Manual of Operations Addendum

ATHENA-HF

Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy – HF

November 5, 2014

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1 ATHENA-HF Contacts

1.1 DCRI Coordinating Center Team

Name	Role	E-Mail	Phone
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Doris Coleman	Project Leader	Doris.coleman@duke.edu	(919) 668-8042
Teresa Atwood	Clinical Research Associate	Teresa.atwood@duke.edu	(919) 668-8841
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Melissa Brockington	Clinical Trials Assistant	Melissa.Brockington@duke.edu	(919) 668-7809
Adam Devore	Medical Monitor	Adam.Devore@duke.edu	(919) 970-4433
Jacob Kelly	Medical Monitor	Jacob.kelly@dm.duke.edu	(919) 970-4433
Lauren Cooper	Medical Monitor	Lauren.b.cooper@dm.duke.edu	(919) 970-4433
Trevorlyn Haddock	Safety Surveillance	Trevorlyn.haddock@duke.edu	(919) 668-8552
Kristy Hwang	Data Management	Kristy.hwang@duke.edu	(919) 668-8059
Jane Winsor	Data Management	Jane.winsor@duke.edu	(919) 668-8645
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1.2 Core Laboratories

BIOMARKER - University of Vermont, Dr. Russell Tracy
208 South Park Drive
Colchester, VT 05446
Rebekah Boyle- Project Manager
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GENETICS - Montreal Heart Institute, Dr. Michael Phillips
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Montréal, Québec H3A 1A4
Hélène Brown RN B.Sc. CCRP Team leader
Montreal Heart Institute
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E-mail: helene.brown@icm-mhi.org

Please refer to the Core Lab Blood Collection Manual of Operations (MOP) for additional details regarding the procedures for the collection, storage and shipment of biomarker samples.

1.3 InForm EDC (eCRF)

Questions regarding technical problems using the eCRF or to reset your password:

U.S. 1-866-999-DCRI [3274]
E-mail: edchelp@dm.duke.edu
Coverage: 6am to 12am Monday through Friday

Questions regarding randomizing a patient in Inform, entering subject data, queries, traffic lights, etc., contact the DCRI Data Management Team. (Contact information listed in Section 1.1.)

1.4 HF Network Clinical Helpline

A physician will be available 24 hours a day to answer urgent questions about recruitment, enrollment, and patient management by calling the HFN Clinical Helpline at 1(919)970-4433. Call the CC first with all your general questions. Sites are encouraged to call the Clinical Helpline to seek assistance on unclear issues that arise when applying the research plan to specific patients. Use of the Clinical Helpline is especially important before randomization of patients with any question regarding eligibility and when a patient is considering discontinuing the study for any reason.

The HFN Clinical Helpline is not for questions related to:

- Core Lab Questions - All Core Lab questions should be directed to the Core Lab. (Contact information listed in Section 1.1 and in the associated MOP.)
- Operational or procedural questions re: an HFN trial
- Re-supply orders should not go through the clinical helpline. Study Coordinators should follow the instructions in the Core Lab MOP for re-supply requests for core lab or the DCRI Coordinating Center (CC) for other site materials.

HFN Fellows, Dr. Adam Devore, Dr. Lauren Cooper, and Dr. Jacob Kelly will take the role as the Medical Monitor on the HFN Clinical Helpline. Study Coordinators should email the HFN Fellow at adam.devore@duke.edu, lauren.cooper@duke.edu, or Jacob.kelly@duke.edu if they do not receive a call back after they page the helpline. If the Study Coordinator still does not receive a response from the Medical Monitor then CC Site Management should be contacted.

2 HF Network Clinical Center Site Activation Process

Site activation by the CC will occur following receipt of an executed contract with the site, the site being determined by the CC as regulatory document complete, and following completion of appropriate protocol training.

A site activation notification from the DCRI CC will be distributed notifying the PI, study coordinator, and other appropriate personnel of approval to initiate study enrollment. This notification should be filed in the regulatory binder as documentation of the date in which the site was activated.

TABLE 1 - Documents for Completion by each Clinical Center (Please refer to the regulatory document completion guidelines provided with the regulatory packet for start-up documents.)

1.	Study Site Staff Delegation and Signature Log (SDSL)	Sites send to the DCRI project team at start-up. The SDSL is a living document and should be updated upon changes in personnel at site. The original is maintained at the site.
2.	Investigator CV / Bio sketch	RCC PIs and site PI must provide current CV. Site sends to the DCRI project team prior to activation.
3.	Medical License	RCC PIs and site PI must send to the DCRI project team prior to activation. Medical licenses must be updated annually and sent to the DCRI project team. The original is maintained at the site.
4.	Protocol and Protocol Amendment Signature Pages	The study PI from each site signs and dates, then sends to the DCRI project team prior to activation. Once activated, if there is a change in PI or a protocol amendment, the signature page should be sent to the DCRI project team. The original is maintained at the site.
5.	COI Form	RCC PIs and site PIs listed on the SDSL must sign a COI at the start of the study and update it annually or upon change in COI status.
6.	Federal Wide Assurance (FWA) Number	FWA Number is updated according to the expiration date. Sites send to the DCRI project team prior to activation and as needed according to expiration date.
7.	Copy of IRB Approval for Protocol & Informed Consents	IRB approval must be updated yearly. Sites send IRB approvals to the DCRI project team prior to activation and throughout study as IRB renewal and amendment approval is obtained. The CC will review and approve all ICFs prior to submission to their local IRBs.
8.	Documentation of Human Subject Protection Training	This documentation is required for all key personnel. Form is located at http://cme.nci.nih.gov. Sites send completed form to the DCRI project team prior to activation and provides updates to the form when new key personnel are added.
9.	Signed Contract with CC	Each RCC and Enrolling Center in the U.S. needs an executed Rapid Start Network-Federally Funded Grants Participation (RSNG) and Contract Addenda prior to activation.
10.	Protocol Training	Training Certifications for each individual protocol will be provided by the DCRI project team. The PI and SC (at minimum) must receive protocol training prior to activation. Ongoing training and training of new study personnel must be documented.
11.	InForm Training	Each site user must complete InForm training. Training will include randomization procedures performed within InForm.

3 Screening

A protocol specific Recruitment Plan will be completed by each enrolling center to define strategies to increase protocol awareness, delegate personnel and adequate resources, identify competing studies and prioritization plans, and list potential recruitment barriers and actions to mitigate barriers. All patients admitted to participating Heart Failure Clinical Research Network Centers with signs and symptoms of AHF should be screened by a study coordinator. Patients meeting eligibility criteria will be approached regarding participation in this study. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the trial.

Sites are to maintain a Master Screening Log to capture the enrollment status of patients. This screening log data will be entered by the research team into SharePoint or the screening logs can be sent to the CC on a weekly basis at the beginning of the study, and then at minimum, monthly, as specified by the CC. Screening log data includes: date of prescreening, failed code(s), reason description, and chart status; failed, pass, or enrolled. (Chart Status definitions: Failed = Screen Failure; Pass = Consented and not randomized, Enrolled = Randomized.)

Pocket Reference Cards will be provided for key inclusion/exclusion criteria and scheduling. This reference card includes the study flow diagram and the schedule of activities table which will be a useful reference at the time of each patient assessment.

Patients ≥21 years old (1) admitted with an AHF diagnosis (verified by ≥1 symptom and ≥1 sign of congestion) and (2) receiving no MRA or low dose spironolactone (12.5 mg to 25 mg daily) at baseline, will be screened. Those with eGFR <30 mL/min/1.73m^2, K^+ >5.0 mmol/L, or systolic blood pressure <90 mmHg will be excluded. Patients will be included if admission or screening BNP ≥ 250 pg/ml or admission NT-proBNP ≥ 1000 pg/ml (Local Lab). (Must be performed within 24 hours prior to randomization.) Complete inclusion/exclusion criteria are as follows:

3.1 Inclusion Criteria

1. Male or female patient ≥21 years old
2. Admitted to hospital for AHF with at least 1 symptom (dyspnea, orthopnea, or edema) and 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography) of congestion
3. Patient must be randomized within 24 hours of first IV diuretic dose administered for the current episode of decompensation (regardless of where the diuretic was given e.g. office, ED, ambulance, hospital etc.)
4. Estimated GFR of ≥30 mL/min/1.73m^2 determined by the MDRD equation
5. Serum K^+ ≤5.0 mmol/L at enrollment
6. NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL, measured within 24 hours from randomization (Local Lab)
7. Not on MRA or on low-dose spironolactone (12.5 mg or 25 mg daily) at baseline

3.2 Exclusion Criteria

1. Taking eplerenone or >25 mg spironolactone at baseline
2. eGFR < 30 ml/min/1.73m2
3. Serum K+ >5.0 mmol/L. If a repeat measurement within the enrollment window is <5.0, the patient can be considered for inclusion.
4. Systolic blood pressure <90 mmHg
5. Hemodynamically significant arrhythmias or defibrillator shock within 1 week

6. Acute coronary syndrome currently suspected or within the past 4 weeks
7. Severe liver disease (ALT or AST >3 x normal, alkaline phosphatase or bilirubin >2x normal)
8. Active infection (current use of oral or IV antimicrobial agents)
9. Active gastrointestinal bleeding
10. Active malignancy other than non-melanoma skin cancers
11. Current or planned mechanical circulatory support within 30 days
12. Post cardiac transplant or listed for transplant and expected to receive one within 30 days
13. Current inotrope use
14. Complex congenital heart disease
15. Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade
16. Previous adverse reaction to MRAs
17. Enrollment in another randomized clinical trial during index hospitalization

4 Obtaining Informed Consent

Informed consent will be obtained as required by the local institutional review boards. Written informed consent must be obtained from the patient prior to beginning any screening activities that are not part of the patient's routine care. Patients should be encouraged to have supportive family member(s) and other advocates present during the consent process. Additionally, they should be given full access to all physicians involved in their care to aid in their deliberation on trial entry. Patients should be informed that their consent can be withdrawn at any time and for unstated reasons. There can be no changes in the protocol without the prior agreement of the Heart Failure Network (HFN) Steering Committee.

5 Randomization

After providing informed consent and signing the IRB approved consent document, subjects who are deemed eligible will be randomized using procedures determined by the CC. A Randomization Worksheet should be completed on each patient prior to randomization to document that the patient meets inclusion/exclusion criteria and that an Informed Consent document is signed before randomization. The completed Randomization worksheet should be filed with the subjects study file.

Randomization will be completed using InForm. All study personnel who are delegated to the task of randomization must attend InForm training, prior to being granted access to this task in InForm.

After completing the ATHENA-HF Randomization Worksheet and verifying subject eligibility, trained site personnel will log into InForm to create the patient and complete subject randomization. Patient specific information required to complete randomization includes: subject's use of prior MRA (yes/no), date of birth, and gender.

5.1 Steps to Create a Patient in InForm and Randomize to ATHENA-HF

Detailed instructions, including screen shots for randomizing a subject in InForm, are included with the eCRF instructions and ATEHNA-HF training slides.

1. Study Coordinator (SC) completes Randomization Worksheet and confirms that subject can be randomized.
2. SC or Principal Investigator (PI) notifies the investigational pharmacist BEFORE starting the randomization process to ensure pharmacy personnel are available to unblind and prepare the study drug.
3. SC or PI log into InForm to create the patient.
    a. Click on "Enroll" button and click "Add Candidate"
    b. Tick box to confirm they want to Screen the subject into the InForm System. Provide subjects DOB and Gender.
    c. "Submit" Screening form and tick box to confirm they want to enroll the subject into InForm.
4. Provide the stratification information on the STRATA form. (Prior MRA use? Yes/No)
5. Tick the box on the Randomization form to confirm the subject should be randomized and "Submit" the form.
6. The Randomization form will show the Randomization Date/Time and show a generic randomization arm on the screen (e.g. "Treatment").
7. Print this screen to provide to the pharmacist.
8. The SC will notify the pharmacist that a subject was randomized and will provide pharmacist with subject ID, Gender, DOB.
9. Pharmacist will run the Unblind Report in Inform to show the Randomization Arm and provide treatment.

Patients must be randomized within 24 hours of first I.V. diuretic dose to receive spironolactone or matching placebo in a double-blind fashion. Randomization and treatment will be stratified according to previous MRA use.

- Patients receiving no MRA therapy at baseline will be randomized to receive either spironolactone 100 mg or placebo daily for 96 hours.
- Patients already receiving low-dose spironolactone at baseline (12.5 mg or 25 mg daily) will be randomized to 100 mg or 25 mg spironolactone daily for 96 hours.

Following randomization, study personnel are to ensure that all K^+ supplements are stopped prior to study initiation, that no K^+ containing salt substitutes are given to the patient, and that the patient is not enrolled in any automatic K^+ replacement protocol in the hospital. Enrolled subjects should also be instructed by the study team not to take any potassium supplements such as potassium citrate, gluconate, or acetate or potassium containing salt substitutes while taking this study drug.

Randomized subjects will receive a copy of the signed informed consent and contact numbers for the research team in the event of questions or to report any concerns related to the study. A patient wallet card will be provided to the patient to present to a hospital, emergency room or urgent care facility following discharge from the hospital through the Day 30, post randomization, follow-up telephone call.

For randomization support contact, contact the DCRI Data Management Team. (Contact information listed in Section 1.1)

6 Study Drug, Administration, and Permitted Dose Adjustments

The FDA determined that the ATHENA-HF protocol is exempt from the IND regulations on August 20, 2014. The therapeutic intervention is a double-blind treatment with 100mg or 25 mg spironolactone or placebo. Study drug will be given once daily, every 24 hours following randomization, for 96 hours in hospital starting within ≤24 hours from the first dose of I.V. diuretic administered for the current episode of decompensation (e.g. office visit, ED, during transfer before admission, or in-hospital).

The daily dose will be adjusted according to the results of daily serum potassium concentration, renal function, and congestion status. The active and placebo study drug will appear identical to preserve the double-blind study design. The initial dosing scheme will be as follows:

- Patients receiving no MRA at home will receive either spironolactone 100 mg or matching placebo (4x25 mg study capsules) once daily for 96 hours.
- Patients already receiving low-dose MRA at home will receive spironolactone 100 mg vs. 25 mg (1x25 mg spironolactone and 3 study capsules) in hospital for 96 hours.

Other Medications

All other medications, including diuretics, will be left at the discretion of the treating physician.

Permitted Dose Adjustments

Recommended actions for administration of study drug are based on 24, 48, and 72 hour serum K^+ levels and changes in serum creatinine levels. Ensure creatinine, blood urea nitrogen (BUN), and electrolytes are drawn 1-2 hours prior to scheduled 24, 48, and 72 hour assessments, so the results will be available for the Principal Investigator's review prior to study drug administration.

Serum K+ must be < 5.0 mmol/L to continue the protocol and to administer the 24, 48 and 72 hour, post randomization, study drug dose.

The enrolling site PI and SC must notify the CC Medical Monitor when a serum K^+ is confirmed > 6.0 mmol/L AND when the study drug is stopped due to a serum K^+ > 6.0 mmol/L.

The decision regarding management of patients with change in serum creatinine will be left to the discretion of the treating physicians. It is however recommended that:

Serum Creatinine Increased by:	**Clinically**	**Protocol**
≤ 0.5 mg/dl	• Diuresing • Improving • Fluid overloaded	Continue protocol
>0.5 mg/dl	• Improving • Fluid overloaded • Not oliguric	May hold protocol or give study drug reduced to half dose, per PI discretion.*
>0.5 mg/dl	• Oliguric	Hold protocol – May continue study drug next day per PI discretion based on renal function.

*Each patient will get 4 capsules (4 placebo, 4 active, or 3 placebo +1 active). If creatinine increases >0.5 mg/dl and investigator wants to continue half dose of study drug, the patient will still get 4 capsules (4 placebo, 2 placebo +2 active, or 3 placebo +1 active). This will be done by the research pharmacy.

6.1 Study Drug Dispensing

Drug dispensing will be managed by the CC in collaboration with Almac Clinical Services. At randomization and every day until 96 hours, the pharmacy at each site will provide the study personnel with study drug. Authorized personnel will administer the study drug.

No previous MRA stratum: 4x25 mg study drug capsules once daily; starting dose 100 mg spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.

Previous low-dose MRA stratum: 4x25 mg study drug capsules once daily; one capsule containing 25 mg spironolactone and 3x25 mg study capsules containing spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.

6.2 Drug Storage, Accountability and Destruction

Storage - Study drug is to be stored at 59 – 77° F (15 – 25° C). Excessive moisture should be avoided. Temperature excursions are to be reported immediately to the CC. Investigators should ensure proper storage conditions and record and evaluate the temperature. Study drug should be stored in a locked and secure environment.

Drug Accountability - All study drug supplies provided by the CC to the sites must be accounted for in written documentation that must be maintained by the investigator. Forms to record dispensing of study medication will be provided prior to the initial shipment of the study drug. A copy of the completed study drug accountability record will be provided to the CC as part of the study closeout activities.

Site Drug Accountability Logs (DAL) – DAL enables tracking of how much drug is available on site. The accountability log should be used to document when a shipment of drug is received, when study drug is dispensed, when drug is lost/damaged, when drug is returned and the balance. The site should initial by each entry.

Destruction - Used and unused study drug can be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure under the direction of the CC. A copy of the drug destruction SOP should be maintained in the pharmacy section of the Regulatory Binder. Study drug destruction should be documented in the comments section of the Site Drug Accountability Log.

The following study drug records should be maintained by designated site personnel:

- All study drug shipment invoices and confirmation
- InForm record documenting randomization
- Drug Accountability Logs

7 Schedule of Assessments

Appendix A. Schedule of Assessments

Baseline assessments, excluding echocardiogram, must be completed within 24 hours prior to randomization. All visits are anchored from the time of randomization.

	In-hospital						Day 30[10] (+3 days)	Day 60[11] (+/- 3 days)
	Baseline	**24 hours**	**48 hours**	**72 hours**	**96 hours**	**Discharge Assessment (post 96 hours)**	**Telephone Follow Up**	**Telephone Follow Up**
Informed Consent	X							
Medical History	X							
Medication Review	X[1A]	X	X	X	X	X[1B]	X	
Physical Exam / Vital Signs	X	X[2]	X	X[2]	X			
Body Weight	X	X	X	X	X	X[9]		
Fluid intake/urine output		X	X	X	X			
Cr, BUN, electrolytes	X	X[3]	X[3]	X[3]	X	X[9]		
Dyspnea Relief (7-point Likert and Visual Analog Scale)[4]	X	X[2]	X	X[2]	X			
Serum pregnancy test[5]	X							
BNP or NT-proBNP (Local Lab)	X							
Biomarkers (NT-proBNP) (Core Lab)	X	X[2]	X	X[2]	X			
Study drug administration	X	X	X	X				
Clinical events[6]							X	
Adverse events[7]		X	X	X	X	X	X	
Randomize	X							
Echocardiogram[8]	X							
Telephone call to assess vital status								X

[1A]Baseline medication review represents pre-hospital medications
[1B]Discharge Assessment (post 96 hours) represents prescribed medications at the time of discharge
[2]Complete ONLY if day of discharge
[3]Draw labs 1-2 hours prior to scheduled 24, 48, and 72 hour assessments
[4]Assess dyspnea supine, off oxygen for 3 minutes or until severe dyspnea
[5]For women of childbearing potential
[6]Death, any readmissions, and emergency care for HF (readmission or ED visits or observational unit stay or need for outpatient IV diuretics)
[7]Non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs need to be reported from the time of randomization through the Day 30 assessment.
[8]Echocardiogram performed within 6 months prior to randomization or prior to the 96 hour assessment to ascertain ejection fraction. Nuclear perfusion study, MRI, or MUGA measuring ejection fraction also acceptable.
[9]Discharge Assessment, if post 96 hour assessment, includes documentation of available Cr/BUN/electrolytes and weight (plus medication review and adverse event assessment)
[10]Performed day 30 (+3 days) post randomization
[11]Performed day 60 (+/-3 days) post randomization

7.1 Evaluations and Procedures

All protocol described assessments should be anchored using the randomization date and time.

All patients will be assessed every 24 hours following randomization for 96 hours:

- 24-hour assessment should occur between 22 and 26 hours post randomization
- 48-hour assessment should occur between 46 and 50 hours post randomization
- 72-hour assessment should occur between 70 and 74 hours post randomization
- 96-hour assessment should occur between 94 and 98 hours post randomization

7.2 Baseline Evaluation and Procedures Conducted Prior to Randomization

Within 24 hours prior to randomization, all study participants will undergo:

1. Medical History
2. Review of medications including pre-hospital loop diuretics, MRA, and potassium doses (Record diuretic dose 7 days prior to admission if available)
3. Physical examination, vital signs and body weight
4. Measurement of creatinine, blood urea nitrogen (BUN), and electrolytes (Sodium, Potassium, Chloride and Bicarbonate)
5. Dyspnea Relief Assessments (7-point Likert and Visual Analog Scale)
    a. Measured supine, off oxygen for 3 minutes. If the patient develops severe dyspnea prior to 3 minutes off oxygen, the patient will complete the dyspnea relief worksheets at the point of severe dyspnea.
6. Serum pregnancy test for all women of childbearing potential
7. Collection of samples for measurement of NT-proBNP levels (Core Lab)

7.3 Assessment at 24 Hours Post Randomization

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes (Sodium, Potassium, Chloride and Bicarbonate)
    **Draw labs 1-2 hours prior to scheduled assessments, so results will be available*
5. Adverse events

If the 24 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
    a. Measured supine, off oxygen for 3 minutes. If the patient develops severe dyspnea prior to 3 minutes off oxygen, the patient will complete the dyspnea relief worksheets at the point of severe dyspnea.
c. Biomarkers (NT-proBNP) (Core Lab)

7.4 Assessment at 48 Hours Post Randomization

1. Review of medications
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Dyspnea Relief (7-Point Likert and VAS)
    a. Measured supine, off oxygen for 3 minutes. If the patient develops severe dyspnea prior to 3 minutes off oxygen, the patient will complete the dyspnea relief worksheets at the point of severe dyspnea.
6. Creatinine, blood urea nitrogen (BUN), and electrolytes (Sodium, Potassium, Chloride and Bicarbonate)
    **Draw labs 1-2 hours prior to scheduled assessments, so results will be available*

7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

7.5 Assessment at 72 Hours Post Randomization

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes (Sodium, Potassium, Chloride and Bicarbonate)
   **Draw labs 1-2 hours prior to scheduled assessments, so results will be available*
5. Adverse events

If the 72 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
   a. Measured supine, off oxygen for 3 minutes. If the patient develops severe dyspnea prior to 3 minutes off oxygen, the patient will complete the dyspnea relief worksheets at the point of severe dyspnea.
c. Biomarkers (NT-proBNP) (Core Lab)

7.6 Assessment at 96 Hours Post Randomization

1. Medication review
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Creatinine, blood urea nitrogen (BUN), and electrolytes (Sodium, Potassium, Chloride and Bicarbonate)
6. Dyspnea Relief (7-Point Likert and VAS)
7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

7.7 Volume Assessment

If patient is clinically euvolemic in less than 96 hours, consider changing loop diuretics to oral dose.

7.8 Ejection Fraction

Ejection fraction data will be obtained from echocardiogram within 6 months prior to randomization. Those patients who do not have an echocardiogram recorded within this time frame will get an echocardiogram, nuclear perfusion study, MRI, or MUGA performed prior to the 96 hour in-hospital assessment to ascertain ejection fraction.

7.9 Discharge

Study drug will be discontinued after 96 hours and further use of MRA will be left to the treating physician's discretion.

If discharge occurs after the 96 hour assessment but prior to the 30 day assessment, the following will be obtained from medical records and documented in InForm:

1. Medication review (prescribed medications at the time of discharge)
2. Body weight (if available)
3. Creatinine, blood urea nitrogen (BUN), and electrolytes (if available)
4. Adverse events

7.10 Follow-Up Telephone Call at Day 30

All participants will be contacted by telephone at day 30 (+3 days) post randomization to assess:

1. Vital status (death)
2. Any readmissions
3. Any HF readmissions or ED visits or observational unit stays for HF or need for outpatient IV diuretics
4. MRA use at day 30
5. Loop diuretic dose at day 30
6. Any adverse events

7.11 Follow-Up Telephone Call at Day 60

All participants will be contacted by telephone at day 60, (+/- 3 days) post randomization to assess vital status (death).

7.12 Patient Discontinuations

It is expected that the Study Coordinator contact the HFN helpline anytime that a patient discontinues or is thinking of discontinuing the study and/or study therapy for any reason. It is very important that you try to obtain as much data as possible for the duration of the trial for all patients. Make every attempt to have the patients complete all study assessments, evaluations and lab work even if he/she is no longer participating in the study treatment. If the patient wishes to withdraw consent at any time for any reasons, the patient must state in writing he or she is withdrawing from the study.

- If a patient states that he/she no longer wants anything to do with the study and withdraws consent then do not contact him/her further.
- If the patient does not want to take the study drug and will not agree to complete the study assessments per protocol then request that he/she allow you to continue to follow him/her via phone, contacting his/her physician and allowing you access to the medical records.
- If they do not want you to contact them any further, ask if you can have access to their medical records for the duration of the study. Please try to obtain mortality status at Day 60, post randomization.

7.13 Lost To Follow-Up Procedures

It is essential to have mortality status on all patients within the study. Below are the procedures for locating a lost to follow-up patient:

- **Five Telephone Contact Attempts -** There should be at least 5 attempts to contact the patient at home. 2 of these contacts should be in the evening hours and 1 attempt should be on the weekend. In addition, these calls should be spread over a 2 week period.
- **Call Primary Care Physician -** Should the above attempts fail, a call to the primary care physician should be made. Often times the primary physician may have additional information that may not have been relayed to the Study Coordinator.
- **Send Certified Letter -** If these attempts fail, then a certified letter should be sent to the patient with return receipt requested. Any information completed on the return receipt will at least give you a date the patient was last known to be alive.

- **Other Methods for Tracking Down Patients:**
  - Hospital medical records – Further assistance in obtaining patient information admission/discharge dates with treating physician names
  - Hospital demographic database – Encounter dates (office visits, ER visits, admissions)
  - Vital records/register of deeds – Verify and obtain actual date of death (verify copy of death certificate), location of death
  - Public Libraries – Assistance in determining/locating death information via obituaries.
  - National Death Index – May be used to determine if a patient is alive
  - Internet – May be used to find patients who may have moved.
  - Ancestry.com - May be a source for death information.

8 Study Treatment

8.1 Randomization, Stratification and Blinding

Randomization will occur within 24 hours of first I.V. diuretic dose given for the current episode of acute HF decompensation (either in the office, ED, ambulance, or hospital). Randomization to active drug or placebo (1:1 allocation ratio) is stratified by site and spironolactone usage at baseline. Blinding is ensured by preparation of identically appearing placebo and active drug (25 mg study drug capsules). Subjects will be randomized using a permuted block randomization to ensure relatively equal distribution of subjects to each arm within each site.

Blinding of the study, with respect to treatment groups will be preserved by the use of matching placebo. Designated site Investigational Pharmacists will be unblinded to dosing assignment to allow for correct dispensing of study drug. The investigator may be asked at the end of the trial if they had obtained any information that may have led to the unblinding of treatment.

8.2 Unblinding

The investigative sites will be given access to the treatment code for their patients for emergency unblinding only by calling the CC. Unblinding should be a very rare occurrence. The potential physiologic actions of the therapy are well characterized. Given the known safety profile of spironolactone, it is anticipated that there should be no need to unblind the study drug. Any suspected study drug-related events should be treated as though the patient received active therapy. Nevertheless, in the rare event of necessary unblinding, the CC Medical Monitor must be contacted to discuss a given case. Randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding. Site pharmacists will be unblinded based on labeling of the active and placebo study drug.

8.3 Concomitant Medications

Patients with AHF should be treated with standard HF guidelines recommended care. Medications should be adjusted during hospitalization and at Day 7 or discharge, as dictated by the guidelines. The following drug interactions have been observed with spironolactone with long-term use:

- ACE inhibitors or ARBs: may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics: maybe associated with hypokalemia

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

9 Electronic Case Report (eCRF)

This study will use InForm, a web-based electronic CRFs developed through a validated, electronic records and electronic signatures (ERES)-compliant platform (21 CFR Part 11). Site staff who will be entering data will receive training on the system, after which each person will be issued a unique user identification and password.

Qualified study staff at each site will perform primary data collection from source-document reviews.

Refer to the ATHENA-HF) eCRF instructions for detailed instructions on entering data into InForm.

The investigator is responsible for the integrity and accuracy of the data. The investigator must ensure completeness, legibility, and timeliness of the data reported. In addition, the PI must review and sign electronically to verify data accuracy. Data will be entered from the subject medical records into the eCRF. Subject medical records will be maintained at the site and considered the source documents for this clinical trial. Study records and regulatory documents will be retained at the study site, along with adequate source documentation, according to NIH requirements. All study records, including source documents, must be available for inspection by the DCRI CC and the NIH.

Data management expectations include:

- Maintain a minimum of 90% on-time data entry and cleaning
- Enter all visit data into InForm within 5 business days of visit completion
- Comply with protocol windows and schedule of assessments
- No visit has missing items for more than 30 business days
- No queries are open for more than 30 business days
- Requests for source documentation are submitted via secure fax or FTP site within 5 business days
- Requests for PI signature on safety events occur within 5 business days
- PI signature is obtained on all subject data in InForm at trial completion

10 Safety Monitoring

The reporting of information from an adverse experience (AE) can lead to important changes in the way a new treatment is developed, provide integral safety data, and foster awareness of new and important information concerning serious adverse events (SAE) among regulators, investigators and other appropriate people. The Site Investigator is responsible for monitoring the safety of patients enrolled in this study at each study site.

10.1 ATHENA Safety Endpoints

1. Change in serum creatinine from randomization to 96 hours
2. Incidence of hyperkalemia (>5.5mmol/L or >6.0mmol/L) from randomization to 96 hours

10.2 Anticipated Disease Related Events

The following AEs are anticipated, disease-related events in patients admitted with AHF:

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias.
- **Sudden Cardiac Death:** This refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy.
- **Acute Coronary Syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI).
- **Cerebrovascular Event:** This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA).
- **Venous Thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus.
- **Lightheadedness, Presyncope, or Syncope:** This includes dizziness, lightheadedness, or fainting from any cause.
- **Acute kidney injury as defined by KDOQI guidelines:** This refers to acute kidney injury, typically defined as a rise in creatinine > 0.3 mg/dL over 48 hours, or progressive loss of renal function over time.
- **In hospital worsening HF:** This refers to treatment for acute heart failure such as receiving intravenous diuretics.
- **Hyperkalemia** (K^+ >5.5 mmol/L)

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the appropriate eCRF module.

10.3 Recording and Reporting of Adverse Events

Non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs need to be reported from the time of randomization through the Day 30 assessment, including subjects who are discontinued prematurely from the study. Unless exempted (anticipated, disease-related events, as described in section 10.2, all SAEs whether or not deemed drug-related or expected must be reported by the investigator or qualified designee within 1 working day of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to DCRI Safety Surveillance at 1-866-668-7138. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

10.4 Follow-up

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. It is understood that complete information about the event may not be known at the time the report is submitted. The Investigator must assign causality to the study drug and should make every attempt to obtain enough information about the event to do so. As additional information pertaining to an SAE becomes available, the eCRF should be updated. It is the responsibility of the Investigator to follow all reportable SAEs until there is a return to the patient's baseline condition, or until a clinically satisfactory resolution is achieved, and to respond to queries for missing data or data clarifications.

DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, until otherwise explained, or until the last subject completes the final follow-up, whichever occurs first. DCRI Safety Surveillance will forward all SAEs to the CC Study Medical Monitors, DCRI ATHENA-HF Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs within 1-2 business day(s) of receipt. Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements. The DSMB will be provided detailed safety data approximately every 6 months throughout the study and will be notified when a trend in hyperkalemia and/or study drug discontinuation related to hyperkalemia is identified.

10.5 Suspected Unexpected Serious Adverse Reaction

Adverse events which meet the criteria of serious, related to study drug, and unexpected for that drug, per product labeling, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events confirmed by DCRI Safety Medical Monitor, as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

A copy of this report should be kept at the site and also forwarded to the DCRI Coordinating Center and to DCRI Safety Surveillance.

Canadian sites will be required to submit 2 forms: CIOMS1and Adverse Reaction form to Health Canada per GCP and as mandated by the protocol. After completing report to the FDA, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr_dceim-eng.php will be accessed to follow the instructions for completion of the Health Canada Adverse Reaction Report. A copy of the CIOMS1 report will be maintained with the subject's file at the site and fax a copy to the DCRI at 919-668-1982.

10.6 Pregnancy

This is a 4-day in hospital study and pregnancy will be ruled out prior to randomization. Thus pregnancy occurrence during the study period is not expected and only those patients who are either post-menopausal or surgically sterile or have a negative pregnancy test will be included in this study. Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking

form. The pregnancy will be followed until final outcome. Any associated SAEs that occur to the mother or fetus/child will be recorded in the SAE eCRF, within InForm.

10.7 Study Site Responsibility

1. The site will identify an SAE.
2. Site will determine whether the event is an anticipated disease related event (See Section 10.2).
3. Enter anticipated disease related events on the **EVNTINT** eCRF page, as these events will not be captured as AEs/SAEs, regardless of relationship to study drug.
4. Enter all serious adverse events on the SAE page, including the SAE narrative, relevant laboratory/diagnostic tests and relevant concomitant medications.
5. Once information is entered on the SAE page in InForm, this will generate an SAE email notification to DCRI or site will complete a paper SAE form and fax/email to DCRI if InForm is down.
6. Sites will complete the online voluntary MedWatch for events confirmed by the safety medical monitor to be **RELATED** to study drug and **UNEXPECTED.**
7. Sites will submit a copy of the voluntary MedWatch to the regulatory authorities, DCRI Safety Surveillance and ATHENA-HF trial Team.
8. Canadian sites will be required to submit 2 forms: CIOMS1and Adverse Reaction form to Health Canada per GCP and as mandated by the protocol, then forward a copy to Project Leader (PL) via HFN-dedicated fax #: 1-919-668-9871.
9. Sites will enter all patient deaths on the **Death eCRF page**, regardless of expectedness or relatedness.

10.8 DCRI Safety Surveillance

1. Will be notified of SAEs via InForm generated emails.
2. Will generate the SAE report from InForm as a PDF document.
3. Will perform a clinical review of all SAE forms to verify that all sections are complete and consistent.
4. Will independently issue queries on the SAE eCRF in InForm or will fax/email queries for incomplete or inaccurate information for the following fields:
   - Serious adverse event term
   - Event onset date and time
   - Event stop date and time
   - Severity
   - Relationship to study drug including rationale (if positive assessment provided)
   - Serious criteria
   - Outcome
   - SAE narrative
   - Relevant concomitant medications
   - Relevant labs/diagnostic test data
   - Study Drug start date and dose
   - Action taken with Study Drug
   - PI verification
5. Will email the SAE reports to the CC Study Medical Monitors, DCRI ATHENA-HF Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs, including any queries generated for the site within 1-2 business days of initial receipt.

6. Will assist with SAE data reconciliation of the ATHENA safety database with the InForm database on the following data variables: Subject ID, Verbatim Term, MedDRA Preferred Term, Onset date, Outcome and Causality.
7. DCRI Safety surveillance will inform site Investigators to submit a voluntary MedWatch if the DCRI safety medical monitor confirmed an event as serious, related to study drug and unexpected per product labeling.
8. DCRI Clinical Operation will be responsible for filing copies of the voluntary MedWatch/CIOMS-I reports (generated by the sites), in the master project file at DCRI.

10.9 DCRI Safety Surveillance Medical Monitor

1. Will review all study drug related SAEs
2. Will review the MedDRA coding for the event
3. Will review the site reported causality assessment
4. Will assess and verify the event for causality assessment and listedness per the product labeling.
5. Request additional follow-up, as needed

10.10 ATHENA-HF CC Responsibilities

1. Will be responsible for reviewing all SAEs/SUSARS for MedDRA coding, and evaluating the event for voluntary reporting to the regulatory authorities.
2. Will send any additional queries to DCRI, as needed, to be entered into InForm.
3. Will assess and confirm the event for listed per the current documents or product labeling.

10.11 Data and Safety Monitoring Board (DSMB)

The DSMB will be provided detailed safety data approximately every 6 months throughout the study including all SAE data in accordance with the HFN DSMB charter. The DSMB will be notified when a trend in hyperkalemia and/or study drug discontinuation related to hyperkalemia is identified.

10.12 SAE Reconciliation

The clinical data, including all SAEs will be housed in the InForm database. A separate safety database will be maintained in Argus. DCRI Safety Surveillance will assist with reconciling the data within InForm, with the information within the Argus safety database to ensure that the data matches and/or is clinically consistent.

10.13 Disposition of Safety Records

DCRI Safety Surveillance will forward the safety files to the ATHENA-HF trial team Project Leader or designee at the end of the study. The electronic safety files will be saved as portable document formats (PDFs) and provided to the HFN Team or designee via compact disc (CD).

11 Record Retention

Records relating to the study, including receipt and disposition of the study materials will be retained for at least 3 years after completion of the research or earlier termination of the study. Source documents, such as patient charts, will be retained for not less than five years.

12 Safety Definitions

Business Day: Any day which is not a Saturday, Sunday or public holiday. Business hours are 08:00 to 17:00 Eastern Standard Time.
Calendar Day: Any 24-hour day of the seven day week.
Receipt Date: The date when DCRI becomes aware of safety related information. The date of receipt of each initial report and follow-up report will be clearly marked on all documents. If information is received on a non-business day or after normal working hours on a business day, the receipt date will be the next business date. Additional information received during processing of the initial version of a case (prior to reporting to the ATHENA-HF DCRI trial team/designee) does not reset the regulatory reporting clock, based on receipt of follow up information at this point; however, new information will be incorporated within the initial case.
Day 0: The calendar day that DCRI Safety Surveillance is notified of an SAE or, if different from day received by DCRI Safety Surveillance, the date the medical monitor has determined the event qualifies for voluntary reporting to the regularity authorities.
Safety Medical Monitor: A physician assigned to the study to perform a review of serious adverse events, review the investigator's brochure or product labeling for listedness, and to confirm the MedDRA coding for the event.
Study Medical Monitor: A physician assigned to answer clinical questions regarding the protocol.
Valid Case: A case that includes each of the following minimum criteria for the purposes of reporting:

- an identifiable patient
- the name of the suspect medicinal product(s) or clinical study if considered related to a clinical study or procedure/design
- an identifiable reporting source
- a serious adverse event

13 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CC	Coordinating Center
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAR	Suspected Adverse Reactions
SUSAR	Suspected Unexpected Serious Adverse Reaction

14 References

(Refer to HFN Website: ATHENA Protocol Manuals, Protocol, Regulatory Documents, Study Coordinator Materials, and Subject Materials)

- ATHENA-HF Pharmacy GUIDE
- ATHENA-HF Drug/Placebo Accountability Logs
- HFN Blood Collection Manual of Procedures
- ATHENA-HF eCRF Instructions
- Dyspnea Relief 7-Point Likert Scale
- Dyspnea Relief Visual Analog Scale
- ATHENA-HF SAE and Death Reporting Process
- ATHENA-HF Back up SAE Form
- ATHENA-HF Back up SAE Form- Completion Instructions
- ATHENA-HF FDA IND Exemption Notice
- ATHENA-HF Regulatory Manual Table of Contents
- ATHENA-HF Resource Manual Table of Contents
- ATHENA-HF Screening Log
- ATHENA-HF Master Subject Log
- ATHENA-HF Randomization Worksheet
- ATHENA-HF Subject Contact Information form
- ATHENA-HF Phone Scripts

15 Revision History

Version 11/05/14: Section 1.1 – Added Co-PI contact information. Section 3, Screening – Clarified admission or screening BNP or NT-proBNP must be performed within 24 hours prior to randomization. Section 7 - Clarified Dyspnea Relief Assessments are measured supine. Section 10.4 Follow-up clarified. Sections 10.7 – 10.9 Minor clarifications. Canadian site reporting requirements added. Section 12 Safety Definitions added.