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MANUAL OF OPERATIONS

TOPCAT TRIAL
MASTER SUBJECT LOG

Site Name: _____ Site Number: ___ ___ ___ ___

Principal Investigator: _____ Site Contact: _____

SUBJECT Initials	Date of Birth	Social Security Number (US Only)	Permanent Address	Home Phone Number	Randomization Date	Date Subject was discontinued from study	Subject Follow-up Status

DO NOT SEND TO CTCC.

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TOPCAT Trial

Inclusion/Exclusion Criteria

Inclusion Criteria

Subject must meet all the following criteria in order to be eligible for study enrollment:

1. Subject (male or female) is ≥ 50 years of age;
2. Subject has been diagnosed with heart failure at screening as defined below (see Table 1). To be diagnosed with heart failure, subject must have at least one symptom present at the time of screening *and* have experienced at least one sign in the last 12 months. Heart failure eligibility should be carefully monitored and documented in the subject's medical record;

TABLE 1. Criteria For Diagnosing Heart Failure

SYMPTOMS (subject must be present with *at least* one symptom at the time of screening)	SIGNS (subject must have experienced *at least* one sign in the last 12 months)
• **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**

3. Subject has left ventricular ejection fraction ≥ 45% (per local reading) within 6 months prior to randomization and after any myocardial infarction (MI) or other event that could potential affect the ejection fraction. Ideally, ejection fraction should be obtained by echocardiography. However, ejection fractions obtained by radionuclide ventriculography or angiography are acceptable as well.
4. Subject has a controlled systolic blood pressure which is defined as a target systolic blood pressure < 140 mm Hg. Subjects with systolic blood pressure ≥ 140 mm Hg and ≤ 160 mm Hg are eligible for study enrollment if subjects are currently taking 3 or more medications to control blood pressure;
5. Subject has a serum potassium level < 5.0 mmol/L prior to randomization;
6. Subject has been hospitalized* at least once in the last 12 months for which heart failure was a major component for hospitalization. Hospitalization as a result of a transient heart failure in the context of MI will not qualify for this inclusion criterion.

   OR

   Subject has a brain natriuretic peptide (BNP) level ≥ 100 pg/ml or N-terminal pro-BNP level ≥ 360 pg/ml in the last 60 days which was attributed to the subject's heart failure and not another disease;
7. Female subjects of child-bearing potential must have a negative serum/urine pregnancy test within 72 hours prior to randomization and must not be lactating. Both male and female subjects must agree to use adequate birth control measures during the entire course of study participation;
8. Subject will comply with study schedule visits as outlined in Table 2 of the study protocol;
9. Subject has signed the informed consent form;

*

Exclusion Criteria

If subject meets any one of the following criteria, he/she is not eligible for study enrollment:

1. Subject has a life expectancy of less than three years;
2. Subject has chronic pulmonary disease requiring home O_2, oral steroid therapy or hospitalization for exacerbation within the previous 12 months, or has significant chronic pulmonary disease in the opinion of the investigator;
3. Subject has known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;
4. Subject has primary hemodynamically significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease that will require surgery during the trial;
5. Subject has atrial fibrillation with a resting heart rate > 90 bpm;
6. Subject had a myocardial infarction (MI) in the past 90 days;
7. Subject had coronary artery bypass surgery in the past 90 days;
8. Subject had percutaneous coronary intervention in the past 30 days;
9. Subject is a heart transplant recipient;
10. Subject is implanted with a left ventricular assist device;
11. Subject had a stroke in the past 90 days;
12. Subject has systolic blood pressure (SBP) > 160 mm Hg;
13. Subject has known orthostatic hypotension;
14. Subject has gastrointestinal disorder that could interfere with study drug absorption;
15. Subject has taken aldosterone antagonist or potassium sparing medication of any kind in the last 14 days or any known condition that would require the use of an aldosterone antagonist during study participation;
16. Subject has a known tolerance to aldosterone antagonists;
17. Subject is currently taking lithium;
18. Subject is currently participating in another clinical trial or has been a participant in another clinical trial in the last 30 days;
19. Subject has a condition that, in the opinion of the investigator, may prevent he/her from adhering to the trial protocol;
20. Subject has a 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. Subject has severe renal dysfunction which is defined as having an estimated glomerular filtration rate (GFR) level < 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 from the study even if their GFR is ≥ 30 ml/min;
22. Subject has a known chronic hepatic disease which is defined as having aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels > 3.0 times the upper limit of normal as read at the local lab.

Randomization of Hospitalized Patients in TOPCAT

Since the protocol makes no specific mention of obligate duration on a stable medical regimen or distance from hospitalization when considering eligibility for TOPCAT, the steering committee has proposed the following guidelines for randomization of patients during an inpatient stay:

Patients may be randomized during a hospitalization (including the qualifying heart failure hospitalization) if:
1) They meet all inclusion and exclusion criteria
2) They are on a stable heart failure regimen defined as :
    1. No IV therapy (diuretics, inotropes, vasodilators, ultrafiltration, etc.)
    2. No active cardiovascular medication titration in last 48 hours
    3. No imminent plans for future adjustment of cardiovascular medications

This will permit investigators (at all TOPCAT sites) to randomize patients in hospital once they are (in the judgement of the treating physician) on a stable medical regimen. Please direct any requests for clarification of clinical 'stability' to the TOPCAT medical monitors (topcatmd@partners.org).

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TOPCAT Trial

Informed Consent Procedure And Patient Confidentiality

Subject Written 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 New England Research Institutes (NERI) 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 sub-study of the main protocol. All sites participating in the sub-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 preserved systolic function (PSF).

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

The informed consent process will be performed in accordance with the ICH guidelines (E6) for Good Clinical Practice (GCP), 21 CFR50, 21 CFR56, and local laws and regulations, as applicable.

The process will involve two steps. In the first step, all potential study subjects will be given a copy of the informed consent form (also called the patient 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 informed consent form/patient information sheet, ask any questions and to decide whether or not he/she would like to participate in the trial. The informed consent form/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 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 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.

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 declaration of consent will be kept in the subject 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.

Patient Confidentiality

Patient confidentiality will be maintained according to ICH guidelines for GCP, the Health Insurance Portability and Accountability Act (HIPAA) and applicable local and national data protection laws. A study identification number will be assigned to each subject. The link between subject name and subject I.D. 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 case report form and any process derived from the case report form is handled confidentially.

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TOPCAT Trial

Randomization Procedure

TOPCAT Trial Randomization Procedure

Randomization of a TOPCAT study subject occurs during the baseline study visit, and should be performed only when the following criteria are met:

- The subject meets all inclusion criteria (i.e. all inclusion questions must be answered "**YES**");
- The subject meets no exclusion criteria (i.e. all exclusion questions must be answered "**NO**");
- The subject has agreed to participate in the study by signing the TOPCAT Study informed consent form. Each eligible subject will be assigned a subject ID# in the ADEPT database once he/she has provided consent. (See the "Assigning a new Subject ID" section of the ADEPT User Guide
- The maximum allowable timeframe between study baseline visit and the randomization date is 14 days. If baseline laboratory values were collected more than two weeks before the date of randomization, the clinic sites should repeat baseline laboratory values, 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 was no inter-current change in medications and/or no borderline laboratory values.

Once all of the above conditions have been met, the subject shall be randomized over the internet using the following procedure:

1. Print out a hardcopy of case report form titled Randomization Form (CRF #T011).
2. Log in to the ADEPT data management system and enter the corresponding subject ID number for the subject ready to be randomized. Print out a hardcopy of case report form titled Randomization Form (CRF# T011).
3. Complete Section A of the Randomization Form (CRF #T011).
   - Under section A1, enter a valid subject I.D. which should be comprised of 8 characters.
   - Under section A2, enter subject's 3 character initials. If subject does not have a middle initial, enter a dash (-) in the space provided. For example, subject Jane Doe will have her initials entered as J - D.
4. Complete Section B of the Randomization Form.
   - Under section B1, enter a valid date of randomization. Please note that the date of randomization cannot occur prior to the date of informed consent.
   - Under section B2, enter subject's date of birth. Please note that if the subject's date of birth does not put him/her at ≥ 50 years of age at the time of informed consent, subject is not eligible for randomization.
   - Under section B3, enter subject's gender (i.e. male or female).
   - Under section B4, indicate whether or not the subject is Black or African American. If subject indicates that he/she is Black or African American, check the Yes box. If subject indicates that he/she is not Black or African American, check the NO box. This information is used to calculate subject's creatinine clearance.
   - Under section B5, enter subject's baseline serum creatinine level. If the subject's baseline serum creatinine level is ≥ 2.5 mg/dL or 221 µmol/L, subject is not eligible for randomization.
   - Under section B6, indicate whether or not subject has been hospitalized within the past 12 months as a result of heart failure.

     Please note that if the subject was hospitalized as a result of a transient heart failure in the context of MI, **he/she will not qualify for this inclusion criterion**. Hence, if subject has had at least one hospital admission in the last 12 months due to heart failure and was not part of an MI, check the YES box.

- Under section B7, indicate whether or not subject has had a brain natriuretic peptide (BNP) in the last 60 days ≥ 100 pg/ml or N-terminal pro-BNP ≥ 360 pg/ml which was solely attributed to subject's heart failure and not another disease or condition.

  Please note that subject must satisfy inclusion criteria B6 or B7 in order to be eligible for randomization. Failure to qualify for either B6 or B7 will automatically disqualify subject from participating in the study.

- Under section B8, indicate whether or not subject has met ALL of the INCLUSION CRITERIA for the study. Please re-review the Inclusion Criteria Section of the study protocol to ensure that subject has met ALL of the INCLUSION CRITERIA. If subject has met ALL of the INCLUSION CRITERIA (i.e. all questions for INCLUSION CRITERIA are answered "YES"), check the YES box. If the subject has failed to meet ANY of the INCLUSION CRITERIA (i.e. if any INCLUSION CRITERIA is answered "NO"), check the NO box.

  Failure to meet ANY of the INCLUSION CRITERIA outlined in the study protocol will automatically disqualify subject from participating in the study.

- Under section B9, indicate whether or not subject has met ANY of the EXCLUSION CRITERIA for the study. Please re-review the Exclusion Criteria Section of the study protocol to ensure that subject has NOT met ANY of the EXCLUSION CRITERIA. If subject has met NONE the EXCLUSION CRITERIA (i.e. all questions for EXCLUSION CRITERIA are answered "NO"), check the YES box. If the subject has met one or more of the EXCLUSION CRITERIA (i.e. if any EXCLUSION CRITERIA is answered "YES"), check the NO box.

  Subject will be automatically disqualified from participating in the study if he/she has met one or more of the exclusion criteria outlined in study protocol.

Enter data from section A and B of the Randomization Form for each subject into the ADEPT database. (Appendix A of the ADEPT User Guide includes information about the ADEPT randomization process.) If subject is eligible to participate in the study, the subject will be randomly assigned a study treatment code (code A thru L). Please print out the subject's treatment code assignment, attach the treatment code to the subject's Randomization Form, and place both forms in the subject's study file.
If subject is not eligible to participate in the study, please complete the case report form titled End of Study Report (CRF# T030) for this subject. Please indicate the reason why the subject was not qualified to participate in the study.

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TOPCAT Trial

STUDY VISIT SCHEDULE

RECORD SCREENING

- Review past medical history (including demographics, cardiac risk factors, and the prior 12 months for recent hospitalizations and procedures)
- Review current medications.
- Review subject's ejection fraction, which must have been obtained within 6 months prior to randomization and after any MI or other event that would affect ejection fraction. The qualifying ejection fraction may be obtained by echocardiography, angiography, or radionucleotide ventriculography. *It is preferred that the qualifying ejection fraction be obtained by echocardiography*.

  If the qualifying ejection fraction was obtained by echocardiography, a copy of the echocardiogram (video copy or digital image is acceptable) from the first two study subjects from each site must be submitted to the ECHO Core Lab. If the qualifying ejection fraction was obtained by angiography, or radionucleotide ventriculography, clinical sites need not submit copies of the angiogram or radionucleotide ventriculogram to NERI.
- Additional echos may be requested at any time during the study from the NERI.

To qualify for the study, subject's ejection fraction must be ≥ 45% (per local reading).

BASELINE VISIT PROCEDURES

After written informed consent is obtained, a baseline visit will occur, during which a subject's eligibility will be confirmed and baseline labs will be drawn.

- Discuss the optional repository sub-study (if applicable) and complete sub-study's Informed Consent, if applicable.
- Obtain subject's demographic information and medical and social history.
- Obtain subject's concomitant medication information.
- Perform and record physical examination, including vital signs.
- Collect blood sample for local laboratory tests (i.e. CBC, electrolytes, BUN, creatinine, blood glucose, and liver function tests). 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.
- If baseline laboratory values were collected more than two weeks before the date of randomization, the clinic sites will repeat baseline laboratory values, 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 was not inter-current change in medications and/or no borderline laboratory values.
- Collect urine sample for local laboratory tests (i.e. urine microalbuminuria and urine creatinine). Site is to report the ratio of urine microalbuminuria (in mg) to urine creatinine (in gram or mmol) in the CRF. Urine samples need not be collected for

clinic sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory practice. Urine dipstick measurement of proteinuria should be reported, if available.

- Calculate subject's estimated golmerular filtration rate (GFR) using the 4-component MDRD Study prediction equation.

  GFR = 186 x (serum creatinine level [in milligrams per deciliter])$^{-1.154}$ x (age [in years])$^{-0.203}$. For women and blacks, the product of this equation is multiplied by a correction factor of 0.742 and 1.21, respectively. Note: GFR is calculated automatically in ADEPT upon entering data.
- Determine subject's eligibility (see inclusion/exclusion criteria of the study protocol).
- Confirm subject's eligibility (i.e. subject has met ALL of the INCLUSION CRITERIA and NONE of the EXCLUSION CRITERIA).
- Obtain subject's most recent ECG and fax it to the ECHO Core Lab at 617-582-6027. Alternatively, if an echo is being mailed to the ECHO Core lab, the ECGs may be included in the mailing.
- For the first two study subjects, obtain their most recent ECHO from the past 6 months and send it to the following address:

  Renee Y. Mercier
  BWH TOPCAT Echo Core Lab
  20 Shattuck Street, PBB Ground Rm A100
  Boston, MA 02155

For detailed instructions on how to perform the baseline echo and how to send it to the ECHO Core Lab, please refer to the ECG_ECHO Core Lab Procedure section (Section 10) of the Manual of Operations.

If the subject has signed the Informed Consent and meets all the inclusion/exclusion criteria for the study, the subject may be randomized into the study. Please refer to the Randomization Procedure (Section 4) of the Manual of Operations for detailed instructions on how to randomize a subject.

BASELINE VISIT CASE REPORT FORMS

- Consent Confirmation (CRF# T001)
- Eligibility (CRF# T002)
- Demographics (CRF# T003)
- Clinical Evidence of Heart Failure (CRF# T004)
- Medical and Social History (CRF# T005)
- Baseline Physical Exam (CRF# T006)
- Medications (CRF# T007)
- Baseline Laboratory Tests (CRF# T008)
- Urine Microalbuminuria (CRF# T009)
  - This laboratory result is a ratio of microalbuminuria (in mg) to urine creatinine (in grams or mmol). This test is not required for clinic sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory

practice. However, sites are still required to report the urine dipstick measurement of proteinuria (if available).

- Electrocardiogram (CRF# T010)
- Repository Sample Collection/Repository Sample Processing only if subject has given his/her consent (CRF# R001 and CRF #R002)
- QOL Coversheet (CRF# Q001)
- QOL: Kansas City Cardiomyopathy Questionnaire (KCCQ) (CRF# Q002)
- QOL: EQ5D Visual Analog Scale (EQ5D) (CRF# Q003)
- QOL: Patient Health Questionnaire (PHQ) – For North American Sites Only (CRF# Q004)
- Randomization Form (CRF# T011)
- Study Drug Dispensing (CRF# T012)

For ADEPT information, refer to the following section of the ADEPT User Guide: "Enrolling a new subject into the TOPCAT trial".

After subject's eligibility has been confirmed, he/she will be assigned to receive the allocated treatment through ADEPT. Subjects will be randomized via a secure internet website to a treatment allocation code which consists of one letter code (A thru L) corresponding to either spironolactone or placebo (blinded). Two bottles of study drug (of the assigned treatment allocation code) will then be dispensed to the subject with instructions from principal investigator.

1 WEEK VISIT FORM

- Follow-up Lab Tests (CRF# T016)

Subjects must have blood drawn for safety labs (i.e. electrolytes and chemistries) at 1 week post drug initiation (i.e. one week after the subject has started taking study drug). Electrolytes will include sodium, potassium, chloride, and bicarbonate or total CO_2. Chemistries will include BUN and creatinine.

4 WEEK VISIT FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)

Subjects must have an office visit and safety labs at 4 weeks post drug initiation. Study drug dose should be increased to 30 mg/day (two tablets daily) at 4 weeks if all safety parameters are acceptable. If the study drug is increased at this time, subjects must have blood drawn at week 5 (i.e. one week after dose change).

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/day (one tablet daily).

If drug discontinuance is indicated by the chemistry panel results at this visit, study drug will be discontinued at this time and a follow-up visit must be scheduled within one week at

which time an additional safety lab assessment will be performed. See Section 18 of this Manual and Section C.3.6 of the protocol for information regarding the permanent discontinuation of study drug.

5 WEEK VISIT FORM

- Follow-up Lab Tests (CRF#T016) (applicable only if study dose was changed at 4 week visit)

Subjects must also have blood drawn for safety labs one week after each dose change.

For details on the study drug titration schedule, please refer to the Study Drug Titration and Safety Assessment section (Section 8) of the Manual of Operations.

8 WEEK VISIT FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)

Subjects will have an office visit and safety labs at 8 weeks post drug initiation.

If drug reduction/discontinuance is indicated by the chemistry panel results at this visit, study drug will be reduced/discontinued at this time and a follow-up visit must be scheduled within one week at which time an additional safety lab assessment will be performed.

4 MONTH VISIT FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)
- QOL Coversheet (CRF# Q001)
- QOL: Kansas City Cardiomyopathy Questionnaire (KCCQ) (CRF# Q002)
- QOL: EQ5D Visual Analog Scale (EQ5D) (CRF# Q003)
- QOL: OTE – For North AmericanSites Only (CRF# Q005)

Subjects will have an office visit and safety labs at 4 months.

If drug reduction/discontinuance is indicated by the chemistry panel results at this visit, study drug will be reduced/discontinued at this time and a follow-up visit must be scheduled within one week at which time an additional safety lab assessment will be performed.

If the subject continues to have ongoing heart failure, the study doctor has the option to increase the study drug dose to 45 mg/day (three tablets daily) at 4 months. If the study

drug is increased at this time, subjects must have blood drawn for safety labs the following week (i.e. one week after dose change). Subject should be given sufficient study drug (anywhere from 1 – 3 bottles depending on the study drug dosage) to carry him/her until the next scheduled study follow-up visit at 8 months.

8 MONTH VISIT FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)

If drug reduction/discontinuance is indicated by the chemistry panel results at this visit, study drug will be reduced/discontinued at this time and a follow-up visit must be scheduled within one week at which time an additional safety lab assessment will be performed.

Subjects will have an office visit and safety labs at 8 months. Subject should be given sufficient study drug (anywhere from 1 – 2 bottles depending on the study drug dosage) to carry him/her over until the next scheduled study follow-up visit at 12 months.

12 MONTH VISIT FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)
- Urine Microalbuminuria (CRF# T009)
    - This laboratory result is a ratio of microalbuminuria (in mg) to urine creatinine (in gms or mmol). This test is not required for sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory practice. However, sites are still required to report the urine dipstick measurement of proteinuria (if available).
- QOL Coversheet (CRF# Q001)
- QOL: Kansas City Cardiomyopathy Questionnaire (KCCQ) (CRF# Q002)
- QOL: EQ5D Visual Analog Scale (EQ5D) (CRF# Q003)
- QOL: Patient Health Questionnaire (PHQ) – For North American Sites Only (CRF# Q004)
- QOL: OTE – For North American SitesOnly (CRF# Q005)
- Repository Sample Collection/Repository Sample Processing only if subject has given his/her consent (CRF# R001 and CRF # R002)

Subjects will have an office visit and safety labs at 12 months. Subject should be given sufficient study drug (anywhere from 1 - 5 bottles depending on the study drug dosage) to carry him/her over until the next scheduled study follow-up visit at 18 months.

Collect urine sample for local laboratory tests at 12 months (i.e. urine microalbuminuria and urine creatinine). Site is to report the ratio of urine microalbuminuria (in mg) to urine creatinine (in gram or mmol) in the CRF. Urine samples need not be collected for clinic sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory practice.

After the 12 Month visit, subsequent follow-up visits will be scheduled every six months thereafter for up to 6 years (i.e. 18 Month, 24 Month, 30 Month, 36 Month, 42 Month, 48 Month, 54 Month, 60 month, 66 month, and 72 month).

Subject should be given sufficient study drug (anywhere from 2 - 4 bottles depending on the study drug dosage) to carry him/her over until the next scheduled study follow-up visit.

Collect urine sample for local laboratory tests at 24, 36, 48, 60 and 72 months (i.e. urine microalbuminuria and urine creatinine). Site is to report the ratio of urine microalbuminuria (in mg) to urine creatinine (in gram or mmol) in the CRF. Urine microalbuminuria need not be reported for clinic sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory practice.

Specifics for study drug titration and dosing regimen are described in the Manual of Operations (MOO) under Study Drug Titration And Dosing Regimen and in Section C.3.4 and Figure 2 of the study protocol.

Unplanned visits will be determined by the treating physician for symptoms, abnormal lab work, or other reasons.

Blood and urine specimens for the repository will be obtained only at baseline and 12 months from consented subjects (not applicable for subjects in the European Union).

If drug reduction/discontinuance is indicated by the chemistry panel results during the study visit, study drug will be reduced/discontinued at that time and a follow-up visit must be scheduled within one week at which time an additional safety lab assessment will be performed.

18 MONTH, 30 MONTH, 42 MONTH, 54 MONTH AND 66 MONTH VISITS FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)
- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)

If at any time there is a change in study drug dose, safety labs should be obtained one week after the dose change.

Subject should be given sufficient study drug (anywhere from 1 – 4 bottles depending on the study drug dosage) to carry him/her over until the next scheduled study follow-up visit.

24 MONTH, 36 MONTH, 48 MONTH, 60 MONTH AND 72 MONTH VISITS FORMS

- Follow-up Physical Exam (CRF# T013)
- Event Questionnaire (CRF# T014)

- Study Drug Information (CRF# T015)
- Follow-up Lab Tests (CRF# T016)
- Medications (CRF# T007)
- Urine Microalbuminuria (CRF# T009)
    - This laboratory result is a ratio of microalbuminuria (in mg) to urine creatinine (in gms or mmol). Urine microalbuminuria need not be reported for clinic sites that do not report the ratio of urine microalbuminuria to urine creatinine as part of their standard laboratory practice. However, sites are still required to report the urine dipstick measurement of proteinuria (if available).
- QOL Coversheet (CRF# Q001)
- QOL: Kansas City Cardiomyopathy Questionnaire (KCCQ) (CRF# Q002)
- QOL: EQ5D Visual Analog Scale (EQ5D) (CRF# Q003)
- QOL: Patient Health Questionnaire (PHQ) – For North American Sites Only (CRF# Q004)

If at any time there is a change in study drug dose, safety labs should be obtained one week after the dose change.

Subject should be given sufficient study drug (anywhere from 1 – 4 bottles depending on the study drug dosage) to carry him/her over until the next scheduled study follow-up visit.

ACCEPTABLE WINDOWS FOR STUDY 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 site-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

DAY 0 = Subject's Randomization Date

Visit	Window	Day Range
Week 1	± 3 days	Day 4 through Day 10
Week 4	± 3 days	Day 25 through Day 31
Week 5	± 3 days	Day 32 through Day 38
Week 8	± 3 days	Day 53 through Day 59
Month 4	±2 weeks	Day 107 through Day 135
Month 8	±2 weeks	Day 229 through Day 257
Month 12	±2 weeks	Day 351 through Day 379
Month 18	± 4 weeks	Day 520 through Day 576
Month 24	± 4 weeks	Day 702 through Day 758
Month 30	± 4 weeks	Day 885 through Day 941

Month 36	± 4 weeks	Day 1067 through Day 1123
Month 42	± 4 weeks	Day 1250 through Day 1306
Month 48	± 4 weeks	Day 1432 through Day 1488
Month 54	± 4 weeks	Day 1615 through Day 1671
Month 60	± 4 weeks	Day 1798 through Day 1854
Month 66	± 4 weeks	Day 1981 through Day 2037
Month 72	± 4 weeks	Day 2164 through Day 2220

END OF STUDY VISIT FORMS

- End of Study Report
- Death Report (if applicable)

STUDY SCHEDULE VISIT

	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 Monitoring					X		X	X	X	X	X	X	X
Ratio of Urine Microalbuminuria to Urine Creatinine^		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 labs):

- 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 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 to North American sites only; 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 to North American sites only.

^ Urine Microalbuminuria and urine creatinine will be done locally.

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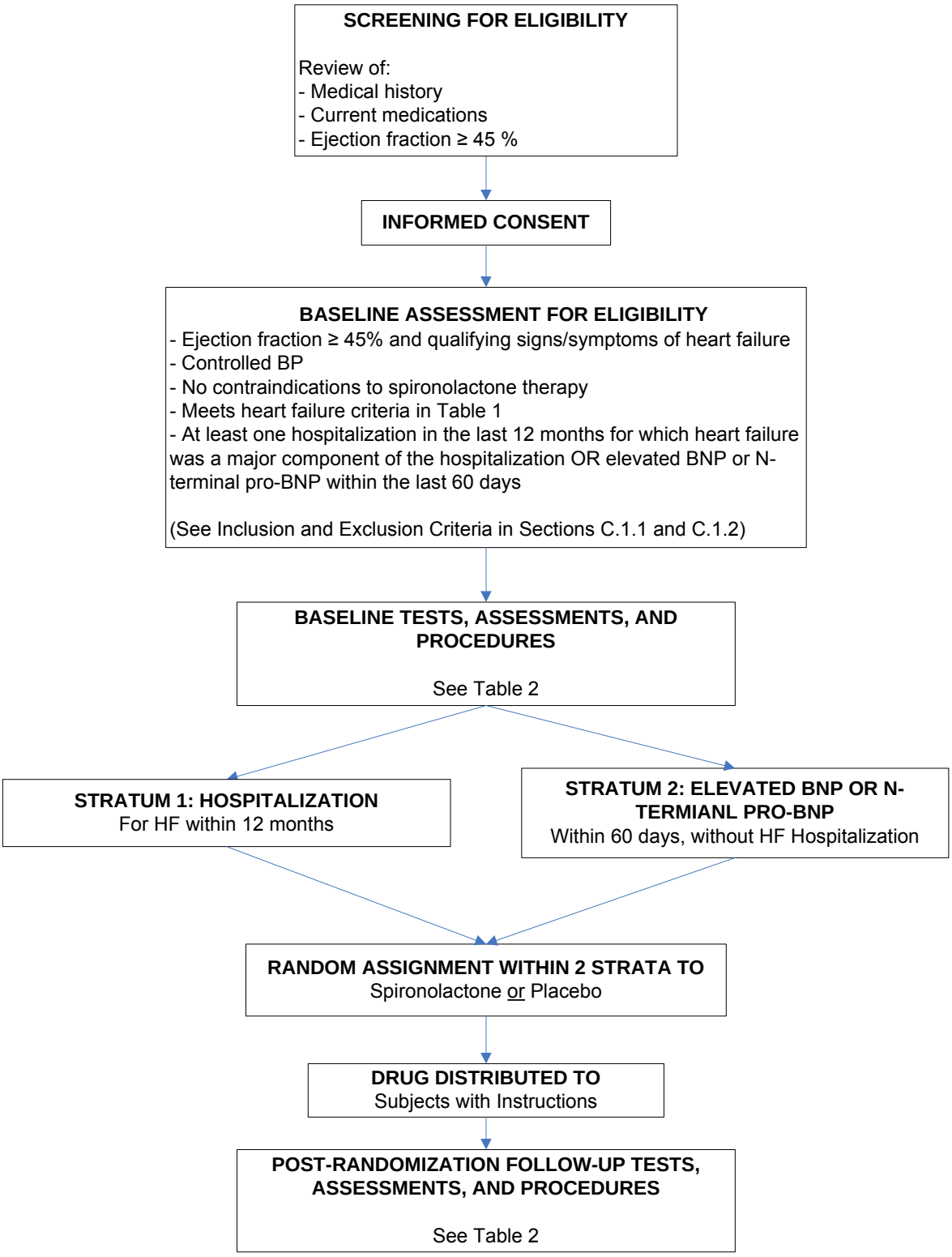
TOPCAT Trial

Subject Flow in Trial

SUBJECT FLOW IN TRIAL



- If baseline laboratory values were collected more than 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 was no inter-current change in medications and/or no borderline lab values.

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TOPCAT Trial

Initial Study Drug Administration
(Day 0 – Randomization)

INITIAL STUDY DRUG ADMINISTRATION

The first dose of study drug, one 15 mg tablet per day, will be administered on the same day the subject has been successfully randomized to a treatment code (A thru L).

Under no circumstances should study drugs be dispensed to subjects not randomized to the TOPCAT trial.

Subjects who are successfully randomized into the study are assigned specific treatment allocation codes. Subjects can only receive study drugs that correspond to their treatment allocation code.

Prior to subject's randomization, the clinic site must have obtained a signed informed consent from the subject, performed all the necessary baseline procedures, confirmed baseline laboratory results are all within acceptable protocol parameters, and confirmed that the subject has met all the inclusion criteria and none of the exclusion criteria in the study protocol.

FOR STUDY DRUG TITRATION AND DOSING REGIMEN, PLEASE SEE STUDY DRUG TITRATION AND DOSING REGIMEN SECTION (Section 8) OF THE MANUAL OF OPERATIONS.

Please refer to Section 9 of the Manual of Operations for study drug dispensing information.

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TOPCAT Trial

Study Drug Titration and Safety Assessment Schedule

STUDY DRUG

The first dose of study drug, one 15 mg tablet, will be administered to the subject on the same day after randomization has occured. Prior to subject's randomization, the clinic site must have obtained a signed informed consent from the subject, performed all the necessary baseline procedures, confirmed baseline laboratory results are all within acceptable protocol parameters, and confirmed that the subject has met all the inclusion/exclusion criteria in the study protocol.

STUDY DRUG TITRATION AND DOSING REGIMEN

All subjects randomized 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 (see page 2). After 4 weeks, the study drug 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 (i.e. three tablets by mouth every 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 (one tablet) or greater than 45 mg daily (three tablets). 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 or 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 (three tablets), the dose should be reduced to 30 mg (two tablets); if the subject is on 30 mg (two tablets), the dose should be reduced to 15 mg (one tablet); and if the subject is already on the lowest dose (i.e. 15 mg), and if there are 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 study drug should not be uptitrated beyond this level for the trial duration. If subject is on a concomitant medication that may be precipitating the hyperkalemia and it is safe to continue study drug, it is appropriate to decrease the study drug dose and recheck the subject's potassium level in one week.
2. Study drug should be permanently discontinued if potassium ≥ 6.0 mmol/L on a non-hemolyzed sample (i.e. a sample drawn into a tube with anti-coagulant), regardless of the dosing regimen, if there are no alternative explanations for the elevated potassium level. Subjects who are no longer on study medication will still be asked to come for follow-up visits for the duration of the trial. If the subject does not want to come in for follow-up visits, the clinic site should continue to follow the subject by telephone or by mail.

   NOTE: Treating physicians should consult the TOPCAT Medical Monitors (topcatmd@partners.org or 617-732-5656, at prompt enter: 18228) 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. A suggested low potassium diet is posted on the PAWS website (https://paws.neriscience.com/siteLogin.asp) under the "Additional Tools" section.

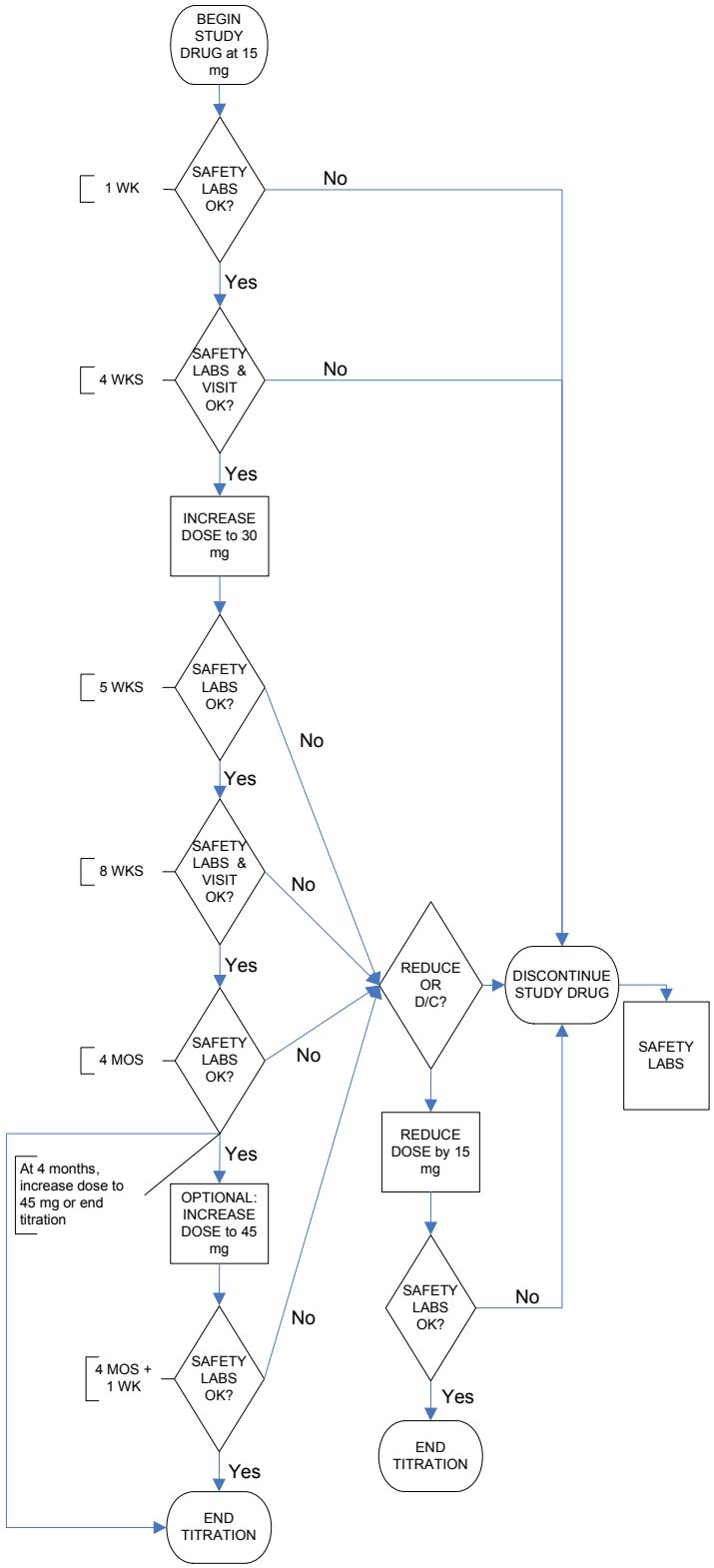
3. Reinitiate study drug, at the discretion of the treating physician, if the dosing regimen is interrupted due to non-compliance. If a subject is eligible for study drug reinitiation, the physician should choose from one the following three options:
   - Reinitiate study drug at the highest previously tolerated dose (dose just prior to drug discontinuation); follow-up labs at 1 week, then resume scheduled study visits
   - Reinitiate study drug at a lower dose; follow-up labs at 1 week, then resume scheduled study visits.
   - 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.
If study drug reduction or discontinuance is indicated by the chemistry panel results, study drug will be reduced/discontinued at this time and a follow-up visit must be scheduled within one week at which time an additional safety lab assessment will be performed.

Once the subject is appropriately titrated, the dosing regimen (i.e. 15mg, 30mg, 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:

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 <u>non-compliance</u>, 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.

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TOPCAT Trial

Study Drug Dispensing

STUDY DRUG DISPENSING

Study drug will be dispensed to subject at Randomization (Day 0), 4 Month visit, 8 Month visit, 12 Month visit, and every 6 months thereafter. At Randomization (Day 0), subject should be given two bottles of study drug (of the assigned treatment allocation code) with specific instructions from study doctor along with a TOPCAT study medication bag. At 4 Month visit, 8 Month visit, 12 Month visit, and every 6 months thereafter up to 66 months subject should be given sufficient study drug (see General Study Drug Dispensing Guidelines below) to carry him/her until the next scheduled study follow-up visit. The site should dispense study drug from the study batch lot # with the earliest expiration date.

An initial shipment of 12 boxes (i.e. 4 bottles per treatment code) will be sent to the site as soon as all required regulatory documents are received by NERI. In addition to the study drugs, the initial shipment will also contain a 50-mL graduated cylinder (for sites to record the volume of study drug tablets in each opened study drug bottle at each scheduled study visit) and 12 TOPCAT study medication bags (one per randomized subject).

General Study Drug Dispensing Guidelines:

4 Month visit

	15 mg/day (i.e. one tablet per day)	**30 mg/day** (i.e. two tablets per day)	**45 mg/day** (i.e. three tablets per day)
# of Study Drug Bottles Dispensed	1	2	3

8 Month visit

	15 mg/day (i.e. one tablet per day)	**30 mg/day** (i.e. two tablets per day)	**45 mg/day** (i.e. three tablets per day)
# of Study Drug Bottles Dispensed	1	2	3

12 Month visit

	15 mg/day (i.e. one tablet per day)	**30 mg/day** (i.e. two tablets per day)	**45 mg/day** (i.e. three tablets per day)
# of Study Drug Bottles Dispensed	1	2	5

Every 6 months thereafter

	15 mg/day (i.e. one tablet per day)	**30 mg/day** (i.e. two tablets per day)	**45 mg/day** (i.e. three tablets per day)
# of Study Drug Bottles Dispensed	1-2	3	4

Previously dispensed study drug bottles are to be brought in by the subject to the clinic site at each subsequent visit to verify drug compliance. The volume of unused tablets and the number of empty bottles will be recorded on the appropriate case report form (CRF# T015), and the tablets will be returned to the subject. Site personnel will instruct study subjects on the importance of compliance.

Under no circumstances should study drugs be dispensed to subjects not randomized to the TOPCAT trial.

Subjects who are successfully randomized into the study are assigned specific treatment allocation codes. Subjects can only receive study drugs that correspond to their treatment allocation code.

All study drug bottles (i.e. empty, unused, unopen, etc.) will be returned to the sponsor at the end of the trial or destroyed at each site according to their standard operating procedures.

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

Echocardiography Core Laboratory

Site Manual of Operations

Scott D. Solomon, MD, Director
Brigham and Women's Hospital Echocardiographic Core Laboratory
Associate Professor of Medicine
Director, Noninvasive Cardiac Laboratory
Brigham and Women's Hospital
Boston, MA 02115

Version: v.5 April 2011

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For technical questions please contact the Echo Core Lab at:
Phone: 1-617-525-6730
Email: echocore@rics.bwh.harvard.edu

I. Introduction

The primary objective of the study is to test the hypothesis that treatment with the aldosterone antagonist spironolactone will reduce the risk of cardiovascular death or heart failure hospitalization in patients with preserved systolic function heart failure. *Please refer to the TOPCAT Protocol for a complete listing of study objectives and study rationale.*

The primary objective of the Echo Core Lab (ECL) is to provide quality control over the echo assessment across study sites.

The purpose of this Site Instruction Manual is to provide sites with instruction on performing the baseline echo and sending it, along with the ECG, to the Echo Core Lab.

Subjects may choose not to release their echo to the ECHO Core Lab. If the echo tapes/CDs have already been sent, they will be sent back to the site. The data collected, however will remain in the ECHO Core Lab database.

II. Echo Visit Schedule

Sites are required to send echos for their first two randomized subjects who qualified by echo at the baseline visit and who provided consent for their echo to be released to the Core Lab. Because in some cases the videotape or digital copy of the echocardiogram may contain personal information that cannot be erased or deleted, subjects will provide a separate consent (within the main trial consent from) regarding their echo data. Only echos from subjects who provided consent for their echos to be released will be sent. If possible, all identifying information must be removed from the echos.

Additional echos will be requested randomly (not to exceed 5% of total). After you have sent in echos from the first two subjects enrolled at your site, you will be notified by the Data Coordinating Center (New England Research Institute) about what additional echos need to be sent to the Echo Core Lab.

III. Echo Supplies

The following echo-related supplies materials should be downloaded from the Project Administrative Web Site (PAWS) at https://paws.neriscience.com/:

1. Echo Media and ECGs Labels
2. Echo Tracking Forms

IV. Echo Media

☝ If your particular machine is capable of producing echos on CD-ROM, we ask that sites send studies on CDs. All digital data must be received in DICOM format. Please contact the Echo Core Lab if you have any questions regarding your machine's capabilities.

☝ Videotapes and 3 ½ inch Magnetic Optic (MO)* discs are also acceptable but not preferred.

☝ Only record one echo study per each echo media - CD/videotape/MO disc.

V. ECL Feedback

The ECL will only contact your site if there are concerns regarding the quality (readability) of the echo.
In this case, the ECL Clinical Project Manager will contact the site. Depending on the nature of the concern, a second tape may be required. If there are no concerns regarding the echo study provided, the ECL will not contact the site.

VI. Instructions for Sending Media to the Echo Core Lab

1. RECORD ECHO

- One Study per each Echo Media (ie per tape, CD).
- No Patient Identifiers should appear on the recording.
- Recording should contain patient's study identifier.

2. COPY ECHO

- Be sure and keep a copy of the study on file at your site. The original recording is sent to the Echo Core Lab.

3. LABEL MEDIA and ECG*

<u>CDs:</u>
- Place square pre-printed study media labels to the case and complete the label.
- Using permanent marker, print the patient identifier and echo interval directly on the CD.

<u>VHS tapes:</u>
- Place square pre-printed study media labels to the case and complete the label.
- Place long label to the VHS tape spine and complete the label.

<u>ECGs:</u> Place long label at the top of the ECG. Remember to blind the patient's name and medical record number.

4. COMPLETE Echo Tracking Form

- ALL fields must be complete and legible.

5. FAX ECG and Echo Tracking Form

- This 'advance fax' notifies the Echo Core Lab to expect the shipment and allows us to process the media quicker once it is received.

6. SHIP

- Using the shipping airbills provided, please ship echo media and original Echo Tracking Form to the Echo Core Lab.

If you do not have the pre-printed airbills, please ship to:

Renee Y. Mercier, 617 525 6730
BWH TOPCAT Echo Core Lab
20 Shattuck St, PBB Ground Rm A100
Boston, MA 02115
Account: TBD

***If you do not have TOPCAT pre-printed labels on hand,** be sure to include Subject ID, Subject Initials and Date Obtained when labeling the media and ECGs.*

QUESTIONS

Please consider the Echo Core Lab a resource should you have any questions - technical or otherwise. We are located in Boston, MA, USA and are available Monday-Friday, 8:00am - 5:30pm EST.

Phone: 1-617-525-6730
Email: echocore@rics.bwh.harvard.edu

VII. Site Sonographer: Echocardiographic Quality and Required Views

Sites are required to send echos performed according to the standard clinical protocol at their respective institutions. Echos will be used to assess ejection fraction (EF) only, thus the principle requirement is that sites provide sufficient echocardiographic information to assess ejection fraction.

VIII. Site Sonographer: Suggestions for Performing Echocardiograms

PLEASE NOTE: **For the TOPCAT substudy protocols (Echo and Echo and Vascular Stiffness) there are two echoes done over the course of the study. To ensure greater consistency, if there is more than one qualified sonographer able to perform study echos at your site, it is recommended that whenever possible, the same person perform both echos on a given subject**

A. Echocardiographic Equipment

- Generally, a 3.5 MHz transducer is recommended for obtaining images. Occasionally, subjects with poor quality images will require a lower frequency transducer (i.e. 2.5 MHz), while some subjects may be imaged with a higher frequency transducer (5 MHz). It is advisable to use the same frequency transducer for all the studies on a given patient.
- In general, use the highest possible frequency that allows adequate penetration for endocardial border definition.
- For digital imaging, please set your equipment to record at least three beats. We recommend recording at least three "loops" per view. If videotape is being used, once the images are optimized at least ten beats (cardiac cycles) from each view should be recorded.
- If present, tissue harmonic imaging should be used, unless this worsens endocardial border definition. Whether or not tissue harmonic imaging will be used is up to the discretion of the sonographer and investigator. It is preferable to be consistent on subsequent studies on the same patient.

B. Recording Images

- The recording must contain the study subject identifier. Whenever possible, **do not send media containing patient identifying information** such as name, medical record number, social security number, etc. The Echo Core Laboratory will not be able to process any data that does not contain the patient's study identification number and initials.

C. Patient Preparation

- The subject should be placed in the steep left lateral decubitus position unless this position is medically contraindicated for the patient.
- Electrocardiographic leads (12-lead) should be placed on the subject prior to imaging and an adequate ECG signal in which the QRS complex is clearly identifiable should be visible on the echocardiographic monitor.
- Echocardiograms should be obtained in a manner that is most consistent with good-quality patient care. Needless to say, subject care issues including subject comfort should always supercede research interests. Indeed, subject cooperation and comfort are extraordinarily important in obtaining the highest quality echocardiographic examination.
- If there are any characteristics of this subject that prohibit or make it difficult to perform the echo, please be sure to document this on the Echo Tracking Form in order that the Echo Core Lab is aware of any difficulties or obstacles in performing the echo.

APPENDIX A. Echo Tracking Form

BRIGHAM AND WOMEN'S HOSPITAL

TOPCAT
Funded by the NHLBI

HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

INSTRUCTIONS FOR SENDING STUDIES TO THE ECHO CORE LAB	
1	**BLIND:** Ideally, the ECL should only receive the patient's study identifier on each Echo. Please make every effort to blind each Echo for patient personal identifying data *(name, medical record number, etc)*
2	**LABEL:** After Echo is performed, please complete the echo media labels which are located on the TOPCAT website. The ECG should also be labeled with the long, thin label (also used for videotape spines) If sending via CD, do not place labels directly on CD. Instead, place the square label on the CD jacket cover and using a permanent marker, fill in the blanks on the label of the CD with the EXACT information that is completed on the pre-printed labels. -If sending via videotape, place the spine label on the tape and the square label on the box cover. -If sending via MO disc, place the square label directly on the disc.
3	**COMPLETE:** Thoroughly complete the Echo Tracking Form using blue or black ink – data must also be LEGIBLE.
4	**FAX**: Fax completed Echo Tracking Form and ECG to ECL at 1-617-582-6027 *(no cover sheet necessary)* in advance of the shipment.
5	**SHIP:** Ship the original Echo media and the original (top white copy) of the Echo Tracking Form to the ECL via FedEx using Account # **283395634 (FedEx 2Day)**. Please write "**TOPCAT**" under the internal billing reference of the airbill. Keep a copy of the echo media at the site along with the bottom yellow copy of the Echo Tracking Form for your records.
For Questions – Please contact the ECL at (1-617-525-6730) or email: echocore@rics.bwh.harvard.edu	

1. ___ ___ ___ ___ - ___ ___ ___ - ___ ____ ____ ____
SUBJECT ID **PATIENT INITIALS**

2. **Patient Date of Birth (dd/MMM/yyyy):** _____

3. **Date Echo Performed (dd/MMM/yyyy):** _____

4. **Date Echo to be sent to Core Lab (dd/MMM/yyyy):** _____

5a. **Courier Name (e.g., FedEx, DHL):** _____ **5b. Tracking Number:** _____

6. **Print Name of Person Performing Echo:** _____

6a. Phone: _____ **6b. Email address:** _____

7. **Were all required views obtained? (circle yes or no)** Yes No → List view(s) that were not able to be obtained and explain why:
_____

8. **Was contrast agent used? (circle yes or no) Yes* No**
*If yes, remember to use on all future studies on this subject.

ECL Use Only: Receipt and Quality Confirmation Section

ETF Logged (date/initials): _____/_____ **Echo Recd on/Logged by (date/initials):** _____/_____

Staff Confirming Quality (date/initials): _____/_____ **Is EF >45%? (meets inclusion criteria)** ☐ **Yes** ☐ **No**

Contacted to discuss quality concerns ☐ **Yes** ☐ **No:** **Site Contacted by (date/initials):** _____

Site Personnel Contacted & Date of Contact: _____

Please cut labels and scotch tape one label to every piece of TOPCAT media submitted to the Core Lab.

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

TOPCAT Study

________ ________ ________
Center No. Subject No. Subject Initials

Date of Echo: ______ / ________ / __________
Day Month Year

Type of Echo: _____ Screening ____Other

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TOPCAT STUDY

Quality of Life Questionnaires

INTRODUCTION

The primary goals of heart failure management are improving subject function, slowing disease progression, and improving quality of life. The quantification of the latter treatment goal requires the use of a health-related quality of life instrument, typically including a range of domains of health status.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQOL Health Status Questionnaire will be administered to TOPCAT study subjects in the appropriate language according to the Schedule of Measurement (Table 2 of the Study Protocol). The McMaster Overall Treatment Evaluation (OTE) and The Patient Health Questionnaire (PHQ) will be administered to TOPCAT study subjects at North American (US and Canada) sites only.

The overall quality of life assessment typically will not exceed 12-15 minutes per subject.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered 23-item questionnaire that will take approximately 5 minutes for the subject to complete. The KCCQ 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. The KCCQ will be administered at baseline visit, 4 month follow-up, 12 month follow-up, 24 month follow-up, 36 month follow-up, 48 month follow-up, 60 month follow-up and 72 month follow-up visits.

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 at baseline visit, 4 month follow-up, 12 month follow-up, 24 month follow-up, 36 month follow-up, and 48 month, 60 month follow-up visit and 72 month follow-up visits.

The McMaster Overall Treatment Evaluation (OTE) and the Patient Health Questionnaire (PHQ) are for North American (US and Canada) Sites Use Only:

The McMaster Overall Treatment Evaluation (OTE) (Juniper et al. 1994) 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 at 4 month follow-up and 12 month follow-up visits.

Finally, the Patient Health Questionnaire (PHQ) is a 9-item health scale derived from the PRIME-MD that includes a measure of depression severity, will be administered (English version has 10-items). Each of the 9 items is scored from 0 (not at all) to 3 (nearly every day). A summary score of >=10 has 88% sensitivity and 88% specificity for depression (DSM-IV) and has been the general cut-off used for diagnosis and screening. The PHQ will be administered at baseline visit, 12 month follow-up, 24 month follow-up, 36 month follow-up, and 48 month, 60-month follow up and 72 month follow-up visits.

Note: The QOLs are posted on the TOPCAT PAWS website (https://paws.neriscience.com/siteLogin.asp) under the "Documents" section. Both standard and large font versions are available.
An optional program has been initiated allowing sites to fax the completed Quality of Life Questionnaires to NERI for data entry. Detailed information on this option is provided on the PAWS website in "QOL Program" section.

Funded by the NHLBI

REPOSITORY SUB-STUDY INSTRUCTION MANUAL FOR NORTH AMERICAN CLINIC SITES

TABLE OF CONTENTS

I. Repository Overview

The purpose of the repository specimen sub-study is to provide a bank of specimens for future studies collected from the study population of preserved ejection fraction heart failure patients from the TOPCAT study.

Each participating clinic site will receive an initial shipment of 4 repository specimen kits. Each kit contains supplies for a complete set of repository specimens for one visit of one patient. (Figure 1). Sites will automatically receive additional specimen kits as needed. To ensure a minimum of 2 repository specimen kits remains in inventory at all times, sites must acknowledge receipt of repository specimen kit shipments in ADEPT so that kit inventory can be tracked (please refer to the QxQs for additional information on how to acknowledge receipt of repository kits).

To track repository samples collected, sites must complete a Repository Sample Collection CRF (R001) (Form 1) and a Processing CRF (R002) (Form 2) in ADEPT for each repository collection visit.

Repository DNA, blood and urine samples will be collected at the baseline and 12 month visits from consenting patients at participating sites (Figure 6 and 7). Baseline repository samples should be collected before subject's initial dose of study drug. Sites will process blood for DNA, plasma, serum and urine samples as soon as possible after sample collection. Processed repository samples should be stored at -70^{0}C or -80^{0}C until they are ready to be shipped out to SeraCare, the NHLBI central repository.

NOTE: Sites without -70^{0}C or -80^{0}C freezers should store specimens in a temperature controlled -20^{0}C freezer (i.e. daily temperature log).

Samples will be shipped to the NHLBI central repository in dry ice shipping boxes provided by SeraCare. For detailed shipping instructions and frequency, please see section VI "Repository Sample Shipping Procedure".

Patients may:

- Consent to the Blood/urine and DNA portions of the repository sub-study
- Consent to only one of the portions (either blood/urine or DNA) of the repository sub-study and decline the other portion
- Decline consent to participate in the repository sub-study and still participate in the TOPCAT study

II. Site Readiness Checklist Prior to Each Repository Specimen Collection Visit

- ☐ Ensure subject has signed Repository ICF and confirm which part(s) of the repository the subject will participate in. Collections should only be made for the consented specimen types.
- ☐ Complete Consent Confirmation CRF (T001)* in ADEPT.
- ☐ Confirm receipt of repository specimen kits from Dept of HHS, Perry Point, MD in ADEPT.
- ☐ Confirm specimen kit contents (see Section III).
- ☐ Print a copy of the Repository Specimen Collection CRF (R001)* and Processing CRF (R002)* available at https://paws.neriscience.com/

* NOTE: For detailed instructions on how to complete CRF T001, R001, and R002, please refer to the QxQs in PAWS.

III. Repository Specimen Kit Contents

Each specimen kit contains the following items:

One **Cryobox** (81 cryovial capacity) (Figure 4)

One **form label** of the parent barcode with the suffix 017 (i.e. RY XXXXXX 017) (Figure 3)

3 Disposable plastic **pipette tips** (Figure 2)

One sterile **Vacutainer™ needle** (Figure 2)

One **Venipuncture Needle-Pro™** needle protection device (Figure 2)

Four *Collection* Tubes (pre-labeled with barcode labels) (Figure 2)

- One Urine collection container (150 mL)
- One EDTA tube (lavender top, 10 mL)
- Two BD Plastic Serum separator Vacutainer tubes (SST tubes, tiger top, 7.5 mL)

Twelve *Storage* Tubes (pre-labeled with barcode labels) (Figure 2)

- Four Serum cryovials (labeled TOPCAT serum 1 thru 4)
- Two Plasma cryovials (labeled TOPCAT plasma 1 and 2)
- Two cryovials for DNA as whole blood and buffy coat (labeled TOPCAT pkd cells 1 and 2)
- Four Urine cryovials (labeled TOPCAT urine 1 thru 4)

Please report any damaged, incomplete, or unusable repository specimen kits to the TOPCAT Mailbox at Topcat@neriscience.com. Sites should check the expiration dates on the repository collection tubes (i.e. the EDTA and SST tubes) prior to sample collection. If any of the collection tubes have expired in the kit (SST tubes have the shortest expiry of all components) please replace with a comparable tube.

IV. Recording Specimen Collection

Print copies of the Repository Sample Collection CRF (R001) and Processing CRF (R002) to use as worksheets prior to the repository sample collection and processing procedure. Attach the barcode form label from the repository specimen kit to worksheet section B2 “Kit Form Barcode Label” of the R002.

V. Repository Sample Collection and Processing Procedure

Collection order (for patients participating in all parts of the repository)

1. EDTA tube*
2. SST tubes

・Urine

* ***To maximize the yield of plasma and DNA samples, clinic sites should collect blood samples in EDTA tube before the SST tubes.***

CHART 1: TOPCAT REPOSITORY SAMPLE COLLECTION FLOW CHART

Subject consented to DNA, blood, and urine portion of the repository

↓

Print out a copy of R001 and R002 CRF to use as worksheets

↓

In the Repository Specimen Kit:

- **Place Form Label on R002 worksheet**
- **Use Urine Container to collect urine samples**
- **Use EDTA tube (lavender top) to collect blood for plasma, DNA*, and buffy coat samples**
- **Use SST tubes (tiger top) to collect blood for serum samples**

*** Collect 2 mL of whole blood for DNA sample only if a full draw was obtained in EDTA tube. A full draw is defined as at least 9 mL of blood (see Figure 7).**

↓

Subject consented to the blood and urine portion of the repository <u>and not the DNA</u>

↓

Print out a copy of R001 and R002 CRF to use as worksheets

↓

In the Repository Specimen Kit:

- **Place Form Label on R002 worksheet**
- **Use Urine Container to collect urine samples**
- **Use EDTA tube (lavender top) to collect blood for plasma samples**
- **Use SST tubes (tiger top) to collect blood for serum samples**

↓

Freeze repository samples at -70°C or -80°C.

Sites without -70^{0}C or -80^{0}C freezers should store specimens in a <u>temperature controlled</u> -20^{0}C freezer.

NOTE: For subjects who have consented to only the DNA portion of the repository: use EDTA tube to collect blood for DNA and buffy coat samples. Urine container and SST tubes should be discarded.

A. EDTA Tube Collection at Baseline and 12M (see Figure 6)

- Draw blood into the EDTA tube

If patients have consented to DNA:

DNA Collection at Baseline and 12 M from EDTA tube

i. **Check if the EDTA collection tube contains at least 9 mL of blood (i.e. blood reaches the top of the tube label; see Figure 7)**
   1. **if yes proceed to step ii;**
   2. **if no, proceed to Plasma and Buffy Coat Collection section and do not collect any sample in the packed cells cryovial labeled TOPCAT pkd cells 1.** This empty cryovial should be discarded.

ii. **After confirming a full draw in step i, gently invert tube 5 times and aliquot 2 mL** of whole blood from the EDTA collection tube into the packed cells cryovial **labeled as *TOPCAT pkd cells 1.***

iii. Place cryovial in cryobox and **freeze packed cell 1 cryovial immediately at -70°C or -80°C**.

Plasma and Buffy Coat Collection at Baseline and 12M from EDTA tube

- Secure top of the EDTA collection tube**.**
- **Centrifuge EDTA collection tube** at 3,000 RPM for 20 minutes at room temperature. After centrifugation, the blood sample will separate into three distinct layers (see Figure 7): a top clear layer (plasma), a thin whitish middle layer (buffy coat), and an opaque red layer (packed red cells).
- **Carefully aliquot 1.8-2 mL of plasma** (top clear liquid) from the EDTA collection tube into each of the 2 plasma cryovials labeled as *TOPCAT plasma 1* and *TOPCAT plasma 2*.
- **Aliquot the buffy coat** (thin whitish middle layer) into the packed cells cryovial labeled as ***TOPCAT pkd cells 2***. To collect the buffy coat, 1) depress the pipette bulb 2) insert the pipette tip into the thin whitish layer 3) pipette up the white layer plus the remaining plasma while minimizing the amount of red packed cells.
  If patient has declined participation in DNA portion of the repository, skip buffy coat step, leave TOPCAT pkd cells 2 empty, and discard this cryovial.
- **Secure** caps on plasma and packed cells cryovials and place all cryovials in cryobox.
- **Store at -70°C or -80°C.**
- **Record** time of sample collection, time of sample process completion, and temperature of sample storage in CRF worksheets.
- Properly discard EDTA collection tube and its content.

B. Blood Serum Collection at Baseline and 12M (see Figure 6)

- Collect a full draw of blood sample (i.e. blood reaches the top of tube label) into each of the two BD Plastic Serum separator vacutainer collection tubes
- Let the serum collection tubes **sit for at least 20 minutes** at room temperature
- **Centrifuge serum collection tubes** at 3,000 RPM for 20 minutes at room temperature
- **Aliquot 2 mL of serum** (top clear liquid) from one of the serum collection tubes into the serum cryovial labeled as *TOPCAT serum 1*
- **Aliquot 1 mL of serum** from the serum collection tubes into each of the 3 remaining serum cryovials labeled as *TOPCAT serum 2*, *TOPCAT serum 3*, and *TOPCAT serum 4*
- **Secure** caps on serum cryovials and place cryovials in cryobox.
- **Store at -70°C or -80°C**.

- **Record** time of sample collection, time of sample process completion, and temperature of sample storage in CRF worksheets.
- Properly discard serum collection tubes and their contents.

C. Urine Collection at Baseline and 12M (see Figure 6)

- **Collect** 30 mL or more of urine into the urine collection container.
- Using disposable pipets, **aliquot** 4.5 ml of urine from the collection tube into each of the 4 urine cryovials labeled as *TOPCAT urine 1*, *TOPCAT urine 2*, *TOPCAT urine 3*, and *TOPCAT urine 4*.
- **Secure** caps on urine cryovials and place cryovials in cryobox.
- **Store at -70°C** or **-80°C.**
- **Record** time of sample collection, time of sample process completion, and temperature of sample storage in CRF worksheets.
- Properly **discard** urine collection container and its content.

VI. Repository Sample Shipping Procedure:

A. Shipping frequency

Once every 6 months from the time of the 1st repository sample collection at the site **or** when site has accumulated 2 full cryoboxes of repository samples (a full STP-310 shipper box). Since a cryobox is included in each repository specimen kit, sites will have an excess of cryoboxes during the study.

B. Requesting shipper boxes and packing supplies from SeraCare

SeraCare will provide STP-310 shipper boxes, packing supplies (absorbent strips and biohazard bags), and return labels directly to all clinic sites. *Please note that one STP-310 shipper box can hold two full cryoboxes.* Sites must request shipper boxes (see Figure 5), packing supplies, and return labels from SeraCare prior to shipping. We recommend that sites contact SeraCare via email at least 10 days prior to the anticipated repository sample shipment date.

To request STP-310 shipper box, packing supplies, and return label, please complete the Request for Safety Pack STP-310 shipper box Form (R010 Form) available at https://paws.neriscience.com/ and fax it to Christine Demasco/NHLBI repository at (301) 208-8829. Please allow one business week to process orders.

PLEASE NOTE THAT SHIPMENTS TO SERACARE CAN BE MADE MONDAYS THROUGH WEDNESDAYS ONLY.

C. Shipping samples to SeraCare

Once site has received the STP-310 shipper box and packing supplies from SeraCare:

1. Generate an electronic manifest for the shipment from ADEPT and also print a paper copy (please refer to the Manual of Operations on how to generate an electronic manifest in ADEPT).
2. Remove Empty Packaging Flap from front of box. A cardboard flap with the words "empty packaging" has been taped to the front of the box to cover the shipping labels when shipped to you. This flap should be cut from the box and removed. Once removed all shipping labels should be present.
    a. Once Empty Packaging Flap is removed the box should contain the following labels. If any of the labels are missing please contact SeraCare for replacements
        i. To Label (To Christine Demasco)
        ii. From Label (From your site)
        iii. 24 Hour Emergency Contact Label
        iv. Responsible Person Label
        v. Class 9 Diamond Label
        vi. UN3373 Biological Substance Category B Label
        vii. Dry Ice Un 1845 Label with space to add weight
2. Place Dry Ice around the small inner brown box (between brown box and Styrofoam container).
3. Place Rubber band (at least ¼" thick) around each cryobox.
4. Place White Absorbent Strip around box.
5. Place Box in Clear Biohazard bag and seal according to instructions on the bag.
6. Place Bag in White Biohazard bag and seal according to the instructions on the bag.
7. Place Bag in the inner brown box (the shipping container can hold 2 x 3" Freezer Boxes) and tape the inner brown box shut.
8. Add additional dry ice to bring total amount to the same level as the top of the brown inner box. Note that the total amount of dry ice will be ~16 lbs or 9 kgs.
9. Place the Styrofoam lid onto the container (do not tape the Styrofoam lid), place the "empty" packaging flap on top of the Styrofoam, and then seal the cardboard box.
10. For *US clinic sites*, complete FedEx Airbill with your shipping address and the amount of Dry Ice placed in box:
    a. Section 2 - The Internal Billing Reference Section must have the following information "138, Biological Substance Category B"
    b. Section 4a - Check the "FedEx Priority Overnight" box
    c. Section 5 - Check the "other" box
    d. Section 6 - Check the box that says, "Yes Shipper's Declaration not required". Check the "Dry Ice box" and write "1" in the first blank line and the "kg" of dry ice used on the second line; i.e., 1 x 9 kg
    e. Section 7 - Check Recipient. The account number is 2541-8815-8

    For *Canadian clinic sites,* complete FedEx Airbill with your shipping address and the amount of Dry Ice placed in box:
    a. Section 3 – Shipment Information
        i. Commodity Description "Biological Substance Category B UN3373"
        ii. Country of Manufacture
        iii. Value for Customs $100.00
        iv. Total Value for Customs $100.00
        v. Commodity Description "Dry Ice ___ kg UN 1845"
            1. write in amount of dry ice being used (i.e. 9 kgs)
        vi. Country of Manufacture
        vii. Value for Customs "$100.00"
    b. Section 4a - Check the "FedEx Intl Priority " box
    c. Section 5 - Check the "other" box

d. Section 6 - Check the box that says, “Yes Shipper’s Declaration not required”. Check the “Dry Ice box” and write “1” in the first blank line and the “kg” of dry ice used on the second line; i.e., 1 x 9 kg
f. Section 7a - Check Recipient. The account number is 2541-8815-8
g. Section 7b - Check Recipient. The account number is 2541-8815-8
h. Section 9 – you will need to sign in the section provided

11. Fill in the Dry Ice Label on box with the amount of dry ice used.
12. Complete the Repository Shipment Notification Form (R011) available at https://paws.neriscience.com/ and send an e-mail to Chem-Tel, (our 24-hour contact), **prior to shipment**, at BBIBIOTECH@chemtelinc.com along with the completed R011 Form. Please cc: SeraCare BioServices on the Chem-Tel e-mail at nhlbi@seracare.com. An electronic copy of the manifest must be submitted with along with the shipment notification to Chem-Tel. **A paper copy of the manifest must be included in the shipment.**
13. For Canadian clinic sites only, complete Customs Invoice Form, USDA Invoice Form, and Commercial Invoice Form available at https://paws.neriscience.com/ and attach forms to STP-310 shipper box. The commercial Invoice should contain the following information:
    a. Date of Exportation
    b. International Airway Bill Number
    c. ~ # of mls being shipped
    d. Weight of dry ice
    e. Total Weight
    f. Signature at bottom of form

Faxes may only be sent to Chem-Tel in an emergency situation when the e-mail system is not functioning at (813) 248-0582.

Sites should contact SeraCare BioServices using the contact information provided below with any questions regarding the repository shipping instructions.

The NHLBI Repository Contact Information:

NHLBI Repository
ATTN: Linda Brunson
SeraCare BioServices
217 Perry Parkway
Gaithersburg, MD 20877
(240) 306-4143
Fax: (301) 208-8829
Email: nhlbi@seracare.com

A confirmation of repository shipment receipt from SeraCare will be sent to the site and CC’d to the TOPCAT mailbox. Queries will be generated and sent to sites regarding any discrepancies in the manifest information and/or repository shipment samples.

ATTACHMENTS

FIGURE 1: REPOSITORY SPECIMEN COLLECTION KIT

FIGURE 2: REPOSITORY COLLECTION TUBES, STORAGE TUBES AND OTHER SUPPLIES

FIGURE 3: FORM LABEL

FIGURE 4: CRYOBOX

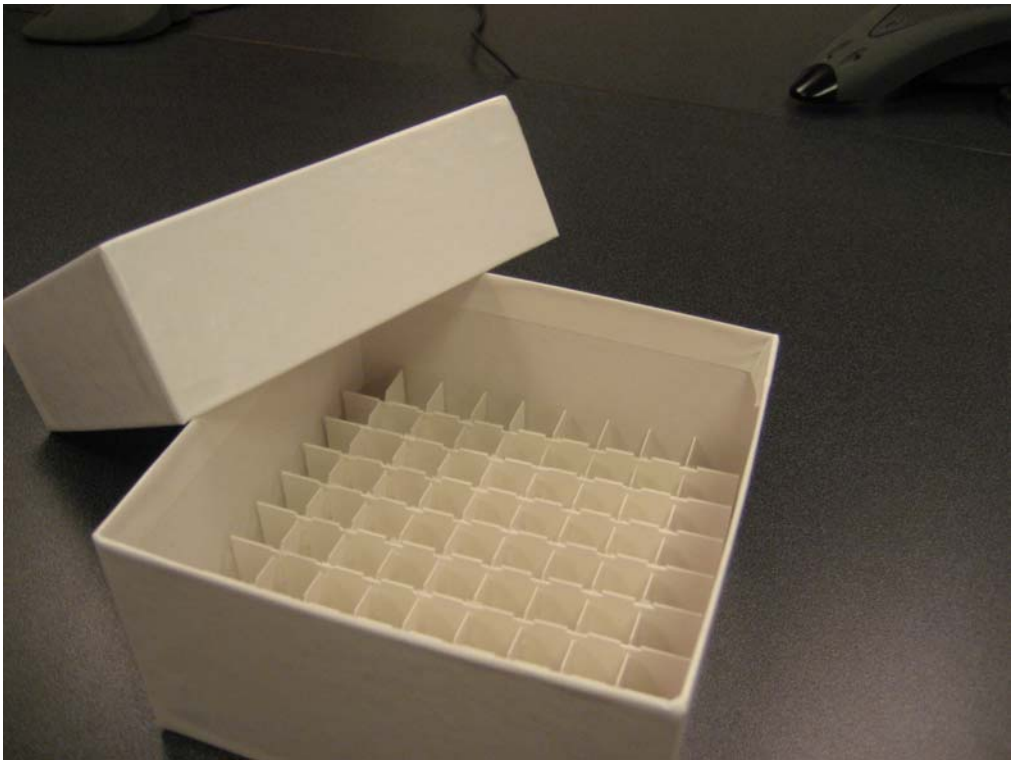


FIGURE 5: SAFETY PACK STP-310 SHIPPER BOX

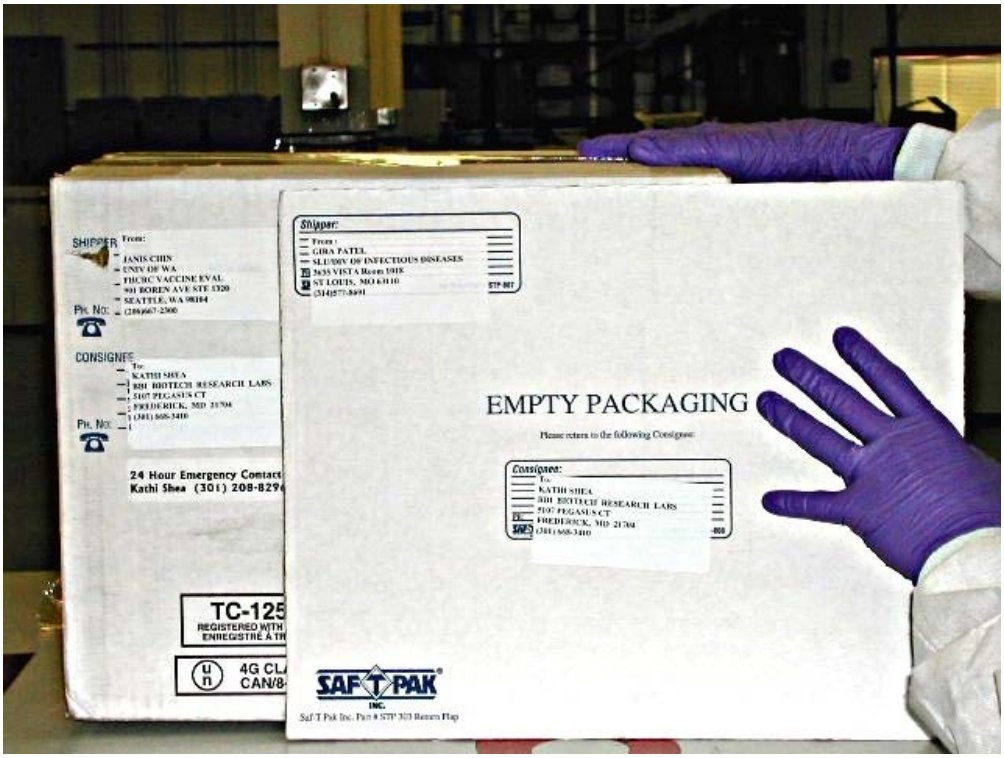
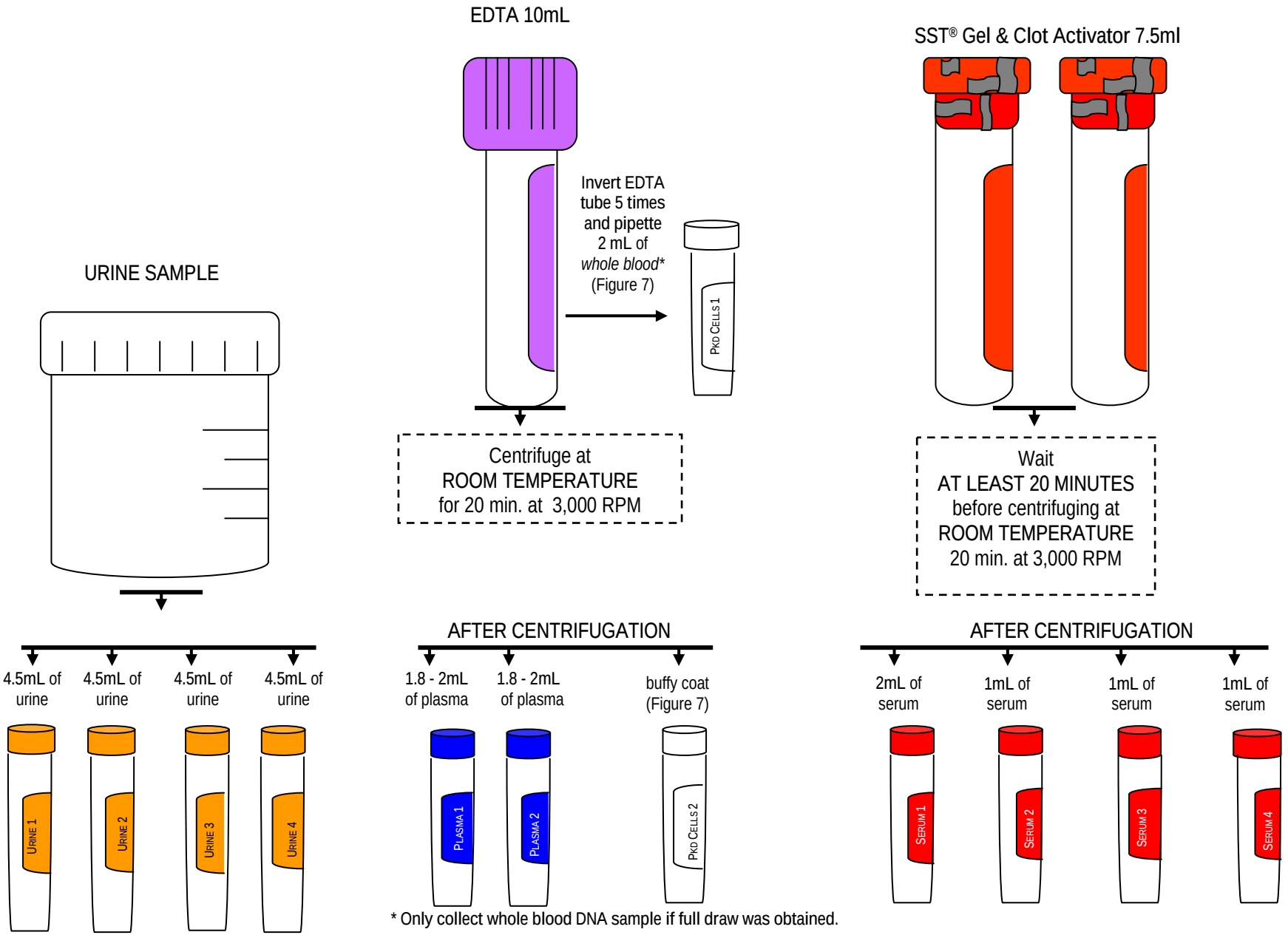


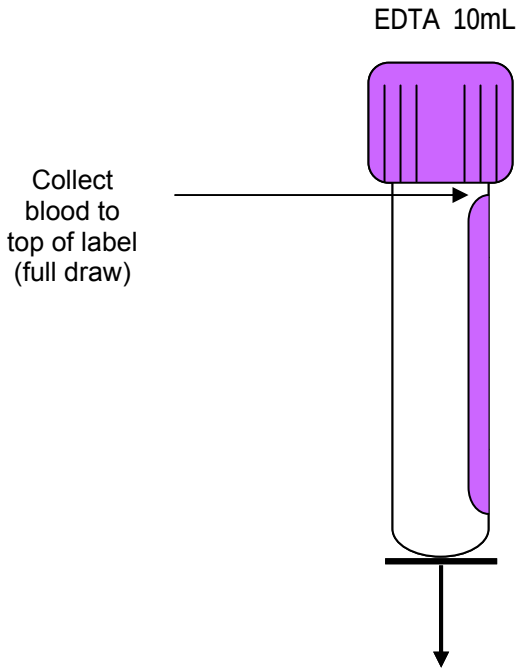
FIGURE 6: TOPCAT REPOSITORY SUB-STUDY SAMPLE COLLECTION – BASELINE AND 12 M



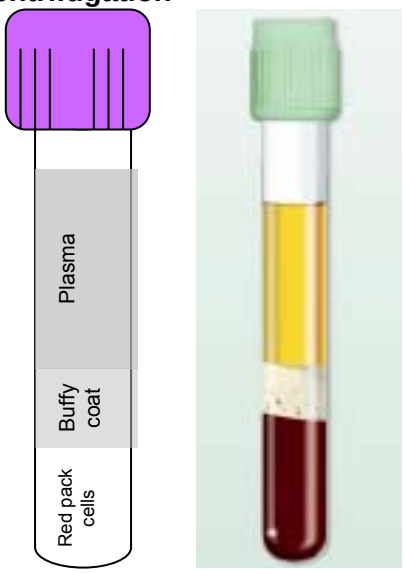
* Only collect whole blood DNA sample if full draw was obtained.

SECURE TUBES AND FREEZE IMMEDIATELY AT -70°C OR -80°C

FIGURE 7: TOPCAT DNA SAMPLE – BASELINE AND 12 M



Blood Sample After Centrifugation



Aliquot 2 mL of whole blood only if a full draw (see above figure) was obtained in EDTA tube

DO NOT CENTRIFUGE
FREEZE SAMPLE IMMEDIATELY at -70°C or -80°C *
until sample is ready to be shipped to SeraCare

* If -70°C or -80°C freezer is not available, please store sample at -20°C

FORM 1: REPOSITORY SAMPLE COLLECTION FORM CRF (R001)

TOPCAT TRIAL

R001

Repository Sample Collection

SECTION A: GENERAL INFORMATION

A1. Subject ID: ___ ___ ___ ___ - ___ ___ ___ - ___

A2. Subject initials: ___ ___ ___

A3. Visit: ☐ Baseline ☐ 12 month

SECTION B: REPOSITORY SAMPLE COLLECTION

B1. Was the EDTA tube (lavender top) collected? ☐1 YES **(B1b)** ☐0 NO

a. If subject consented to repository and sample was not collected, please provide a reason: _____ **(B2)**

b. EDTA tube collection date: __ __ - __ __ __ - __ __ __ __

D D - M M M - Y Y Y Y

c. EDTA tube collection time (24 hour clock): ___ ___ : ___ ___

B2. Was the BD Serum tube (tiger top) #1 collected? ☐1 YES **(B2b)** ☐0 NO

a. If subject consented to repository and sample was not collected, please provide a reason: _____ **(B3)**

b. BD Serum tube #1 collection date: __ __ - __ __ __ - __ __ __ __

D D - M M M - Y Y Y Y

c. BD Serum tube #1 collection time (24 hour clock): ___ ___ : ___ ___

B3. Was the BD Serum tube (tiger top) #2 collected? ☐1 YES **(B3b)** ☐0 NO

a. If subject consented to repository and sample was not collected, please provide a reason: _____ **(B4)**

b. BD Serum tube #2 collection date: __ __ - __ __ __ - __ __ __ __

D D - M M M - Y Y Y Y

c. BD Serum tube #2 collection time (24 hour clock): ___ ___ : ___ ___

B4. Was a urine sample collected? ☐1 YES **(B4b)** ☐0 NO

a. If subject consented to repository and sample was not collected, please provide a reason: _____ **(END)**

b. Urine collection date: __ __ - __ __ __ - __ __ __ __

D D - M M M - Y Y Y Y

c. Urine collection time (24 hour clock): ___ ___ : ___ ___

FORM 2: REPOSITORY SAMPLE PROCESSING FORM CRF (R002)

TOPCAT TRIAL

R002

Repository Sample Processing

SECTION A: GENERAL INFORMATION

A1. Subject ID: ___ ___ ___ ___ - ___ ___ ___ - ___

A2. Subject initials: ___ ___ ___

A3. Visit: ☐ Baseline ☐ 12 month

SECTION B: REPOSITORY SAMPLE PROCESSING

B1	Label Description	i Aliquot obtained? Yes	No	Volume in ml. Expected	ii Actual	iii Processing Completion Date/Time (Sample put in freezer) D D - M M M - Y Y Y Y	H H : M M
a	plasma 1	☐1	☐0 **(b)**	1.8 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
b	plasma 2	☐1	☐0 **(c)**	1.8 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
c	pkd cells 1	☐1	☐0 **(d)**	2.0 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
d	pkd cells 2	☐1	☐0 **(e)**			__ __ -__ __ __ - __ __ __ __	__ __ : __ __
e	serum 1	☐1	☐0 **(f)**	2.0 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __

f	serum 2	☐1	☐0 **(g)**	1.0 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
g	serum 3	☐1	☐0 **(h)**	1.0 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
h	serum 4	☐1	☐0 **(i)**	1.0 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
i	urine 1	☐1	☐0 **(j)**	4.5 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
j	urine 2	☐1	☐0 **(k)**	4.5 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
k	urine 3	☐1	☐0 **(l)**	4.5 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __
l	urine 4	☐1	☐0 **(B2)**	4.5 ml	___. ___	__ __ -__ __ __ - __ __ __ __	__ __ : __ __

B2. Kit Form Barcode Label: __ __ - __ __ __ __ __ __ - __ __ __

Attach barcode here

B3. Freezer temperature:
☐1 -70 degrees C
☐2 -20 degrees C
☐3 Other, specify: _____

NOTE: This worksheet must be destroyed either at the close of the study or when requested by the Coordinating Center.

FORM 3: REQUEST FOR SAFETY PACK STP-310 SHIPPER BOX (R010)

TOPCAT TRIAL

R010

Request for Safety Pack STP-310 Shipper Box

SECTION A: SHIPMENT INFORMATION
Please complete all fields (A1 to A13) to indicate site shipment address.

A1. Site Name: _____

A2. First Name: _____

A3. Last Name: _____

A4. Address: _____

A5. Address 2: _____

A6. Address 3: _____

A7. City: _____

A8. State/Province: _____

A9. Postal Code: _____

A10. Country: _____

A11. Phone: _____

A12. Fax #: _____

A13. Email: _____

Please allow one business week to process orders.

Item Description	Quantity of Each Item Requested
Pre-Labeled Shipping Container (STP 310)- holds two 3" cryoboxes	
Fed Ex Airbills	
Absorbent Strips (1 per cryobox)	
Clear Biohazard Bags for 3" Cryoboxes (1 per cryobox)	
White Biohazard Bags for 3" Cryoboxes (1 per cryobox)	

Please fax this completed page Form 3 to SeraCare at (301) 208-8829
ATTN: Linda Brunson/NHLBI Repository
Phone: (240) 306-4143

FORM 4: REPOSITORY SAMPLE SHIPMENT NOTIFICATION (R011)

TOPCAT TRIAL

R011

Repository Sample Shipment Notification

SECTION A: SHIPPER'S INFORMATION

Please complete all fields (A1 to A14) to indicate site shipment address.

Please send this completed 1 page From 4 as an email attachment to Chem-Tel, (our 24-hour contact), **prior to shipment**, at BBIBIOTECH@chemtelinc.com. Please cc: SeraCare BioServices on the Chem-Tel e-mail at nhlbi@seracare.com.

Subject Line of E-mail should read: TOPCAT study, FedEx, "insert tracking number", "insert date of shipment"

A1. Shipper's Name: _____

A2. Shipper Address: _____

A3. Shipper Address 2: _____

A4. Shipper Address 3: _____

A5. City: _____

A6. State/Province: _____

A7. Postal Code: _____

A8. Country: _____

A9. Shipper's Phone: _____

A10. Shipment Date: _____

A11. FedEx tracking #: _____

A12. Package Weight + Unit of Measurement (i.e. 20 kg): _____

A13. Total Volume _____

A14. Sample Identifier: _____

A15. Shipment Temperature: Dry Ice, UN1845, ___ kg (insert weight of Dry Ice)

Dangerous Goods Classification: Biological Substance Category B, Dry Ice
Manifest: A copy of the electronic manifest must be provided via e-mail along with the shipment notification.
A paper copy of the manifest must be included in the actual shipment per IATA regulations.
Recipient: Linda Brunson
217 Perry Parkway, Gaithersburg, MD, 20877
(301) 208-8100

APPENDIX 1: CUSTOMS FORMS FOR CANADIAN SITES

USDA INVOICE

To whom it may concern:

The enclosed package is intented for delivery to:

SeraCare

_____

_____

_____

THIS PACKAGE CONTAINS BIOLOGICAL SUBSTANCE, CATEROGY B, FROZEN, PACKED IN _____ KG OF DRY ICE

_____ mL Human Blood

_____ mL Human Urine

_____ mL Human Plasma

(Human material that was neither inoculated with nor exposed to infectious agents of agricultural concern, including zoonotic agents; the material contains no animal or non-human primate material and is not of tissue culture origin.) These specimens are for medical laboratory testing purposes and for research use only in conjunction with a pharmaceutical study.

Sincerely,

_____

Signature in blue ink only

Date: _____

Shipment air waybill number ☐☐☐☐ - ☐☐☐☐ - ☐☐☐☐

Diagnostic specimen (UN3373) packed in compliance with IATA Packing instruction 650.

CUSTOMS INVOICE

Shipper: _____

_____

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Consignee: SeraCare

_____

_____

_____

Tax ID : EIN-XXXXXX

Contents : **BIOLOGICAL SUBSTANCE, CATEGORY B, FROZEN**

This package contains biological substance, category B, frozen, packed in _ kg of dry ice :

_____ mL Human Blood

_____ mL Human Urine

_____ mL Human Plasma

These specimens are for medical laboratory testing purposes and for research use only in conjunction with a pharmaceutical study.

NO commercial value. The value for customs purposes only is $1.00

Sincerely,

_____

Signature in blue ink only

Date: _____

Shipment air waybill number ☐☐☐☐ - ☐☐☐☐ - ☐☐☐☐

Diagnostic specimen (UN3373) packed in compliance with IATA Packing instruction 650.

COMMERCIAL INVOICE/ FRACTURE COMMERCIALE

Please note that the Commercial Invoice Form in only available in PDF format and can be located at https://paws.neriscience.com/.

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TOPCAT Trial

Adverse Event/Serious Adverse Event Reporting

Definitions of Events

The Adverse Event/Serious Adverse Event CRFs (CRF# T050, T051,T053) are to be used as documentation of all reportable events as described in Section C.5.1. through C.5.6 of the study protocol. (Appendix D of the ADEPT User Guide includes AE/SAE data entry information.)

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

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 signing of the informed consent form, 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. 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.

Subjects who have been permanently discontinued from the study drug for 30 days or more are the only exception. Once 30 days have passed since the date of permanent discontinuation from study drug, untoward medical occurrences no longer need to be captured as adverse events.

Please note that all study outcomes (including hospitalization for the management of heart failure and all other hospitalizations, deterioration of renal function, myocardial infarction, new onset diabetes mellitus, stroke, new onset atrial fibrillation, aborted cardiac arrest and death) are reported regardless of a subjects' status on the study drug. For study outcome events, all relevant study outcome eCRFs must be completed and relevant source documentation submitted to NERI so events can be adjudicated.

A. Classification of Adverse Events

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.

B. Relationship of Adverse Events

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 (definitely related) to the study drug.

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

Possible: Maybe related (low suspicion) to the study drug.

Unrelated: Clearly not related (definitely not related) to the study drug.

C. Definition of Serious Adverse Events (SAEs)

An adverse event 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 NERI within 48 hours. SAEs are automatically reported to NERI 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.

D. Definition of Unanticipated Adverse Drug Effects (UADEs)

An Unanticipated/Unexpected Adverse Drug Effect (UADE) is defined as any serious adverse effect on health or safety, or any life-threatening problem, or death that is caused by, or associated with, a 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 associated with a drug that relates to the rights, safety, or welfare of subjects.

After the initial event, subjects should be followed clinically until there is either:

- A return to the baseline status,
- All parameters have returned to normal, or
- No further improvement is anticipated.

It is anticipated that UADEs will be rare events as this study drug is well documented.

E. SAE Reporting

Sites must report all SAEs, regardless of relationship to study drug, in ADEPT within 48 hours of the site being notified of the SAE unless the SAE onset date is greater than 30 days after the subject permanently discontinued study drug. The AE and SAE CRFs must also be completed and signed by the PI within 48 hours.

The study personnel (PI, Co-Investigator and Study Coordinator) at the clinical site will assess whether an Adverse Event (AE) or Serious Adverse Event (SAE) has occurred with the subject at each study visit. Adverse Events and Serious Adverse Events will be collected throughout the study. If an AE has occurred, the study personnel (usually the study coordinator) will enter the AE in the AE eCRF (CRF T050) or the combined AE/SAE eCRF (CRF #T053) of the ADEPT database system. All SAEs and UADEs are time-sensitive adverse events that must be reported to NERI within **48 hours** in order to meet the FDA reporting guidelines as specified by regulations. Therefore, all reportable SAEs and UADEs must be reported by the clinic site immediately to NERI by entering the SAE/UADE in the SAE eCRF (CRF #T051) or the combined AE/SAE eCRF (CRF (#T053) of the ADEPT database system within 48 hours of the enrolling clinic site being notified of the event. Also, within 48 hours, any required additional documentation (as discussed on the telephone or in an email) should be faxed to NERI at 617-923-9514 or emailed to the TOPCAT mailbox at TOPCAT@neriscience.com once subject identifiers (other than subject I.D.) have been removed by the clinic staff. A summary of all other adverse events will be reported to the FDA at the time of the annual and semi-annual reports to the DSMB.

REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS (IRBs) OR ETHIC COMMITTEES (ECs)

TOPCAT Principal Investigators should follow their local or central IRB/EC adverse event reporting requirements. In addition to local reporting procedures, the Office of Human Research Protection (OHRP), DHHS issued a memorandum dated January 15, 2007, Guidance on Continuing Review, which authorizes IRBs or ECs to rely on current statements from a DSMB monitoring a study. The statement will inform each participating center IRB or EC that the DSMB has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research.

Providing Follow-up Information to Local IRBs/ECs

If the DSMB does not identify any safety or other protocol-related concerns, within 30 days after a DSMB meeting, the NHLBI Project Officer will prepare a Summary Report that will state that:

- A review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date;
- The observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;
- A review of recent literature relevant to the research took place; and
- The DSMB recommended that the study continue without modification of the protocol or informed consent.

The report will be sent to NERI for distribution to each participating center's Principal Investigator (PI). It is the responsibility of each PI to forward this information to their local or central IRB/EC.

If the DSMB recommends protocol or informed consent changes, and the director, NHLBI accepts the recommendations; the NHLBI Project Officer will send those recommendations to NERI for distribution to the participating PIs. The rationale for such changes and any relevant data will be provided. The data provided will be determined by the DSMB members and Institute staff and will not go beyond what is necessary to explain the actions taken. The nature of the changes will determine how quickly the information is distributed.

Requests from an IRB or EC for Additional Information

Requests for additional information, whether for a data coordinating center or a site, may be made to the NHLBI Project Officer. Decisions as to how to handle each request will depend on the nature of the request, whether or not the DSMB had identified safety concerns, the kind of trial, the stage of the trial, and perhaps whether the IRB or EC is for a coordinating center or a site.

MEDICAL MONITOR HOTLINE

For all study related medical questions (i.e. inclusion/exclusion questions, safety questions), please contact our TOPCAT Medical Monitors at topcatmd@partners.org. In case of emergency, please contact the Medical Monitors by phone at 617-732-5656 (an automated system). After the introductory message, you will be prompted to enter a beeper number. The TOPCAT hotline beeper number is 18228. The caller may leave a call back number or a message and it will be sent to the medical monitor for the study. *The TOPCAT medical monitor hotline is available from 8 am – 8 pm EST Monday through Friday*.

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TOPCAT Trial

Concomitant Medication

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:

- Angiotension Converting Enzyme (ACE) inhibitors or Angiotension Receptor Blockers (ARB) – may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics – may be associated with hypokalemia
- Corticosteroids or Adrenocorticotropic Hormones (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
- Non-steroidal anti-inflammatory drugs (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

If the subject is temporarily or permanently discontinued from study drug, the site must record the reason and circumstances for study drug discontinuation. If the subject is permanently discontinued from study drug, the subject will continue to be followed until the end of the study.

MEDICATIONS KNOWN TO INCREASE SERUM POTASSIUM

Many commonly prescribed drugs can cause hyperkalemia. The following list is not exhaustive and is intended only as a general guide. If there is concern about preparations which are unlisted, please discuss with the medical monitor. You may also search side effect profiles on various medication references (e.g., the Physician's Desk Reference).

- Mineralocorticoid Receptor Antagonists (e.g. spironolactone, eplerenone), including in combination products with thiazide or loop diuretics ***These drugs are excluded per protocol in TOPCAT*
- Potassium-sparing diuretics (e.g. amiloride, triamterene) including in combination products with thiazide, loop diuretics, and anti-hypertensives ** *These drugs are excluded per protocol in TOPCAT*
- Angiotensin-Converting Enzyme (ACE) Inhibitors (e.g. lisinopril, perindopril, captopril, etc.)
- Angiotensin Receptor Blocking Drugs (e.g. candesartan, valsartan, losartan, etc.)
- Non-steroidal anti-inflammatory agents (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) Inhibitors (e.g. celecoxib, rofecoxib, etc.)
- Beta-adrenergic receptor blocking drugs (e.g. metoprolol, atenolol, propranolol, etc.) (Rare)
- Trimethoprim and trimethoprim-containing combination products

- Herbal remedies and dietary supplements (e.g. salt substitutes, potassium supplements, noni juice)
- Pentamidine
- Cyclosporine
- Tacrolimus
- Digitalis (at toxic levels)
- Heparin
- Succinylcholine
- Certain intravenous amino acids (e.g., lysine, arginine)

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TOPCAT Trial

Study Drug Accountability

STUDY DRUG ACCOUNTABILITY

By signing the Statement of Investigator (FORM FDA 1572), the Investigator agrees to conduct the study in an efficient and diligent manner, in conformance with the protocol, generally accepted standards of Good Clinical Practices (ICH Guidelines E6), and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study. The Investigator will maintain complete and accurate study documentation, including study drug accountability showing the receipt and dispensing of study drugs (i.e. Spironolactone or Placebo).

It is the responsibility of the Investigator to ensure that all study drugs (i.e. Spironolactone or Placebo) used in the TOPCAT Trial are appropriately accounted for throughout the study with the results recorded in the appropriate Drug Accountability Log kept in the Site study documentation. Site must fax Drug Accountability Log on the first Friday of every month to NERI at 617-673-9514. NERI will closely monitor all Drug Accountability Logs.

Under no circumstances should study drugs be dispensed to subjects not randomized to the TOPCAT trial.

Subjects who are successfully randomized into the study are assigned specific treatment allocation codes. Subjects can only receive study drugs that correspond to their treatment allocation code.

The Investigator is responsible for keeping accurate records of accountability logs.

Study drug will be packaged and shipped by Department of Health and Human Services Program Support Center at Perry Point, Maryland to all participating sites in the USA. Study drug for international sites will be distributed by the national/regional leaders of each country in accordance with the country's import regulations. Study drug will be packaged in bottles (150 tablets per bottle; 4 bottles per package) and should be stored at room temperature (25 degrees Celsius or 77 degrees Fahrenheit). **Study drug must be stored in a secured area with restricted access.**

An initial study drug shipment of 12 packages (i.e. 4 bottles per treatment code) along with a 50-mL graduated cylinder (to measure the volume of study drug per study visit) and 12 TOPCAT study medication bags (one per randomized subject) will be sent to the site as soon as all required regulatory documents are received by NERI. Sites must acknowledge receipt of each study drug shipment (i.e. verify the shipment's content) under the Data Management Tool in the ADEPT database. (Appendix B of the ADEPT User Guide includes Drug Shipment Confirmation information.) Request for subsequent shipments of study drug will be automatically generated and forwarded to Perry Point by the ADEPT database. Sites that are actively enrolling subjects can expect to receive additional study drug shipment from Perry Point on a monthly basis. **Study drug will ONLY be shipped to clinic sites Monday through Wednesday by express courier.** Study drug shipments should be received by one designated person at the study site. Sites should notify NERI by sending an email to the TOPCAT mailbox as soon as possible if any of the shipment's content has been damaged or tampered with.

Randomized subjects must return all study drug containers, whether empty or containing study drug. The enrolling sites must document the number of study drug bottles dispensed

and returned by each randomized subject. At each study follow-up visit (i.e. 4 weeks, 8 weeks, 4 months, 8 months, 12 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months, 60 months, 66 months, and 72 months), sites are required to measure and record (CRF# T015) the volume (in ml) of study drug tablets in each opened study drug bottled using a 50 ml graduated cylinder or record the number of tablets. The Investigator must retain and store all original containers returned by the subjects until these containers are inventoried. NERI will notify sites when all unused and returned study drug are to be destroyed. Appropriate documentation of destruction, in accordance with the guidelines of the institution and countries, must be faxed to NERI at 617-673-9514. A copy of the completed records of study drug accountability for all the supplies received for the study must be provided to NERI as part of the close-out procedure for the study. The original copy must be kept in the regulatory binder at the site.

Neither the Investigator nor designee may supply the study drug to any person except to eligible study subjects who have signed the informed consent, and have been successfully randomized in the TOPCAT trial.

The Investigator is responsible for keeping accurate study drug accountability..

Country Leaders must copy NERI of all correspondence in relation to study drug accountability and distribution.

TOPCAT TRIAL

Master Drug Accountability Log

SITE #: _____ **SITE NAME:** _____

SITE COUNTRY: _____ **PI NAME:** _____

Date DD-MMM-YYYY	Lot Number	Allocation Code	QUANTITY (Rcvd, Disp, Destroyed)			PI Initials	NERI USE ONLY		
			Received	Dispensed	Destroyed		Balance Forward		Initials

PLEASE FAX DRUG ACCOUNTABILITY LOG ON <u>THE FIRST FRIDAY OF EVERY MONTH</u> TO NERI AT 617-673-9514

MASTER DRUG ACCOUNTABILITY LOG IS TO BE MAINTAINED AT THE SITE IN THE REGULATORY BINDER.

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TOPCAT Trial

Unblinding Procedure/Code Breaking

Subjects and treating physicians in the study will be blinded to whether subjects are receiving either spironolactone or placebo after written informed consent is obtained. Randomization is done over the Internet using randomization software accessed via a secure website. A Treatment Allocation Code (letters A thru L) corresponding to either spironolactone or placebo will be assigned to the study patient.

Treatment Allocation Code (A thru L) 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 subject will remain in the trial and will continue adherence to the protocol after the event is resolved. Therefore, every effort should be made to maintain 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. It is expected that unblinding will need to occur only rarely and consultation with the TOPCAT medical monitors (available 24 hours a day via medical monitor hotline 617-723-5656 at prompt enter: 18228) is strongly encouraged prior to any unblinding. Additionally, every effort should be made to ensure the blind is broken for as few people as possible at the clinical site. Investigators are responsible for breaking the blind and should ensure study coordinators and other site staff are not aware of the results of the unblinding procedures, unless absolutely necessary.

Once a subject is unblinded, he/she must be discontinued from study drug.

If a study subject is in an emergency situation in which the Investigator has deemed it necessary to unblind the subject in order to determine the proper course of treatment, and the Investigator has consulted with the TOPCAT medical monitors if appropriate, the Investigator should proceed with the following web based unblinding procedure :

WEB BASED UNBLINDING PROCEDURE

Appendix E of the ADEPT User Guide includes information regarding the ADEPT Unblinding Procedures.

- Go to the ADEPT website at https://study.neriscience.com/topcat;
- Login using your unique username and password;
- Under the menu bar, click on the "Data Management Tool" link;
- Under the Data Management Tool bar, click on the "Subject Unblinding" link;
- At this point, an unblinding warning statement will appear on the screen. Please read the unblinding warning statement and then click the Accept box to acknowledge that you have read the unblinding warning statement;
- You will be asked to enter the subject's ID number (XXXX-XXX-X) and a text explanation of why unblinding was necessary. To proceed with the unblinding process, please click the OK button;
- A statement will appear asking you to confirm your request to unblind the treatment arm for subject ID XXXX-XXX-X. To proceed with the unblinding process, please click the OK button;
- Upon your confirmation, the treatment arm for patient ID XXXX-XXX-X will be displayed on the screen. In addition, a special table containing the reason for unblinding, the subject's ID, the user's name, the date, and time of the unblinding process will also be displayed on the screen. An e-mail containing the unblinding information in the special table will be automatically generated and sent to the TOPCAT mailbox.

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TOPCAT Trial

Permanent Discontinuation of Study Drug or Withdrawal From Study

PERMANENT DISCONTINUATION OF STUDY DRUG

The following indications will result in the Permanent Discontinuation of Study Drug:

- Persistent hyperkalemia (potassium ≥ 6.0 mEq/L or mmol/L, based on a non-hemolyzed sample), if there are no alternative explanations for the elevated potassium level.
- Potassium ≥ 5.5 mEq/L or mmol/L, based on 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 µmol/L, 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.

NOTE: Treating physicians should 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.

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.

WITHDRAWAL FROM STUDY

The following indications will result in the subject's withdrawal from the study:

- Subject refusal to continue in the study
- Physician decision to withdraw subject from 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, 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, 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 repository sub-study.

WITHDRAWAL FROM STUDY PROCEDURE

Complete End of Study Case Report Form (CRF# T030) by providing the study end date, the main reason for withdrawing subject from the study, and the last study visit that was completed by the subject. Complete Subject Participation Case Report Form (CRF# T017).

Please note that Subject Participation Case Report Form (CRF# T017) should be completed every time there is a change in the subject's study participation status.

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TOPCAT Trial

Clinical Endpoints Committee (CEC) Adjudication

CLINICAL ENDPOINT ADJUDICATION

New England Research Institutes, Inc. (NERI) will serve as the primary liaison to the sites for reporting of study endpoints. NERI will be responsible for ensuring the required endpoint-related data are collected. Brigham and Women's Hospital in Boston will serve as the Clinical Endpoint Committee (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 atrial fibrillation, new onset of diabetes mellitus, 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 reviewed by a Physician Reviewer. 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 Reviewer is 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.

ENDPOINT ADJUDICATION PROCEDURE:

The role of the CEC is to insure that all primary endpoints are adjudicated uniformly.

First, NERI will identify all study related endpoints and assign a unique adjudication number to each event. Adjudication numbers are assigned once the relevant ADEPT CRF event forms have been entered. NERI will periodically send requests out to the clinic sites to submit all the necessary documents, reports, and hospital records required for CEC Adjudication to NERI by email (i.e. TOPCAT@neriscience.com) or fax (617-673-9514).

Second, site will gather all the required documents, remove any patient identifiers, and label each document with the appropriate adjudication number prior to faxing or emailing to NERI.

Third, NERI will check to ensure confidentiality and, if required, have the records centrally abstracted onto standard forms by trained NERI staff.

Fourth, centrally prepared forms and documents will be circulated to CEC members for assessment.

One expert on the CEC independently review materials and completes a standard assessment form. Agreement between these two assessments is sufficient. Any disagreement will result in an in-person (or teleconference) consensus review with at least a third expert involved. Consensus may involve one or a subset of the CEC.

Adjudicated outcomes for all endpoints will be recorded on case report forms provided by NERI. These forms will be sent to NERI and subsequently entered into the TOPCAT database. All DSMB reports relating to endpoints will be based on these adjudicated results. No direct contact between the CEC and DSMB is to occur, however, to maintain the objective functioning of these two independent committees.

The CEC will receive for review and adjudication the following events:

- Cardiovascular vs. non-cardiovascular death
- Hospitalization for congestive heart failure
- Cardiac arrest
- Myocardial infarction
- Stroke
- New onset diabetes mellitus
- New onset of atrial fibrillation
- Hospitalization for the management of ventricular tachycardia

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TOPCAT Trial

Data Collection Overview

DATA COLLECTION OVERVIEW

INTRODUCTION

This section describes the subject groups to be enrolled in TOPCAT (Section C.1 of the study protocol version 1.6); reviews the sequence of events required to enroll patients in the TOPCAT Trial (Section C.4 of the study protocol version 1.6); and summarizes the data collection procedures to be followed (Section C.4 of the study protocol version 1.6).

Subject Groups

TOPCAT Study: All subjects at a clinical site who:

- Meet ALL the criteria for inclusion and NONE of the criteria for exclusion;
- Provide written informed consent to participate in the study;
- Are randomly assigned to one of the twelve treatment codes (code A thru L)

TOPCAT Optional Repository Sub-Study:

- Eligible subjects who agree to participate in the study and agree to have additional blood and urine specimens collected at baseline and 12 months for later use in future ancillary studies. A whole blood sample for DNA extraction will also be collected at baseline and 12 months for those subjects who consented to the process.

Sequence of Events

Data collection will take place over the course of approximately 6 years.

All CRFs associated with the study visit must be entered into the ADEPT database within 7-days of the completion of the study visit. Please note that site payments are contingent on the completion of the CRFs for each study visit including the Principal Investigator's electronic signature.

If a site has > 25% of the study data outstanding, the site will be suspended from further study enrollment.

The specifics of the data collection process, from screening through randomization, are described below.

STEP 1. Screening for Eligibility: All potential subjects should be screened for preliminary eligibility. Subject's medical history, list of current medications, and most recent ejection fraction reading should be used as part of the screening process.

STEP 2. Obtaining Written Informed Consent: All eligible subjects should be given a copy of the approved Informed Consent Form and adequate time to read and understand the information. The Investigator should be on hand to answer any questions the subject may have regarding the main research study and the optional sub-studies (repository, echo, and/or echo and vascular stiffness). Subjects who agree to participate in the main research study must provide written consent by signing the Informed Consent Form. Subjects may opt to participate or not participate in any of the sub-studies (repository, echo and/or echo and vascular stiffness). Subjects who chose to participate in sub-studies must sign separate Informed Consent Forms for each sub-study.
The date of consent for the subject must be documented on the Consent Confirmation Case Report Form (CRF# T001). The original signed informed consent form will be kept in the subject's study binder, a signed copy of the informed consent will be given to the subject, and a copy will also be retained in the subject's medical record.

STEP 3. Completing Baseline Study Visit Procedure: In addition to obtaining subject's informed consent, the following procedures must be completed as part of the baseline visit:

- Obtain subject's demographic information and medical and social history.
- Obtain subject's concomitant medication information.
- Perform and record physical examination, including vital signs.
- Collect blood sample for local laboratory tests (i.e. CBC, electrolytes, BUN, creatinine, blood glucose, and liver function tests). If baseline laboratory values were collected more than two weeks before the date of randomization, the clinic sites should repeat the baseline laboratory values, 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 was no inter-current change in medications and/or no borderline lab values.
- Collect urine sample for local laboratory test (i.e. microalbuminuria)
- Calculate subject's estimated GFR using the 4-component MDRD Study prediction equation.

  GFR = 186 x (serum creatinine level [in milligrams per deciliter])$^{-1.154}$ x (age [in years])$^{-0.203}$. For women and blacks, the product of this equation is multiplied by a correction factor of 0.742 and 1.21, respectively.
- Determine subject's eligibility (see Inclusion/Exclusion criteria of the study protocol version 1.7 and Section 2 of Manual of Operations).
- Confirm subject's eligibility (i.e. subject has met ALL of the INCLUSION CRITERIA and NONE of the EXCLUSION CRITERIA).
- Obtain subject's most recent ECG and send it to the ECG Core Lab at Brigham and Women's Hospital (see section 10 of Manual of Operations for specific instructions)
- If subject's qualifying ejection fraction was obtained by echocardiography from the past 6 months, site should send a video or digital image of the echocardiogram to the ECHO Core Lab at Brigham and Women's Hospital (see section 10 of Manual of Operations for specific instructions)
- Obtain Quality of Life Questionnaires.

STEP 4. RANDOMIZATION: Once a subject has signed the Informed Consent and meets all the inclusion/exclusion criteria for the study, the subject may be randomized onto the study. Randomization is carried out over the internet using randomization software via a secure website. To randomize a subject, please refer to the Randomization Procedure of the Manual of Operations for detailed instructions.

Data Collection: Follow-up

1 WEEK FOLLOW-UP: At this visit, safety lab tests are collected and CRF# T016 Follow-up local lab tests should be completed.

4 WEEK FOLLOW-UP: At this visit, physical exam, safety lab tests, current medications, study drug information, event questionnaire information are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, and CRF# T007 Concomitant Medications form should be completed.

5 WEEK FOLLOW-UP: At this visit, safety lab tests are collected and CRF# T016 Follow-up local lab tests should be completed.

8 WEEK FOLLOW-UP: At this visit, physical exam, safety lab tests, current medications, study drug information, event questionnaire information are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, and CRF# T007 Concomitant Medications form should be completed.

4 MONTH FOLLOW-UP: At this visit, physical exam, safety lab tests, current medications, study drug information, event questionnaire, and quality of life questionnaires are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, CRF# T007 Concomitant Medications, CRF# Q001 QOL Coversheet, CRF# Q002 QOL KCCQ, CRF# Q003 QOL EQ5D, CRF# Q004 QOL PHQ – *For North American Sites Only*, and CRF# Q005 QOL OTE - *For North American Sites Only* should be completed.

8 MONTH FOLLOW-UP: At this visit, physical exam, safety lab tests, current medications, study drug information, event questionnaire information are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, and CRF# T007 Concomitant Medications form should be completed.

12 MONTH FOLLOW-UP: At this visit, physical exam, safety lab tests, current medications, study drug information, event questionnaire, and quality of life questionnaires are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, CRF# T007 Concomitant Medications, CRF# Q001 QOL Coversheet, CRF# Q002 QOL KCCQ, CRF# Q003 QOL EQ5D, CRF# Q004 QOL PHQ – *For North American Sites Only*, and CRF# Q005 QOL OTE - *For North American Sites Only* should be completed.

18 MONTH, 30 MONTH, 42 MONTH, 54 MONTH and 66 MONTH FOLLOW-UP: At these visits, physical exam, safety lab tests, current medications, study drug information, event questionnaire information are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, and CRF# T007 Concomitant Medications form should be completed.

24 MONTH, 36 MONTH, 48 MONTH, 60 MONTH and 72 MONTH FOLLOW-UP: At these visits, physical exam, safety lab tests, current medications, study drug information, event questionnaire, and quality of life questionnaires are collected and CRF# T013 Follow-up Physical Exam, CRF# T014 Event Questionnaire, CFR# T015 Study Drug Information, CRF# T016 Follow-up local lab tests, CRF# T007 Concomitant Medications, CRF# Q001 QOL Coversheet, CRF# Q002 QOL KCCQ, CRF# Q003 QOL EQ5D, CRF# Q004 QOL PHQ – *For North American Sites Only*, and CRF# Q005 QOL OTE - *For North American Sites Only* should be completed.

Funded by the NHLBI

TOPCAT Trial

Quality Control/Quality Assurance Plan

1. Introduction

The goal of the Quality Control/Quality Assurance (QC/QA) Plan for the TOPCAT Trial is to ensure standard administration of all study protocols and procedures by all TOPCAT staff at every study site. When properly implemented, the QC/QA plan protects the scientific integrity of the study by maximizing the reliability and validity of the data collected.

The main objective of the QC/QA plan is to ensure that complete and accurate information is gathered in the data collection process. The plan ensures that all study procedures are performed in a standardized manner, across all study sites and all data collectors.

Standard application of the protocol will be accomplished by the following methods:

- Comprehensive Manual of Operations
- User-friendly ADEPT data management system and detailed Question-by-Question (QxQ's) instruction sheets (i.e. Case Report Form Guide) for each Case Report Form (CRF) in the ADEPT system
- ADEPT User's Manual
- Centralized and/or web-based training of Study Coordinators
- Certification of staff performing data entry
- Standardized guidelines/techniques for data collection
- On-going monitoring of data collection activities via real-time reports generated by ADEPT
- Visits to study sites by representatives of the New England Research Institutes, Inc. (NERI) or Brigham & Women's Hospital (BWH), clinical trial coordinating center (CTCC) for the TOPCAT trial

2. Protocol, Manual of Operations and Data Forms

Protocol development will be led by the Clinical Trial Coordinating Center at NERI and BWH. NERI will be responsible for developing and updating the Manual of Operations and the data forms (including the QxQ's). NERI will also be responsible for maintaining official updates to all study documentation and distributing them to the sites and other study personnel as needed. The manual will be posted on the TOPCAT administrative website at https://paws.neriscience.com/ with a version date on each page such that updated instructions can be generated and posted on the TOPCAT administrative website by NERI. Each TOPCAT Trial staff member will be required to refer to these manuals to ensure standardized application of the study protocols and procedures.

3. Question-by-Question Specifications (QxQ's)

To ensure utilization of consistent methods and to minimize response bias, the TOPCAT Trial investigators have carefully designed each study form and constructed detailed instructions referred to as "Question-by-Question Specifications" (QxQ's) for each form (also called the Case Report Form Guide). Question-by-Question Specifications explain

the purpose of questions, clarify terminology, describe response choices, and provide additional instructions that will assist the person completing the form. When creating TOPCAT Trial data forms, the designers attempted to include as much pertinent information as is possible directly on the form. However, some questions and data points require more lengthy explanations, which are detailed fully in the QxQ's. The designers also tried to foresee dilemmas that may occur during the data collection process and provide resolutions in the QxQ's. The TOPCAT Trial site personnel who will be completing forms should refer to the QxQ's often, especially at the beginning of data collection, to ensure that they fully understand the objective of each question in order to collect complete and accurate data.

4. Advanced Data Entry and Protocol Tracking (ADEPT) System

NERI will provide web-based access to and training on NERI's proprietary web-based ADEPT system to manage all aspects of multi-site research including data entry, data management, protocol monitoring, and reporting. ADEPT will contain electronic versions of the forms identical to the Case Report Form Worksheets and perform validity checks on each field as the form is entered, notifying the user immediately of any out of range values or incomplete responses. All sites will receive an ADEPT Data Management User Guidelines Manual at the start of the study.

5. Central Training, Certification and Performance Monitoring

A major contributor to data quality and consistency is standardized, centralized training, and regular monitoring of data collection so that additional training may be provided as needed. TOPCAT Trial staff will receive training in the study protocol, all study procedures, completion of data collection forms, and data entry/editing and report generating using the ADEPT system.

6. ADEPT Users

Data entry certification will be required for the site staff responsible for entering data into ADEPT. The goals of the TOPCAT Trial data entry certification is to ensure that

- Data is entered accurately into the ADEPT system;
- ADEPT users are familiar with its features, including entering/changing data, and running reports;
- Users know how to use ADEPT to monitor the status of data forms; and
- Certified users are familiar with the TOPCAT Trial edit reports, know how to correct data entry errors, and how to deal with missing or out of range information on data forms.

There will be two types of TOPCAT Trial data management system user accounts assigned to staff at the study sites:

- **Full user:** Users who complete data entry certification will have access to all functions of the ADEPT system. They will be able to enter subject data forms, view data and resolve edits for their site, and run reports.

- **Limited user:** Users who have not completed data entry certification will only be able view subject data and run certain reports. They will not be able to directly enter or modify subject data.

The certification process involves the following steps:

1. Registering with NERI so that the name and email address of the person to be certified can be recorded and dummy subject IDs can be assigned to use when entering data for certification.

2. Receiving a packet from NERI that includes instructions, user ID and password for logging in to ADEPT, sample forms completed with dummy data for data entry, and a checklist of items to be completed during certification.

3. Entering pre-coded dummy forms and completing other certification tasks (printing edit reports, re-entering forms to correct errors), checking off items on the checklist as they are completed.

4. NERI will evaluate the accuracy of the data that has been entered into ADEPT. If entered data has more than a specified number of errors, the data entry exercises will need to be repeated. NERI will also check that all of the required items on the form have been completed correctly.

Principal Investigators may request ADEPT data entry access through a separate training process that does not involve completion of the ADEPT certification packet.

7. Electronic Signatures

The TOPCAT trial is using electronic signature executed by a Principal Investigator on electronic case report forms entered in the ADEPT Data Management System.

The Site Principal Investigator is responsible for verifying data accuracy by signing electronically on every data form in ADEPT except the form listed below

Q001 – QOL Coversheet.

The site Principal Investigator will be granted ADEPT access which allows him/her to view data forms in browse mode and sign individual forms or select batch signing for forms.

8. Regulatory Procedures and Source Documentation

The *TOPCAT Trial* is sponsored by the National Heart, Lung, and Blood Institute (NIH/DHHS) and as such, it is extremely important that each Principal Investigator and Coordinator be aware of their responsibilities regarding Clinical Research Practice and Conduct. This study is also conducted under 21 CFR 312 Investigational New Drug by the Food & Drug Administration.

8.1 *IRB APPROVAL*

Informed Consent Forms

NERI will create and distribute a template for the informed consent. Required elements to be included in the Consent form will be identified in a checklist to be distributed to all participating sites. The site version of the Consent form must include all of the elements, regardless of site-specific policies to be followed. In accordance with the NHLBI Policy on Oversight of Consent forms in Multicenter Clinical Studies, NERI will review each site's Consent form prior to submission to the site's IRB/EC to make sure it contains all the required elements and the same meaning as the template. NERI will confirm the Consent form is acceptable and will respond to each site in a timely manner.

Each site will provide NERI with the site's IRB approval letter as well as the stamped approved Informed Consent form.

8.2 Health Insurance Portability and Accountability Act (HIPAA)

The TOPCAT trial will be conducted in accordance with HIPPA privacy and security rules. The HIPAA privacy regulations can be found under the Standads for Privacy of Individually Identifiable Health Information (45 CFR parts 160 and 164). Additional information about the HIPAA privacy rule can be obtained through the United States Department information of Health and Human Services website: http://www.hhs.gov/ocr/hipaa.

8.3 Regulatory Documents

Each site is responsible for complying with all regulations of their local Institutional Review Board (IRB)/Ethics Committee (EC). All adverse reactions or untoward events and any serious complications (including death) during or following a study visit should be reported promptly to the IRB/EC and NERI as well as in a yearly summary.

The following documents should be on file at NERI and also on file and available for review at each Study Center:

1. Signed Contract (also called the Clinical Trial Agreement or Clinical Study Agreement)

2. IRB/EC approvals and all yearly renewals with current approved consent forms, including HIPAA consent forms.

3. Curriculum Vitae (Biographical Sketch) of the Principal Investigator, Investigators and Co-Investigators (e.g., Cardiology Fellows assisting in the study and obtaining consent for subject enrollment).

4. Medical License for all investigators listed on the FDA FORM 1572

5. Financial Disclosure Forms for all investigators listed on the FDA FORM 1572

6. Statement of Investigator – FDA FORM 1572
7. IRB/EC Membership List

8. IRB/EC Assurance/FWA Number or Letter

9. Protection of Human Subjects in Research and HIPAA Training Certification for all study personnel who see participants

10. All numbered Operations Memos from NERI

11. Annual Progress Report to the local IRB/EC and all other IRB/EC correspondence

12. Summaries of all Data and Safety Monitoring Board (DSMB) meeting recommendations

Status changes in TOPCAT Trial personnel (Cardiology Fellows, Study Coordinator, co-investigators) must be reported by the Study Coordinator to NERI immediately so that the Study Center's documentation file at NERI can be updated and the FDA can be informed.

8.4 Source Documentation

This regulation requires that information entered into the ADEPT system be written either in the medical record or in the subject's file so that it can be confirmed on a document separate from the ADEPT data management system. During site visits, the monitor will review records to determine if source documentation is available to supply all data entered into ADEPT. The following procedures should be followed in regard to the subject's study file at the Study Center:

1. The original of the signed consent form must be filed in the subject's folder, with one copy in the medical record and another copy given to the subject.

2. Source documentation for any data field not regularly recorded as part of the subject's medical record should be established and signed by the principal investigator. It should be placed in the subject's file as a document to confirm information entered into the ADEPT system.

3. If allowed, it is helpful to keep in the subject's study file copies of portions of the subject's medical record that pertain to information extracted for the ADEPT data management system.

CRF Worksheets cannot be used as source documents.

9. Study Coordination and Communication

Each participating Clinical Center will have one or more Clinical Research Coordinators who, along with the lead investigator, are responsible for ensuring the study protocol is properly implemented as outlined in the Manual of Operations. Data obtained for entry into the ADEPT data management system will be extracted from medical records, progress notes, lab reports, catheterization reports, surgery reports, anesthesia flowsheets, nursing notes, office visit notes, etc.

The Clinical Research Coordinator is responsible for the following:

- Ensure that potential TOPCAT subjects are provided with appropriate information about the study, including the Informed Consent documents;
- Maintain a study file for each subject, which contains a signed informed consent document;
- Communicate with NERI regarding participant enrollment, randomization, and data processing matters;
- Maintain a file of correspondence with NERI, IRB/EC and the NHLBI;
- Maintain a regulatory binder;
- Maintain an up-to-date TOPCAT specific Manual of Operations, and TOPCAT protocols;
- Ensure data entry to the Data Management System (ADEPT) takes place in a regular and timely manner (i.e. within 7 days of a completed study visit);
- Ensure that participant names, social security numbers, and any other personal identifiers are removed from all materials sent to NERI (e.g., adverse event documentation) in compliance with privacy regulations;
- Respond to data queries from NERI in a timely manner;
- Coordinate with NERI to ensure that the personnel performing TOPCAT procedures are properly trained and certified;
- Assist and collaborate with the Study Monitor during site visits at the Clinical Center;
- Identify and report irregularities or problems that may affect the data quality to the Principal Investigator and NERI;
- Maintain complete and accurate study documentation, including study drug accountability showing the receipt, dispensing, and destruction of all study drugs.

10. Site Monitoring

As part of the Quality Assurance plan and in full agreement with the NIH policy that states all clinical trials require monitoring to ensure the safety of participants and the validity and integrity of the data (NIH Guide, NIH Policy for Data and Safety Monitoring, June 10, 1998), monitoring will be a continuous, ongoing and multifaceted process. This includes external review by the Data Safety Monitoring Board (DSMB) and IRB/EC, as well as all data quality control, review and evaluation. NERI will be conducting remote monitoring or in-person monitoring visits. If remote monitoring occurs, sites must fax all the requested source documents to NERI within 5 business days. To ensure patient eligibility, NERI may perform regular remote monitoring “visits” on all clinic sites by requesting specific source

documents from a random group of subjects from each clinic site throughout the study. Source documents for study eligibility monitoring purposes may include ECHO reports, lab data, and hospital discharge summaries. Site Monitoring visits are central to this process, and will include reports to appropriate individuals with oversight responsibilities.

Site visits will be conducted at least once during the study period by representatives of NERI. The purpose of the site visit is to: (1) review study procedures with the clinical center's Principal Investigator and study staff; (2) assess the clinical center's proficiency in executing the TOPCAT Protocol; and (3) assess the data quality by comparing source documents to the data entered into the ADEPT system. A complete outline of Monitoring Visit objectives and procedures is included in the Manual of Operations.

11. Data Monitoring

The Data and Safety Monitoring Board (DSMB) reviews the accumulating study data approximately every six months. In addition, the Chair of the DSMB and the FDA will review serious adverse events on a more frequent basis.

All FDA reports will be provided to the DSMB. At DSMB meetings, the data are reviewed to assess expected vs. actual recruitment, completeness of data, subject safety, and treatment effect. If a very large treatment effect is observed before the planned end of the trial, the DSMB will follow guidelines for possible early termination of the trial. The DSMB will review all adverse events on a semi-annual basis.

The ADEPT system is designed to track all protocol deviations for reporting purposes.

Any protocol deviation that does not have a clear justification (based on clinical or technical reasons) will be considered a protocol violation.

Protocol violations may include inability or refusal to complete a study test and study visits conducted outside of defined time windows.

If protocol violations occur, the enrolled subject should remain in the study and complete all remaining study events, as applicable.

11.1 Monitoring

NERI will perform regular audits in house to check for accuracy and congruency of information within and across all data forms for an individual participant. Clinical Centers will be notified of any inconsistencies.

NERI will track the progress of study recruitment at each site. NERI will also monitor the clinics' adherence to randomization and protocol procedures and deviations from the protocol, including enrollment of ineligible subjects. Enrollment, protocol compliance, and violations will be reported to the Steering Committee at least quarterly.

11.2 Quality Assurance Reports

In addition to reports mentioned above, routine Quality Assurance and Subject Monitoring reports including these listed below will be available to sent to program officers at NHLBI and specific study staff at participating Clinical Centers, and will also be made available in real-time (i.e. on a continuous basis) via the web-based data management system. Study staff at participating centers will only be able to review reports for subjects enrolled at their site or affiliated sites.

Data Quality / Assurance Reports

- Protocol Violations
- Outstanding Forms (forms expected, but not yet data entered or formally noted as permanently missing)
- Outstanding Edits (by form)

Subject Accounting Reports

- Number of subjects recruited
    - By race/ethnicity
    - By gender
    - By site
- Number of subjects who have completed study