COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: High-dose Aldosterone antagonist for Acute Decompensated Heart Failure

NCT number: NCT 02823626

IRB Approval Date: 06-09-17

Unique Protocol ID: HSC20160252H

Protocol Template Form

Item 1 UTHSCSA Tracking Number	HSC20160252H

Item 2 Abstract / Project Summary	Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific. **DO NOT EXCEED THE SPACE PROVIDED**.

Purpose/Objectives: Primary Aims

1: Evaluate the safety of high-dose spironolactone in combination of Patiromer in acute decompensated heart failure patients.

2: Evaluate the efficacy of high-dose spironolactone in combination of Patiromer in causing volume loss and symptom relief in patients with ADHF treated with high-dose spironolactone.

Secondary Aims

1: Evaluate the effect of high-dose spironolactone on urinary sodium excretion and renal function.

Research Design/Plan: We propose a prospective exploratory single-arm, open-label pilot study to assess the safety and efficacy of high dose spironolactone in combination with Patiromer in patients hospitalized with decompensation of chronic heart failure who shows sign of resistance of loop diuretics. Patients admitted with decompensated heart failure will be identified from the inpatient cardiology and internal medicine services.

Methods: Study Protocol

Pre-screening: Patients meeting the inclusion and exclusion criteria will be approached to participate in the study. Informed consent will be taken at this time. These patients will receive intravenous loop diuretic per the discretion of treating physician and will be closely followed for weight loss and symptoms relief.

Screening: The patients who don't respond as measured by symptoms relief or <0.5 kg weight loss/day

a) Despite furosemide ≥ 160 mg IV total daily dose or equivalent dose of torsemide or bumetanide. (1 mg bumetanide = 10 mg torsemide = 20 mg furosemide). OR
b) After 48 hours of admission irrespective of diuretic dose.

will be considered for the study intervention. Patients who have not participated in the pre-screening phase and do not respond adequately to furosemide >160 mg iv daily dose will directly be enrolled into active intervention part of the study.

Intervention (High-Dose Spironolactone + Patiromer): Patients will be initiated on spironolactone 100 mg orally once daily along with patiromer 8.4 gm orally (if serum K >4.3 meq/L). The dose of loop diuretic will stay same during rest of the study period. On day 2, the dose of spironolactone will be titrated to 200 mg orally once a day depending on the diuretic response and lab results. Serum potassium and magnesium will be monitored twice a day. An EKG will be performed any time electrolytes are out of range. The dose of patiromer will be increased to 16.8 gm in patients with potassium levels exceeding 5.5 meq/L; or it will be held for serum K <4.3 mEq/L. Treatment will continue till patients achieve euvolemia or get discharged. Euvolemia is defined as resolution of symptoms and signs of volume overload.

Treatment Failures: Patients will be considered high dose spironolactone failure if they do not achieve a net negative body weight after a minimum of 5 days. High-dose spironolactone may be stopped anytime per the discretion of the treating physician. The patients that do not respond to high-dose spironolactone are considered treatment failures and will be included in the primary endpoint analysis.

Concomitant Medications/diet: Patient taking concomitant heart failure medications such as ACEi, ARB and/or beta-blockers are to be continued throughout the study as tolerated. If these medications have not been administered at the time of randomization, timing and sequence of the starting ACEi, ARB or beta-blockers will be left to the discretion of the treating physician. All the patients will be prescribed low Na (<1.5gm/day) and low potassium (50-75 mEq/day) diet.

Clinical Relevance: Insert response here

Item 3 Background	
Describe past experimental and/or clinical findings leading to the formulation of your study. *For research involving unapproved drugs, describe animal and human studies.* *For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.*	Congestive heart failure currently affects an estimated 6.6 million adults in the United States and ADHF accounts for ~ 1 million hospitalizations yearly[1]. The main focus in the management of ADHF is on therapies directly responsible for removal of excess sodium and water. The most widely used therapy at present is higher than usual dose of oral or intravenous loop diuretics including furosemide, torsemide and bumetanide alone or in combination with thiazide like diuretics including chlorthalidone, hydrochlorthiazide or metolazone. However, resistance to the natriuretic effect and declining kidney function during diuresis are common occurrences. The mechanisms behind these relationships are complex and patient specific. The heart failure patients have severe underlying secondary hyperreninemic and hyperaldosteronism state due to reduced effective arterial blood volume (EABV) as a result of decreased cardiac output[2]. Long-term loop diuretic use causes further RAAS activation by inhibiting sodium chloride transport at the macula densa and relative volume depletion as a result of failure to transfer the fluid from interstitium to vascular compartment at an acceptable rate. In addition, chronic use of loop diuretics causes enhanced sodium chloride co-transporter expression at distal collecting tubules leading to increased sodium absorption at this site resulting in resistance to natriuretic effect[3]. Addition of thiazide like diuretics overcomes the later problem; however, relative volume depletion causing further RAAS activation and excessive proximal tubular and collecting duct sodium absorption remains an issue. Recently many other strategies including extracorporeal ultrafiltration and human recombinant low dose B-type natriuretic peptide – nesiritide have been used for removal of excessive fluid in addition to or in place of diuretics[4,5]. However, none of these therapies have shown to be more beneficial than loop diuretics. In addition, blood based extracorporeal ultrafiltration requires use of invasive device and anti-coagulation. The possible explanation for failure to achieve the better outcomes with the above strategies is similar to the use of loop diuretic, i.e. further stimulation of neurohumoral system and RAAS by either rapid fluid removal or vasodilating property, respectively.
Item 4 Purpose and rationale *Insert purpose, objectives and research questions/hypotheses here.* *If you cut and paste from another document, make sure the excerpted material answers the question*	Patients with CHF and cirrhosis share the same pathophysiology of arterial underfilling due to either decreased cardiac output or splanchnic vasodilatation respectively, resulting in stimulation of the sympathetic nervous system (SNS) and RAAS[3]. Subsequent hyperaldosteronism causes sodium retention and contributes to volume accumulation in both cirrhosis and HF. High-doses of aldosterone antagonists (spironolactone up to 400 mg/day) is a standard therapy to achieve negative sodium balance in cirrhotic patients[6]. However, in HF a low-dose aldosterone antagonist (spironolactone 25 mg/day) is recommended since it was shown to decrease mortality through anti-fibrosis action. Of note, this low dose of spironolactone does not have natriuretic effect[7]. Given that severe neurohormonal activation and hyperaldosteronism as a result of heart failure and further enhanced by loop diuretic is the pathophysiological basis of sodium retention and loop diuretic resistance in patients with ADHF similar to cirrhotic patients, neutralizing the effects of aldosterone with natriuretic doses of aldosterone antagonists may be a potential option to treat these patients[8]. In this regard, in a small trial of 6 avidly sodium retaining patients with heart failure, spironolactone 200 mg BID caused a marked increase in sodium excretion and indeed led to sodium balance over a few days with a clinically negligible rise in serum potassium concentration[9]. In another study, 81% of the patients with severe heart failure, who were resistant to high-dose loop diuretics (10 mg of bumetanide) and captopril, responded with increased natriuresis with the use of 100 mg/day spironolactone[10].

	However, main issue with the use of spironolactone, especially along with the use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), is the development of hyperkalemia. If used in conjunction with adequate doses of loop diuretics, the renal potassium retaining properties of aldosterone antagonists is counterbalanced by potassium-losing effect of loop diuretics by increasing the distal sodium delivery. Nonetheless, hyperkalemia is the most common reason for withdrawl for aldosterone antagonists. Patiromer, a nonabsorbed potassium binder, is a new FDA approved agent and has been shown to normalize serum potassium in patients with CKD and hyperkalemia on RAAS inhibitor in both outpatient as well inpatient setting. When given to hospitalized CKD patients with sustained modertate to severe hyperkalemia receiving at least one RAAS inhibitor while consuming a 60 mEq/day potassium diet in the controlled environment, single dose of patiromer caused a significant reduction in mean serum potassium by 7 hour. Mean serum potassium continued to decrease and after a second dose of patiromer fell to <5.5 mEq/l by 20 h. By 24 h, more than 80% of patients had a serum potassium <5.5 mEq/l. At 48 h, after four doses of patiromer, mean serum potassium had fallen by 0.75mEq/l, and more than 90% of patients had serum potassium values <5.5mEq/l. Over the entire study, mean serum potassium did not increase before the next dose of patiromer[15].

Item 5 Study Population(s) Being Recruited In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number:	Identify the criteria for **inclusion**:	Identify the criteria for **exclusion**:
e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc. <u>List each different population</u> on a separate row and provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *To add rows use copy & paste*		
Insert response here	1. Patients ≥ 18 years old 2. Hospitalized with history of chronic heart failure and at least one symptom (dyspnea, orthopnea or edema) and one sign (rales, peripheral edema, ascites, or radiographic pulmonary edema or pleural effusion) **3.** Women of child bearing age with negative urine pregnancy test	1. Acute coronary syndrome 2. Patients with a baseline eGFR < 30 ml/min by MDRD equation 3. Baseline potassium concentration ≥ 5.5 mEq/L 4. Requirement for intravenous vasodilators or inotropic agents 5. Systemic infection 6. Patients with concomitant end-stage liver disease 7. Hemodynamically significant uncorrected valvular disease

		8. Patients with pulmonary embolism 9. Patients with high output heart failure 10. Pregnant patients
Insert response here	Insert response here	Insert response here

Item 6
Research Plan / Description of the Research Methods *a.* *Provide a **comprehensive narrative** describing the **research methods**. Provide the **plan for data analysis** (include as applicable the **sample size calculation**).*

Step-by-Step Methods:

Pre-screening: Patients meeting the inclusion and exclusion criteria will be approached to participate in the study. Informed consent will be taken at this time. These patients will receive intravenous loop diuretic per the discretion of treating physician and will be closely followed for weight loss and symptoms relief.

Screening: The patients who don't respond as measured by symptoms relief or <0.5 kg weight loss/day

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Patients will be followed till achievement of euvolemia or discharge. Daily assessment will be done for symptoms, and signs of volume overload including shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, abdominal bloating, lower extremity edema, JVD, and body weight changes. Serum chemistry will be assessed twice a day and urine electrolytes once a day. Neurohormonal analysis will be done at the pre-screening, and at the end of the study duration.

Primary Safety measures:

1) Incidence of hyperkalemia as defined by serum K >5.5 meq/day.
2) Incidence of hypokalemia as defined by serum <3.5 meq/day
3) Renal function: assessed by daily serum creatinine

Primary Efficacy measures:

1) Weight loss: using same calibrated scale every day in hospital gown.
2) Symptom relief: assessed using a 5-point Likert scale describing magnitude of shortness of breath while the patient is in the supine position.

Secondary Efficacy measures:

	1) Urine sodium excretion: assessed by FENa% 2) Urine Sodium/Potassium ratio as a biomarker of aldosterone activity
	Data Analysis Plan: This is a pilot exploratory study to assess safety and efficacy of high dose spironolactone with patiromer to find the sample size for large randomized study. A previous study utilizing combination of loop diuretics and high dose spironolactone had generated mean weight loss of 4.49±1.51 kg compared to 0.57±1.14 kg[16]. Given that this weight loss seems inflated, a mean weight loss of 2 ± 1.3 kg with two-sided t-testing, and a significance level of 5%, provides a power of 90% with 20 subjects [PASS Version 08.0.8, NCSS, Kaysville Utah 2008]. Assuming that loop diuretics resistance will be seen in 50% of the patients and there will be some lost to FU during active intervention period, we propose to pre-screen at least 300 subjects to enroll 60 subjects with the goal to have at least 20-30 completers in active intervention arm.

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures *example:* • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Risks** List the reasonably expected risks under the following categories as appropriate:
Insert procedure here	Serious and likely; ○ Insert risk here or enter "none" Serious and less likely; ○ Insert risk here or enter "none" Serious and rare; ○ Insert risk here or enter "none" Not serious and likely; ○ Insert risk here or enter "none" Not serious and less likely ○ Insert risk here or enter "none"
Insert procedure here	Serious and likely; ○ Insert risk here or enter "none" Serious and less likely; ○ Insert risk here or enter "none" Serious and rare; ○ Insert risk here or enter "none" Not serious and likely; ○ Insert risk here or enter "none" Not serious and less likely ○ Insert risk here or enter "none"
Insert procedure here	Serious and likely; ○ Insert risk here or enter "none" Serious and less likely; ○ Insert risk here or enter "none" Serious and rare; ○ Insert risk here or enter "none" Not serious and likely; ○ Insert risk here or enter "none" Not serious and less likely ○ Insert risk here or enter "none"