% and 99.6%, and the NNT would be about 14.7 at year 25. For TOPCAT, the NNT will be calculated for 1 year, 2 years, 3 years, 4 years, and 5 years.

- A sensitivity analysis will be carried out, if there are any primary outcome events reported by the sites which the CEC cannot adjudicate as either meeting or not meeting their standardized criteria for that type of event. A worst-case Cox regression will be performed, in which it is assumed that all events in this situation will be assumed to have met the criteria if the subject was randomized to spironolactone, and not to have met the criteria if the subject was randomized to placebo. A best-case Cox regression will also be performed, in which it is assumed that all events in this situation will be assumed to have met the criteria if the subject was randomized to placebo, and not to have met the criteria if the subject was randomized to spironolactone. Hazard ratios and 95% confidence intervals will be compared between the primary analysis and these two extreme-case analyses.

AIM 4)

1) Comparison of spironolactone vs. placebo as a function of treatment compliance
   - Use >=80% compliance vs. < 80% compliance vs. missing.
   - Fit a Cox model with treatment group, compliance category, and their interaction.
   - If the interaction is significant at the 0.05 level, calculate hazard ratios for spironolactone vs. placebo separately for each compliance category, with confidence intervals and p-values.
   - If the interaction is not significant at the 0.05 level, drop the interaction from the Cox model, and calculate a hazard ratio for spironolactone vs. placebo, with confidence interval and p-value, adjusting for compliance category.

2) Estimation of the treatment effect after adjustment for important covariates that are known to impact the outcome of patients with PSF heart failure.
   - Cox proportional hazards regression will be used to estimate the treatment effect after adjustment for important covariates. For this analysis, age at baseline, diabetes at baseline (insulin-treated vs. non-insulin-treated vs. no diabetes), and hospitalization for the management of heart failure in the 6 months prior to enrollment will be used for covariate adjustment, as specified in protocol Section C.6.2.b. There will be very few subjects with missing data on any of the covariates. Therefore a complete-case analysis will be used. The number of subjects excluded due to missing data on one or more covariates will be presented.
   - An additional Cox proportional hazards regression will be performed, similar to that described above, but substituting heart failure hospitalization in the 12 months prior to enrollment (the variable used to stratify randomization) for heart failure hospitalization in the 6 months prior to enrollment.

3) A descriptive dose response analysis
   - Currently prescribed mg/kg will be used as a time-varying covariate in a Cox model, for subjects randomized to the active treatment only. Subjects may have had more than one dose value and each dose (mg/kg) value prior to the primary outcome, or censoring time will be used. Time-dependent Cox hazards regression models will be used to assess the relationship between currently prescribed dose (mg/kg) and the primary outcome. The hazard ratio (HR) and 95% confidence interval (CI) will be used to quantify associations between the outcome variable and the prescribed dose. Dose (mg/kg) will be modeled as a time-dependent covariate, using the counting process style of input. Using this approach, multiple records will be created for each subject, one record for each distinct pattern of the time-dependent measurements. Each record will contain a *T1* value and a *T2* value representing the time interval (*T1*,*T2*] at which each subject is considered at risk and during which the value of the dose variable remains unchanged. Each record will also contain the censoring status at *T2*.

AIM 5)

- Time-to-event analyses (KM plots and log-rank tests, unadjusted Cox models, covariate-adjusted Cox models, and dose response analyses) will be carried out for each of the components below. For each component, censoring will be at heart transplant or last follow-up for clinical outcomes, whichever occurs earlier.
  - CV mortality
  - Aborted cardiac arrest
  - Hospitalization for the management of heart failure
- Incidence rate of heart failure hospitalization, compared using Poisson regression
- Recurrent events analysis to compare frequency of heart failure hospitalization between the two treatment arms.

AIM 6)

- Report SAEs by treatment arms.
- Do Poisson regression for frequency of SAEs in each treatment arm

- Analyses for each time-to-event safety outcome. For each outcome, the primary analysis will be by intention-to-treat, comparing the two treatment arms with no covariate adjustment. A Kaplan-Meier plot, log rank test, and unadjusted Cox model will be carried out. A secondary analysis for each outcome will analyze the currently prescribed dose in mg/kg as a time-varying covariate, only in the spironolactone group. Except for all-cause mortality, censoring will occur at heart transplant or last follow-up for clinical outcomes, whichever occurs earlier.
-
  1) All-cause mortality through the date of the subject's last potential semi-annual study visit, based on their date of enrollment; e.g. for subjects enrolled in March or September of any year, the last potential

semi-annual visit would have been in March 2013. Note that for some subjects this last potential visit date may be later than the end-of-study date. For example, this could occur if the subject or physician withdrew consent or the subject was lost to follow-up. Censoring will occur at heart transplant, last date known alive, or date of last potential semi-annual visit, whichever is earliest. Some subjects may be confirmed deceased but not have complete data on the date of death. For all-cause mortality, if the month and year of death are known but not the exact date, the analyses will assume that death occurred on the first of the month. The number of subjects in each treatment arm who have the exact date imputed in this way will be reported. If the year of death is known, but not the month of death, censoring will occur on December 31 of the year before the year of death. The number of subjects in each treatment arm who have information on only the year of death will be reported. If a subject is known to be deceased, but not even the year of death is known, censoring will occur at heart transplant, last date known alive, or date of last potential semi-annual visit, whichever is earliest. The number of subjects in each treatment arm who were reported dead but are missing the year of death will be reported.

2) Hospitalization for any reason

3) Time to renal deterioration (deterioration of renal function is defined as a twofold increase in baseline serum creatinine level that at a minimum exceeds the upper limit of normal)

4) Time to renal failure (renal failure is defined as a serum creatinine value ≥ 3.0 mg/dL.)

- Incidence rate of all-cause hospitalization, compared using Poisson regression.
- Recurrent events analysis to compare frequency of all-cause hospitalization between the two treatment arms.
- Analyses for each laboratory safety outcome (potassium, creatinine, sodium, chloride, and estimated GFR) will use longitudinal linear regression methods, with normalizing transformations as appropriate. The primary analyses will not be adjusted for any covariates. A secondary analysis for each outcome will analyze the currently prescribed dose in mg/kg as a time-varying covariate, only in the spironolactone group.
- Cross-tabulation and Mantel-Haenszel test to compare treatment arms with respect to prescribed dose of study drug at Month 8 visit (0, 1, 2, or 3 pills/day).
- ANOVA comparing the two treatment groups on the mean change in SBP from baseline to the Month 8 visit, adjusting for the baseline SBPGraph of median SBP by treatment arm at each visit
- ANOVA comparing the two treatment groups on the mean change in DBP from baseline to the Month 8 visit, adjusting for the baseline DBP
- Graph of median DBP by treatment arm at each visit.

AIM 7)

- Subgroup analyses will be conducted only for the primary outcome.

- Interaction effect with treatment group and each covariate listed in Section C will be tested whether the treatment effect is homogenous across subgroups.
- Subgroup analyses will be performed using the Cox proportional hazard model, with treatment group, the subgroup variable, and their interaction as predictor variables.
- The results (HRs and 95% CIs) for each subgroup will be reported in a figure only for any covariates with the interaction test p-value < 0.05.
- However, the subgroup analyses carried out that have p >= 0.05 will be listed.

- **SHELLS FOR TABLES AND FIGURES**

NOTE: NEJM limits the manuscript to a total of 5 tables and/or figures. Depending on the results of the analyses, it is possible that one or more of the tables and figures listed below may be omitted, with the results only described in the text. For example, if there are several significant interactions found during the subgroup analyses, we may want to include a forest plot showing the significant subgroup analyses, and drop one of the other tables or figures.

NOTE: The example graphs are made using FAKE DATA, just to provide an idea of the format the graphs would have.

Table 1. Baseline characteristics of randomized patients

Variable	Spironolactone % or Mean (SD) or Median (IQR)	Placebo % or Mean (SD) or Median (IQR)

Table 2: Cox model time-to-event analyses for primary composite outcome and its components, and for safety outcomes

Outcome	# and % of Subjects with Event, and Annualized Event Rate		Unadjusted Cox Model HR vs. Placebo 95% CI p-value	Adjusted Cox Model 1* HR vs. Placebo 95% CI p-value	Adjusted Cox Model 2* HR vs. Placebo 95% CI p-value
	Spironolactone (N = XXX)	Placebo (N = XXX)			
Primary Outcome	XX (XX%) XX% per year	XX (XX%) XX% per year	XX (XX – XX) XX	XX (XX – XX) XX	XX (XX – XX) XX
CV Mortality**					
Aborted Cardiac Arrest**					
Hospitalization for Heart Failure**					
All-Cause Mortality***					
All-Cause Hospitalization***					
Renal Deterioration***					
Renal Failure***					

* Adjusted for age (as a continuous variable), diabetes history at baseline (insulin-treated, not insulin-treated, or no history of diabetes), and whether or not the subject had been hospitalized for heart failure in the six months prior to enrollment (adjusted model 1) or in the twelve months prior to enrollment (adjusted model 2).

** Components of primary composite endpoint

***Safety outcomes

Table 3: Number of subjects experiencing one or more Serious Adverse Events, overall and by body system

Event	Spironolactone (N=XXX)	Placebo (N=XXX)
Any SAE	XX (XX%)	XX (XX%)
Auditory/Ocular		
Cancer – basal skin cancer		
Cancer – all other cancers		
Cardiovascular		
Endocrine and Metabolic		
Gastrointestinal		
Hematological		
Hepatobiliary/Pancreas		
Infection		
Musculoskeletal/Skin		
Neurological/Psychiatric		
Pulmonary/Upper Respiratory		
Renal/Genitourinary		
Sexual/Reproductive Function		
Vascular (non-cardiac)		
Other		

Figure 1. Kaplan-Meier plots for primary outcome and its composites (panels A through D)

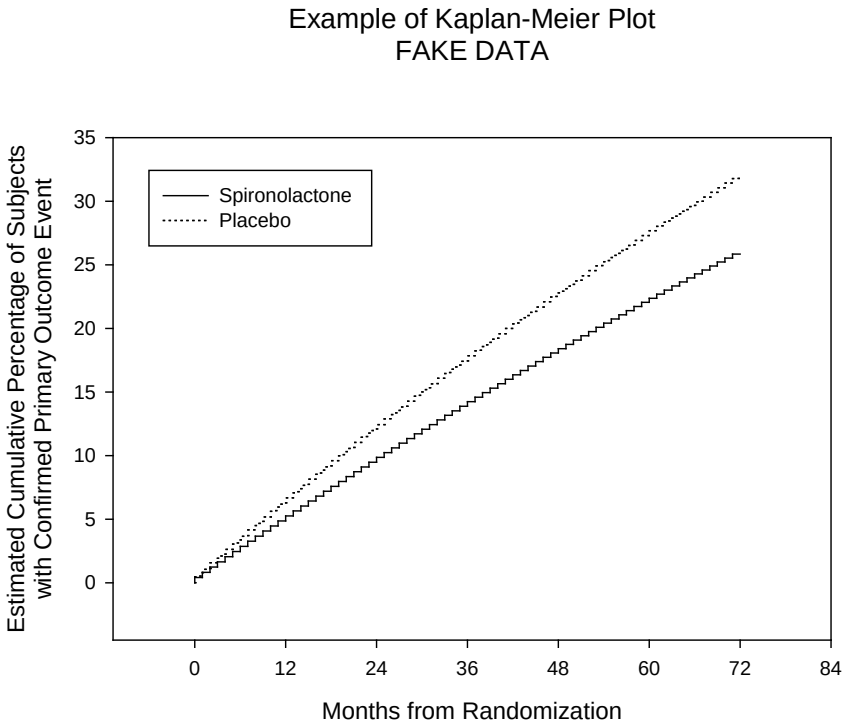
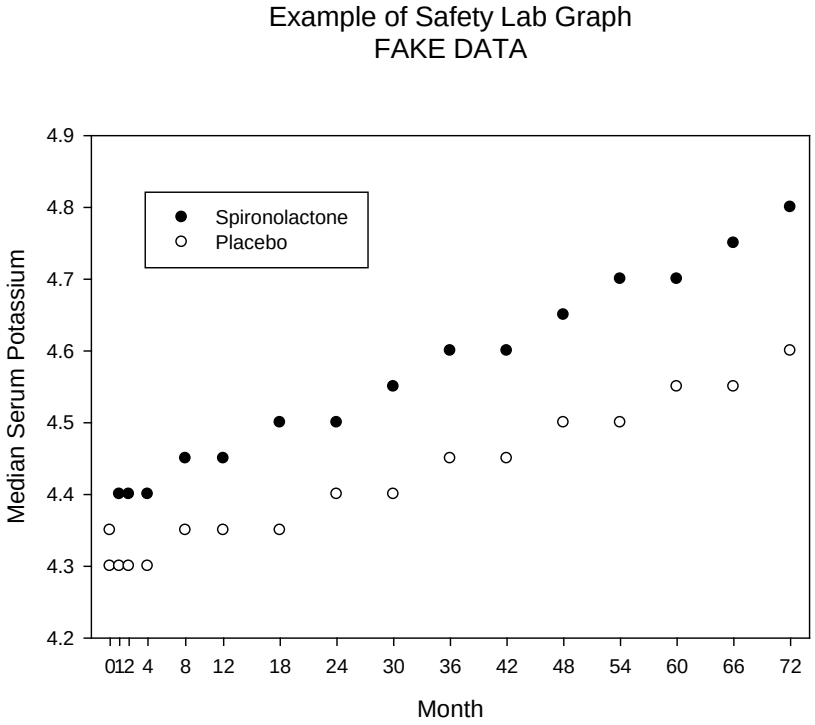


Figure XXX: K-M plot for the Primary Outcome

NOTE: Each K-M figure would also give # at risk in each treatment group under the X axis.

Figure 2. Kaplan-Meier plots of the four time-to-event safety outcomes (panels A through D), and graphs of the medians for safety laboratory tests at each visit (panels E through K). Note that some of these plots will probably appear in the Supplement rather than in the main published manuscript.



NOTE: The K-M plots would also show the number at risk under each tick mark. The lab plots would also show the number with measurements performed in each treatment group under the X axis.

Supplemental Table: CONSORT worksheet

Supplemental Figure 1S. CONSORT flow diagram, starting with 3445 randomized subjects.

Supplemental Figure 2S. Kaplan-Meier plot of time to premature ending of study follow-up for clinical outcomes (subject withdrawal, physician withdrawal, loss to follow-up), by treatment group

Supplemental Figure 3S. Kaplan-Meier plot of time to early permanent discontinuation of study drug (i.e. before end-of-study date), by treatment group

Supplemental Figure 4S. Whatever panels from Figure 2 do not make it into the actual published manuscript.