INVESTIGATIONAL PLAN

Fluid management of Acute decompensated heart failure Subjects Treated with Reprieve Decongestion Management System (DMS) -

FASTR Trial

Protocol Number:	**RCV-0006**
Sponsor:	Reprieve Cardiovascular, Inc. 459 Fortune Blvd Milford, MA 01757 USA
Manufacturer:	Reprieve Cardiovascular, Inc. 459 Fortune Blvd Milford, MA 01757 USA
Protocol Version Number:	**1.6**
Protocol Date:	September 5, 2023

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with applicable regional and/or national regulations [(i.e., United States (US) Code of Federal Regulations (CFR), including 21 CFR parts 50, 54, 56, 812, and 45 CFR part 46, as applicable] and Good Clinical Practices (GCP). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the governing regulatory body (e.g. FDA), sponsor, with documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), as appropriate.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Fluid management of Acute decompensated heart failure Subjects Treated with Reprieve Decongestion Management System (DMS)
Short Title:	FASTR Trial
Device Name:	Reprieve Decongestion Management System (Reprieve DMS)
Intended Use:	The intended use of the Reprieve DMS is to provide an efficient manner to monitor urine output and deliver personalized diuretic dosing and fluid replacement, to facilitate consistent high-volume diuresis of patients with acute decompensated heart failure (ADHF).
Objectives:	The objective of this study is to prospectively compare decongestive therapy administered by the Reprieve DMS system to Optimal Diuretic Therapy (ODT) in the treatment of patients diagnosed with acute decompensated heart failure (ADHF). The main objective is to determine if the Reprieve DMS can more efficiently decongest ADHF patients in comparison to Control Therapy.
Background	This study will evaluate the safety, performance, and clinical utility of the Reprieve DMS device (previously named the Reprieve Cardiovascular System) in comparison with "control" diuretic therapies. The Reprieve DMS ADHF study was developed based upon the initial conclusions drawn from the feasibility studies conducted outside the US (OUS). The OUS feasibility studies provided the clinical experience to optimize the Reprieve DMS system algorithm to identify and efficiently deliver an individualized diuretic dose for each subject based upon their measured response. Using real time information from the minute-to-minute measurement of urine output, the system automatically identifies a target responsive diuretic dose by sequentially increasing the rate of diuretic infusion until the patient achieves a clinically significant rate of urine production or until a set limit of diuretic has been infused. The system then transitions to a continuous diuretic infusion rate based on a percentage of the amount

	of diuretic required to reach the target urine output rate. The subject also receives a personalized partial fluid/salt replacement of these urinary losses to ensure each subject has adequate intravascular volume and avoidance of activating renal sodium conserving pathways.
Study Design:	A prospective, multicenter, randomized, controlled pilot trial (1:1) to compare the rate of decongestion for up to 72 hours with the Reprieve DMS compared to optimal diuretic therapy (ODT).
Study Population:	Adult patients with acute decompensated heart failure (ADHF) admitted to the hospital or presenting to the Emergency Department who require decongestion.
Number of Subjects:	A maximum of 100 subjects randomized 1:1 to Reprieve DMS and ODT. A maximum of three roll-ins per site will be treated prior to randomization. Sites will be asked to use the roll-in arm of the trial after implementation of the latest version of the study protocol (version 1.6) regardless of previous enrollment activity at their respective sites. In addition, sites will have the opportunity to enroll subjects in an ongoing registry who meet the study criteria but refuse to participate in the trial. A maximum of 20 subjects per clinical site will be enrolled in the registry.
Number of Sites:	A maximum of twenty-five clinical sites located in the United States and Europe.
Study Sites:	A list of study sites is maintained in the study file.
Treatment Description:	<u>DMS Therapy</u> a. DMS begins by administering IV furosemide to achieve the target urine rate of 525 ml/hr. using an exponentially increasing ramp dose until the target urine output rate is met or maximum IV furosemide dose (200 mg) is infused ("Dose Finding Phase"). b. Once the target urine output rate is met, the IV furosemide infusion rate is reduced to an hourly infusion rate that is 20% of the total furosemide dose delivered during the Dose Finding Phase (minimum 4 mg/hr., maximum 40 mg/hr.) to maintain effective plasma concentration of furosemide and thus maintain the desired target urine output rate. (For example, if a total of 160

	mg of furosemide was delivered during the Dose Finding Phase, the hourly infusion rate would be set to 32 mg/hr.). c. The DMS provides a proportional saline replacement designed to maintain adequate intravascular volume and prevent activation of renal sodium retaining mechanisms. No saline is infused when the urine output rate is between 0 and 225 ml/hr. Urine output rate above this level triggers 100% IV saline replacement to match urine output between 225 ml/hr and 425 ml/hr. For urine output rates above 425 ml/hr to 1025 ml/hr., IV saline infusion is increased to add a 50% match of the urine output above 425 ml/hr up to 1025 ml/hr for a maximum infusion rate of 500 ml/hr. (Note: This saline infusion is adjusted based on the lab urine sodium entered into the system as described below). d. Every time the urine collection bag is emptied, a sample should be sent to the laboratory for determination of sodium concentration. When the result is returned from the lab, the value will be entered into the DMS by a clinical staff member. The DMS will then calculate an "adjusted urine output rate", and the treatment algorithm will use this rate to determine the saline infusion rate optimized for the patient's urine sodium level. This process is repeated each time the urine bag is emptied. e. If the urine output rate meets the criteria for sustained very high urine output rate, the DMS down-titrates the diuretic dose automatically. f. If the patient's urine output rate drops below the desired urine output rate for a sustained period, the DMS provides the investigator with the option to resume the diuretic IV furosemide Dose Finding Phase provided the previous Dose Finding Phase did not reach the maximum dose of 200 mg. g. If the patient's urine output rate remains low, the DMS provides the investigator with the option of administering additional adjunctive therapies (i.e., thiazide/thiazide like diuretics). *Note: Subjects receiving high dose oral loop diuretic at home (≥ 240 mg furosemide, 3 mg bumetanide, or 60 mg torsemide per 24 hours) must be administered an oral long half-life thiazide/thiazide like diuretic (10mg metolazone, 50mg chlorthalidone, 100mg HCTZ or equivalent) 2 to 12 hours prior to initiating Reprieve therapy.*

	Optimal Diuretic Therapy (ODT) Consider best practices of optimal diuretic dosing such as those demonstrated in recent randomized trials (DOSE[31], ADVOR[32], CLOROTIC[33]). The Reprieve DMS can infuse a maximum dose of 1,120 mg/day of furosemide. It is recommended that subjects randomized to ODT should also not exceed maximum dose of 1,120 mg/day of furosemide. *Note: Consideration can be given to up-front use of oral long half-thiazide diuretic with appropriate adjustment of IV loop diuretic dose in patients receiving high dose loop diuretic prior to enrollment (≥ 240 mg furosemide, 3 mg bumetanide, or 60 mg torsemide per 24 hours).* Reprieve DMS, ODT Groups As standard background therapy, all patients must receive 2 g daily sodium diet and a 2 L daily oral fluid intake restriction, in addition to strict fluid input and output recording and daily weights.
Inclusion Criteria:	Candidates for participation in the study must meet all of the following inclusion criteria. 1. Hospitalized with a diagnosis of heart failure as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema/swelling) AND 1 sign (peripheral edema, ascites, jugular venous distension). 2. ≥10 lb (4.5 kg) above dry weight either by historical weights or as estimated by health care provider. 3. Prior use of outpatient oral loop diuretics within 30 days prior to admission. 4. Patients ≥ 18 years of age able to provide informed consent and comply with study procedures. The sponsor expects that the Medicare population who are Medicare-eligible due to either age or End Stage Renal Disease (ESRD) will be included under these criteria.

Exclusion Criteria:	Candidates for participation will be ineligible for the study if any of the following exclusion criteria apply: 1. Inability to place Foley catheter or IV catheter or other urologic issues that would predispose the patient to a high rate of urogenital trauma or infection with catheter placement. 2. Hemodynamic instability as defined by any of the following: systolic blood pressure <90 mmHg, use of vasopressors, use of IV inotropes to treat hypotension (systolic blood pressure <90 mm Hg) or suspected/confirmed low cardiac output/shock, mechanical circulatory support, uncontrolled arrhythmias, active severe bleeding, or confirmed or suspected cardiogenic shock. *Note: In the absence of the above conditions, use of inotropes to augment diuresis is permitted.* 3. Dyspnea due primarily to non-cardiac causes (e.g., severe chronic obstructive pulmonary disease or pneumonia). 4. Acute infection with evidence of systemic involvement (e.g., clinically suspected infection with fever or elevated serum white blood cell count). 5. Estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m^2 calculated using the MDRD equation or current use of renal replacement therapy (RRT). 6. Significant left ventricular outflow obstruction, uncorrected complex congenital heart disease, known severe stenotic valvular disease, infiltrative or constrictive cardiomyopathy, acute myocarditis, type 1 acute myocardial infarction requiring treatment (within previous week), or any other pathology that, in the opinion of the investigator, would make aggressive diuresis poorly tolerated. 7. Inability to follow instructions or comply with follow-up procedures. 8. Other concomitant disease or condition that investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the study instructions or follow-up procedures. 9. Severe electrolyte abnormalities (e.g., serum potassium <3.0 mEq/L, magnesium <1.3 mEq/L or sodium <125 mEq/l). *Note: These are based on baseline/screening labs. Subjects whose*

	electrolyte levels are repleted cannot be reassessed for inclusion in the trial. 10. Presence of active COVID-19 infection. 11. Enrollment in another interventional trial during the index hospitalization. 12. Inability to return for follow-up study visits. 13. Life expectancy less than 3 months. 14. Women who are pregnant or intend to become pregnant. The sponsor does not expect that these exclusion criteria will disproportionately exclude the Medicare population who are Medicare-eligible due to either age or ESRD.
Primary Endpoints:	The primary objective of this study is to determine if Reprieve DMS can more efficiently decongest ADHF patients in comparison to control therapy without clinically significant acute kidney injury. The trial will employ co-primary endpoints, one for efficacy and one for safety. All study endpoints will be evaluated in two study cohorts (subjects with home dose of <u>≥ 80 mg of furosemide equivalent and subjects with home dose of <80 mg of furosemide equivalent).</u> Primary efficacy endpoint is total urine sodium output at 24 hours post-treatment initiation. Primary safety endpoint includes clinically significant acute kidney injury defined as KDIGO stage 2 or greater AKI [≥ doubling of baseline serum creatinine or use of renal replacement therapy (RRT)], severe electrolyte abnormality (serum potassium <3.0 mEq/L, magnesium <1.3 mEq/L or sodium <135 mEq/L*), symptomatic hypotension or hypertensive emergency. *For subjects enrolled with baseline sodium levels of <u>≤</u>135 mEq/L, there needs to be drop of at least 5 mEq/L to be considered against primary safety endpoint.
Secondary Efficacy Endpoints:	• ***Net fluid loss*** at end of randomized therapy. • ***Time on IV loop diuretic*** Defined as the time from initiation of randomized therapy to last dose of IV loop diuretic administered for ADHF.

Secondary Safety Endpoints:	The assessment of all Device and Procedure related AEs and SAEs in the study population as determined by an Independent Clinical Events Committee (CEC), as outlined in the committee charter. It should be noted that episodes of hematuria associated with Foley catheter placement that can be adequately managed will not be included as a secondary safety endpoint, since this is an anticipated adverse event commonly associated with Foley placement.
Ancillary Endpoints:	• ***Home days***: Defined as the number of days alive and at home (e.g., without a visit to an emergency room, unscheduled clinic visit or acute care facility, skilled nursing facility, inpatient rehab) within the initial 90 days after randomization. • ***Length of stay*** Defined as the time from initiation of randomized therapy to discharge. • ***Net fluid loss*** at day 7 or discharge (whichever occurs first), following initiation of randomized therapy. • ***Total urine output*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy. • ***Sodium output*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy (in ODT group total sodium output, in DMS group net to the system) • ***Change in Weight*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit. • ***Dyspnea VAS*** AUC at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit. • ***Change in creatinine based eGFR*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit. • ***Change in NT-proBNP*** at discharge. • ***Change in RAAS markers:*** Renin, aldosterone, plasma renin activity, measured at discharge. • ***Change in serum electrolytes*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit.

	• ***Time to and total death and rehospitalization:*** through 90 days**.** • ***Average rate of weight loss*** during the IV therapy (i.e., initial randomized IV diuretic dose to the cessation of IV therapy) for a maximum of 72 hours after randomized therapy initiation. • ***Change in KCCQ*** at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. • ***Change in Dyspnea Score (5 and 7-point Likert scale)*** at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. • ***Change in Modified Congestion Score*** (based on sum of score for degree of edema, pleural effusion and ascites) at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. • ***Changes in Serum Creatinine and Weight*** at end of randomized therapy. • ***Ototoxicity:*** Shift in audiometry measurements from baseline to discharge and 7 day post-discharge visit, meeting any one of the following: o Decrease of 10 dB at 2 consecutive frequencies from 250-8000 Hz, or o Decrease of 20 dB at 1 frequency from 250-8000 Hz, or Loss of response at three consecutive test frequencies where responses were previously obtained (where baseline responses are obtained close to the limits of audiometric output and later responses cannot be obtained at the limits of the audiometer).
Safety Oversight:	The study will utilize an Independent CEC and Data Safety and Monitoring Board (DSMB). The CEC will be charged with adjudicating clinical safety events. The main objective of the DSMB is to advise regarding the continued safety of the subjects and those yet to be recruited to the trial; and to ensure the validity and scientific merit of the trial. The details around CEC and DSMB will be documented in the respective charters.
Subject Evaluation:	Subjects randomized to the Reprieve DMS therapy shall be evaluated over the course of Reprieve DMS therapy for a maximum of 72 hours, whereupon use of the Reprieve DMS shall be terminated.

	Serum and urine chemistry as well as hemodynamic parameters will be collected in accordance with the **Table 1: Schedule of Assessments** to ensure safe operation of the device and optimization of fluid removal throughout the course of the study.
Safety Thresholds:	The DMS or ODT treatment shall be suspended or terminated if any of the following criteria are observed for greater than 15 consecutive minutes: • Progressive dyspnea or respiratory failure • Sustained systolic pressure <80mmHg; or • Symptomatic hypotension; or • Hemodynamic instability that in the opinion of the investigator requires treatment suspension or termination. • ≥ doubling of serum creatinine from the baseline value. • Electrolyte abnormality(s) uncorrectable with standard therapy that in the opinion of the investigator require treatment suspension or termination. • Increase in serum sodium >12 mmol/L per day. All of the safety mitigation techniques shall be utilized to ensure safe operation of the Reprieve DMS to optimize diuresis.
Treatment Termination:	Treatment with either DMS or ODT will be stopped upon: • Achieving the patient's optimal volume status as determined by the investigator. Patients' optimal volume status is defined as either euvolemia, or continued hypervolemia but further decongestion is limited by worsening clinical status (e.g., worsening kidney function or hypotension). ○ Additionally, patients randomized to DMS therapy should have urine output of < 325 mL/hr. with either: 1) a non-productive second diuretic ramp (urine output (UOP) returns to <325/hr. within 3 hours) or 2) the patient is already at maximal furosemide dose (40 mg/hr). • Worsening heart failure requiring higher level of HF therapy (e.g., addition of inotropes (only for treatment of hypotension or low cardiac output) aside from dopamine <5mcg/kg/min,

	mechanical support, ultrafiltration or renal replacement therapy, mechanical ventilation, etc.)
Follow-Up Assessments:	Follow-up clinical assessments will be performed at 7 days, 30 days and 90 days post discharge.
Central Laboratory for Blood and Urine Specimens:	A central laboratory will be utilized to perform analysis of urine and blood specimens collected for the clinical study. Details surrounding specimen collection, processing and shipping will be provided to study sites.
Sponsor:	Reprieve Cardiovascular, Inc. 459 Fortune Blvd Milford, MA 01757 USA
Estimated Study Duration:	The estimated study duration is as follows: Enrollment initiation date: Q1-2022 Enrollment completion date: Q1-2024 Last 30-Day Follow-up: Q2-2024 Last 90-Day Follow-up: Q3-2024 Study end date: Q4-2024
Participant Duration:	It is anticipated that each subject's participation in the study will be for approximately 13 weeks total, including the final follow-up visit at 90 days.

2 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Procedures/ Assessments	**Screening/ Baseline[1]**	**Initiation of Randomized Treatment[2] (Within 60 min of start of therapy)**	**During Treatment (When urine bag is emptied)**	**During Treatment (Every 12 hr. ±4 hr.)**	**During Treatment (Every 24 hr. ± 4 hr.)**	**During Treatment (Every 24 hr. ± 12 hr.)**	**Post - treatment (Within 12 hr. after treatment end)**	**Post - treatment (Within 24 hr. after treatment end)**		**Post - treatment 7 days after treatment initiation (±12 hr.) *[Only required if subject is still hospitalized]***	**Discharge**	**7 Day post-discharge visit (±2 days)**	**30 days post-discharge visit (±5 days)**	**90-day post-discharge visit (±5 days)**
Eligibility Criteria	X													
Informed Consent	X													
Weight	X	X			X		X			X	X	X	X	
Clinical estimate of excess volume[‡]	X					X		X						
Randomization		X												
Medical History	X													
Hemodynamic (BP, Heart rate, O_2 saturation, Respiratory rate)	X	X			X		X			X	X	X	X	
Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Peripheral/Sacral Edema, Ascites, Pleural Effusion, NYHA)[‡]	X					X		X		X	X	X	X	

Procedures/ Assessments	Screening/ Baseline[1]	Initiation of Randomized Treatment[2] (Within 60 min of start of therapy)	During Treatment (When urine bag is emptied)	During Treatment (Every 12 hr. ±4 hr.)	During Treatment (Every 24 hr. ± 4 hr.)	During Treatment (Every 24 hr. ± 12 hr.)	Post - treatment (Within 12 hr. after treatment end)	Post - treatment (Within 24 hr. after treatment end)		Post - treatment 7 days after treatment initiation (±12 hr.) *[Only required if subject is still hospitalized]*	Discharge	7 Day post-discharge visit (±2 days)	30 days post-discharge visit (±5 days)	90-day post-discharge visit (±5 days)
Fluid Balance (Replacement fluid input, Oral intake, Other IV input, Urine output, other output)				X			X			X	X			
Pregnancy Test[3]	X													
Clinical Pathology: Serum														
• Complete Blood Count		X[5]					X[5]			X[5]	X[5]	X[5]	X[5]	
• Comprehensive Metabolic Panel	X[4,5]	X[5]		X[5]			X[5]			X[5]	X[5]	X[5]	X[5]	
• Calcium		X[5]		X[5]			X[5]			X[5]	X[5]	X[5]	X[5]	
• Magnesium	X[4,5]	X[5]		X[5]			X[5]			X[5]	X[5]	X[5]	X[5]	
• NT-proBNP		X[6]									X[6]			
• RAAS Markers (Renin, aldosterone, plasma renin)		X[6]									X[6]			
Urine Sample Collection		X[6]	X[9]		X[7]		X[7]				X[6]			

Procedures/ Assessments	**Screening/ Baseline[1]**	**Initiation of Randomized Treatment[2] (Within 60 min of start of therapy)**	**During Treatment (When urine bag is emptied)**	**During Treatment (Every 12 hr. ±4 hr.)**	**During Treatment (Every 24 hr. ± 4 hr.)**	**During Treatment (Every 24 hr. ± 12 hr.)**	**Post - treatment (Within 12 hr. after treatment end)**	**Post - treatment (Within 24 hr. after treatment end)**		**Post - treatment 7 days after treatment initiation (±12 hr.) *[Only required if subject is still hospitalized]***	**Discharge**	**7 Day post-discharge visit (±2 days)**	**30 days post-discharge visit (±5 days)**	**90-day post-discharge visit (±5 days)**
Concomitant Medications (including diuretics)	X				X		X			X	X	X	X	X
Oral Diuretic dosing and rationale‡[8]	X									X	X	X	X	X
Auditory Testing (Shoebox)	X										X	X		
KCCQ	X						X				X	X	X	
Dyspnea Score *(5 and 7-point Likert scale)*	X						X				X	X	X	
Adverse Events		X		X			X			X	X	X	X	X

[1] Screening activities should be performed as close to randomization as possible. All screening activities (except for informed consent) must be repeated if the subject is not randomized within 24 hours of screening.
[2] Randomized treatment must start within 12 hours of randomization.
[3] For females of childbearing potential only.
[4] Within 24 hours of informed consent.
[5] Site will use site's clinical laboratory (per Institutional methods) for testing serum samples.
[6] Samples will be processed and sent to a central core laboratory for analysis.
[7] 24-hour urine collection and analysis will be performed by the site's clinical laboratory.
[8] Rationale for oral diuretic dosing is not required at screening/baseline.
[9] Only urine sodium assessment is required, result to be returned within 2 hours where possible.

‡Items in **bold** must be completed by a physician or another advanced practitioner

3 INTRODUCTION

3.1 BACKGROUND

The high clinical, societal, and economic burden of Acute Decompensated Heart Failure (ADHF) are well documented. Current estimates suggest that 6.8 million individuals are affected by Heart Failure (HF) in the USA, a number expected to rise to 8.5 million by 2030[1]. Heart failure is also the primary diagnosis for hospital discharge in about 1 million patients annually, with another 2 million patients having heart failure as a secondary diagnosis upon discharge[2]. The incidence of HF increases significantly with age, with 80% of HF-related hospitalizations and 90% of HF-related deaths occurring among patients aged 65 years or older[3]. Today, heart failure is the leading cause of hospital admission in patients over 65[2]. In addition to the high and increasing prevalence, the prognosis of patients with HF is poor, with more than half of all patients dying within 5 years of diagnosis.[1]

Additionally, Emergency Department (ED) data show that about 80% of all Heart Failure Hospitalizations are admitted directly from the ED[4,5]. Patients are typically admitted with Acute Decompensated Heart Failure (ADHF) and present with signs of congestion such as elevated jugular venous pressure, rales, ascites, peripheral edema, and symptoms such as rapid weight gain, orthopnea, dyspnea on minimal exertion, and/or peripheral swelling.

Despite significant therapeutic advancements, patients with HF continue to require frequent hospitalization for cardiovascular (CV) conditions such as uncontrolled hypertension, ischemia, arrhythmias, congestion, and hypervolemia, as well as non-CV comorbidities. Medicare beneficiaries represent 70% to 80% of all patients hospitalized with heart failure (HF) each year.[6] In a national 5% sample of Medicare beneficiaries study, all-cause 30-, 60-, and 90-day readmission rates following a HF index event were 22.3%, 33.3%, and 40.2%[7], respectively. Within the first 30 days, approximately 50% of readmissions occurred during the first 2 weeks post discharge. Despite all patients having initially been hospitalized for HF, only just over half of these readmissions were CV-related, a result that can be explained by the high rate of comorbidities found in patients diagnosed with HF. The immediate goal of ADHF treatment is to reduce congestion. However, in addition to ADHF symptoms, patients typically have numerous other co-morbidities (such as diabetes, pulmonary disease, kidney dysfunction and/or frailty) which further complicates the care pathway. Rates of rehospitalization and mortality are consistently lower when patients are free of clinical congestion upon discharge[8,9]. If guided by symptom relief alone, treatment will often be stopped too soon. Despite attempts at optimization of medical care, it is estimated that greater than 50% of patients still present symptoms of congestion at discharge[10] and up to 20% of patients fail to lose any weight during hospitalization[11,12]. Evidence suggests that many patients hospitalized with HF are also discharged too early, before fully meeting the criteria.

The average length of stay in the U.S. has decreased to 4 days, compared with an average of at least 7 days in the rest of the world[13]. Premature discharge, inefficient transition to oral diuretics, and lack of a comprehensive post-discharge care plans[14,15,16] can lead to Excess Days in Acute Care (EDAC) within 30 days of discharge.

3.2 ADHF TREATMENT OBJECTIVES AND PATHWAY

In October 2019, the American College of Cardiology published an Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure[2]. the pathway relies on the concept of continuous Trajectory Checks by a broad multi-disciplinary care team to ensure total patient care is incorporated. Three main in-hospital trajectories have been defined according to changes in patient symptoms, clinical signs, laboratory markers and imaging if done, presence or absence of complications, assessment and treatment of comorbidities, and treatment alignment with goals of care.

1. Improving towards target;
2. Stalled after initial response; or
3. Not improved/worsening.

Different trajectories require unique management strategies throughout the hospitalization and post-discharge. Patients improving toward target should be considered for initiation and/or further optimization of Guideline Directed Medical Treatment (GDMT). In those who are not improved/worsening, therapy should be intensified, and additional diagnoses, including conditions other than HF, should be considered. If deterioration continues, hemodynamic assessment and advanced therapies merit consideration. Further deterioration should prompt discussion about prognosis and goals of care. Patients who are stalled represent those whose symptoms may have improved initially but in whom residual congestion remains and diuretic resistance and/or kidney function, or other problems, may be limiting progress. The key issue in such patients is whether escalation of therapy will suffice to bring about complete decongestion, or whether that target needs to be modified, allowing a compromise with congestion.

Medicare beneficiaries are significantly impacted by delayed heart failure management strategies, as their multiple concomitant diseases put them at a higher risk for recurrent hospitalizations or death.

3.3 CURRENT STANDARD OF CARE IN DIURETIC MANAGEMENT

Loop diuretics are likely to remain the cornerstone of decongestive therapies for heart failure patients intended to maintain a euvolemic state (having a normal amount of body fluids). Multiple previous studies of new therapeutics have failed to show clinical improvements over loop diuretics in large RCTs[17,18,19]. Intensification of loop diuretics can reverse the course of volume

accumulation and obviate hospitalizations[20]. Diuretic response, broadly characterized by the ability to achieve natriuresis (the excretion of a large amount of sodium in the urine), diuresis (the excretion of a large amount of urine), and ultimately clinical decongestion following administration of appropriate doses of diuretic, depends on multiple factors.

Additionally, it is important to understand how Trajectory Checks are undertaken within current hospital workflows as they may vary by site, system, and country health system. Once hospitalized, only 13% of patients are admitted directly to an intensive care unit (ICU). Hospital care for the vast majority of patients with HF is provided in telemetry units (66%), on the ward (10%), and in step-down units (9%) based on the severity and complexity of the patient[21]. The administration of loop diuretics is typically either started in the ED or in care settings where patients are then monitored by the care teams including nursing staff and attending physicians. Physicians typically will round on the patients at a minimum every 24 hours, with the nursing staff checking on patients much more frequently. However, it is important to note that these patients are not being continuously monitored for decongestion symptoms/signs.

3.4 CURRENT STANDARD OF CARE IN KIDNEY FUNCTION IN PATIENTS WITH ADHF

Sodium retention drives volume overload, with fluid retention largely a passive, secondary phenomenon. However, the parameters (urine output, body weight) used to monitor therapy in ADHF measure fluid rather than sodium balance. This is because they are much easier to attain in the clinical setting. Thus, the accuracy of fluid-based metrics alone hinges on the incorrect assumption that urinary sodium content is consistent with healthy patients[22,23].

Diuretic resistance is a common complication impairing decongestion during hospitalization for ADHF. The current understanding of diuretic resistance mechanisms in ADHF is based upon extrapolations from other disease states and healthy volunteers. However, accumulating evidence suggests that the dominant mechanisms in other populations have limited influence on diuretic response in ADHF populations. Additionally, the ability to diagnose diuretic resistance rapidly and reliably is inadequate using currently available tools[24].

We also know that most patients admitted with acute decompensated heart failure have significant renal impairment, which can influence treatment paradigms and outcomes. For instance, at admission only 9.0% of patients had normal renal function (GFR => 90)[25]. As such, avoiding further harm to long-term kidney function is an important consideration for both the physicians and patients. Lastly and critically important, sodium excretion is strongly associated with 6-month mortality, whereas traditional fluid-based metrics were not. Poor sodium excretion, even in the context of fluid loss, portends a worse prognosis[33].

The administration of loop diuretics remains the standard of care today in treating ADHF patients. Even though over 90% of ADHF patients admitted to the hospital are given a diuretic[20], about 20% of patients do not lose any weight and greater than 50% lose less than 5 lbs. with this therapy[11.]

ADHF patients can exhibit reduced responsiveness to diuretics, often referred to as diuretic resistance. Several studies have shown that a poor diuretic response is associated with a higher risk of rehospitalizations and death[26,27]. Although the clinical phenomenon of diuretic resistance is well known to clinicians, precise definition of this phenomenon has been challenging. Nevertheless, the literature reports up to 20% to 50% of hospitalized patients with ADHF have a poor response to IV loop diuretics, and the overwhelming majority have some degree of reduced diuretic responsiveness[28,29]. Additionally, diuretic dosing is inherently unique to each patient based on their individual cardio-renal physiology. Dosing at too low a rate can fail to decongest the patient and/or unnecessarily extend the hospital length of stay, while dosing at too high a rate risks exposing the patient to excess diuretic unnecessarily.

3.5 RATIONALE FOR USE OF REPRIEVE DMS

To overcome the limitations of current standard of care therapy for patients with congestive heart failure, the Reprieve Decongestion Management System (based on the original RenalGuard System, NCT#01098032) will be utilized in this feasibility clinical study. The overall aim of DMS therapy is to safely remove the desired net amount of fluid from volume overloaded patients with congestive heart failure. The results from the two earlier feasibility trials (RCV-0002, RCV-0004), collectively included the data from 70 human subjects treated with Reprieve Cardiovascular System, demonstrates safety of subjects who presented with ADHF and had undergone treatment with the Reprieve Cardiovascular System. The favorable safety profile and improved subject outcomes suggest that additional studies of the DMS device in subjects are reasonable and warranted.

4 DEVICE DESCRIPTION

4.1 OVERVIEW

The Reprieve Decongestion Management System, or Reprieve DMS, is a hospital bedside fluid management console designed to provide personalized and automated infusion of the IV diuretic furosemide and physiological saline in response to the patient's real-time urine volume output and urine sodium concentration to safely and rapidly decongest patients suffering from ADHF, also known as Acute Heart Failure (AHF).

The Reprieve DMS incorporates a urine collection bag suspended from a weighing scale to accurately measure real time patient urine excretion. This measured urine output rate is used to control a syringe pump to infuse the IV diuretic furosemide and a peristaltic pump to infuse normal saline. The system is controlled by a touch screen computer that acts as the system user interface

and displays all relevant data to the health care professional such as urine output over time, diuretic infusion rate and saline infusion volume. An image of the system is shown below in Figure 1.

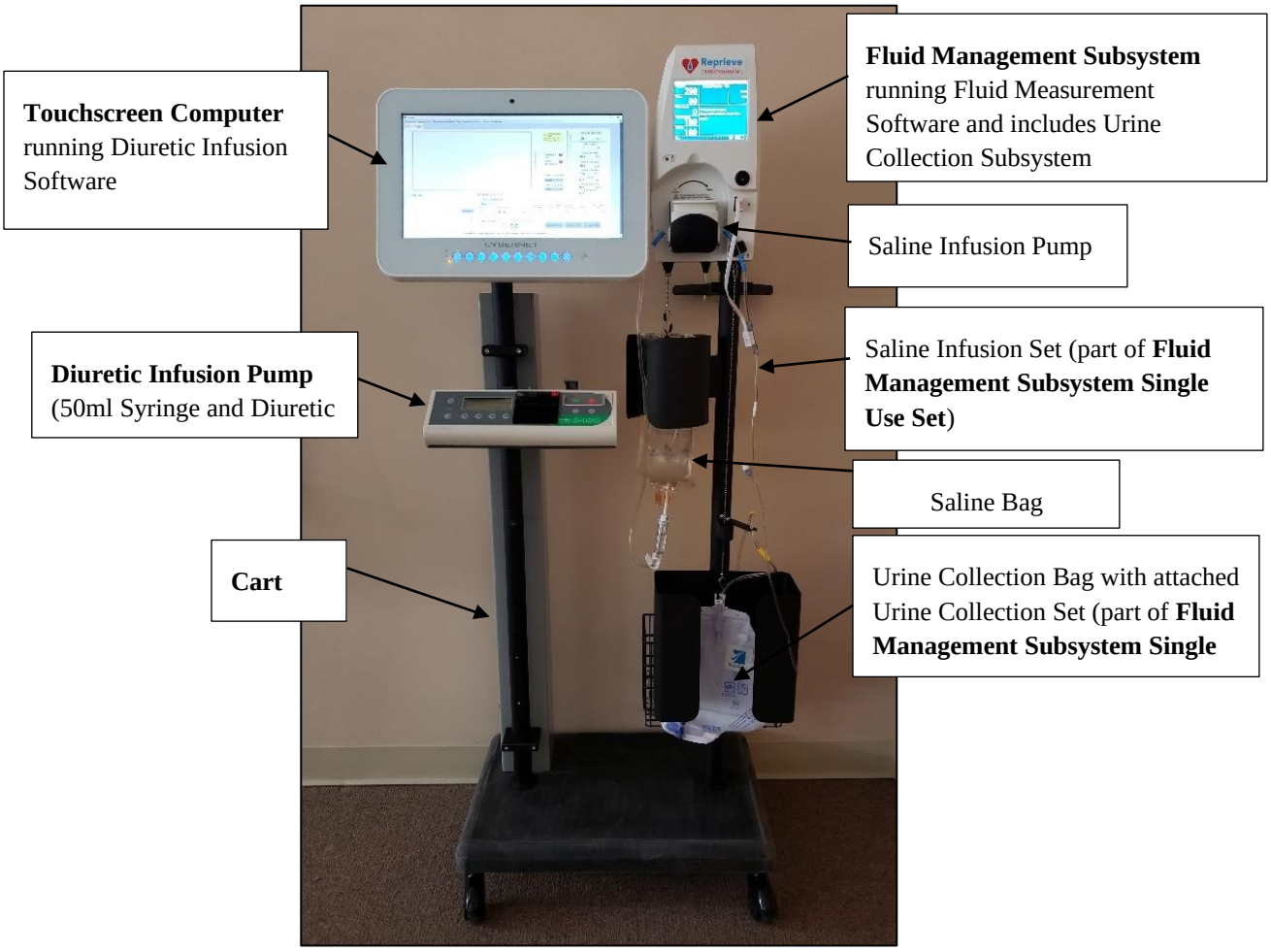

Figure 1: Reprieve DMS

As can be seen in the figure, all components are mounted to a mobile cart, which supplies power to each component, facilitates electrical connections and includes wheels to allow the system to be moved.

The Reprieve DMS hardware incorporates the following components:

Component	Description
Touchscreen Computer	Touchscreen computer running dedicated Diuretic Infusion Software to control the Diuretic Infusion Pump to automatically infuse IV furosemide at a rate varied based on

	the patient's real time measured urine output rate and lab measured urine sodium concentration.
Diuretic Infusion Pump	Infuses IV furosemide to the patient at a controlled rate.
Fluid Management Subsystem (FMS)	Comprised of two parts: 1) a Urine Collection Subsystem designed to measure the amount and rate of urine output, and 2) a Saline Infusion Pump designed to automatically infuse partial fluid replacement based on the measured urine output rate and lab measured urine sodium concentration manually entered into the FMS by the healthcare professional. Both are controlled by the Fluid Management Software running on the FMS.
Cart	Mobile cart that supports all components, facilitates electrical connections, and includes wheels to allow movement of the system.

The following consumable components are required to operate the Reprieve DMS:

Component	Description
Fluid Management Subsystem Single Use Set	Custom disposable tubing set that includes the Saline Infusion Set for infusing saline into the patient. This connects to a standard peripheral IV catheter, and the Urine Collection Set that connects to the patient's Foley Catheter to allow collection of urine and real time measurement of urine output. The Single Use Set (SUS) also contains a 3 ft. extension set if the healthcare professional wishes to extend the Urine Collection Set.
Diuretic Infusion Set	Commercially available extension set provided to the clinical site to allow controlled infusion of IV diuretic through the patient's standard peripheral IV catheter.
50ml Syringe	Commercially available disposable syringe provided to the clinical site and filled with IV furosemide by the hospital pharmacy.
Peripheral IV Catheter	Commercially available IV catheter set provided by the hospital and inserted into the

Component	Description
	patient to provide vascular access for diuretic and saline infusion.
Foley Catheter	Commercially available urinary drainage catheter provided by the hospital and inserted into the patient to allow urine collection.
Saline Bag	Commercially available one liter bags of physiological saline provided by the hospital for controlled fluid infusion to the patient.

A high-level block diagram of the system is shown below in

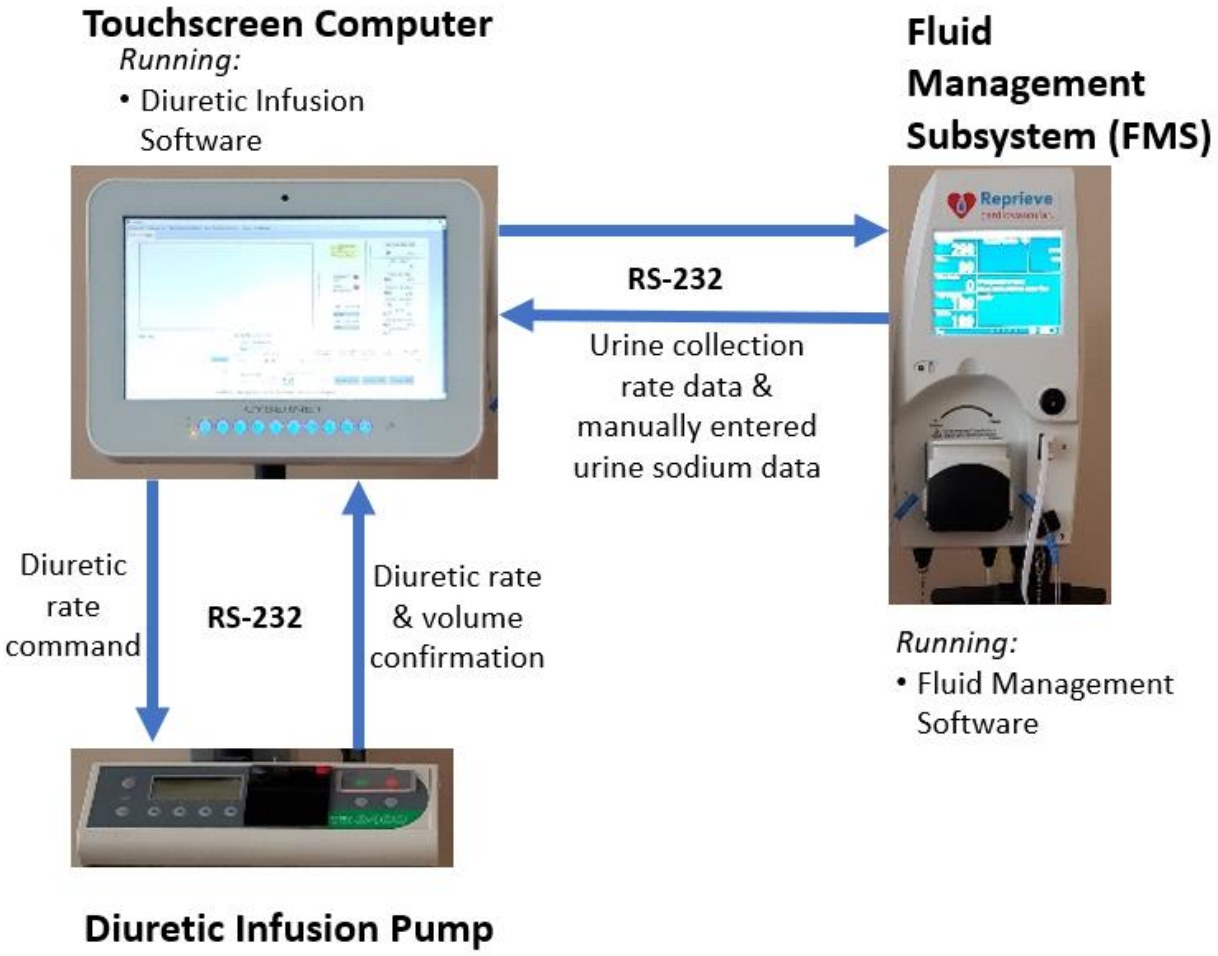

Figure 2.

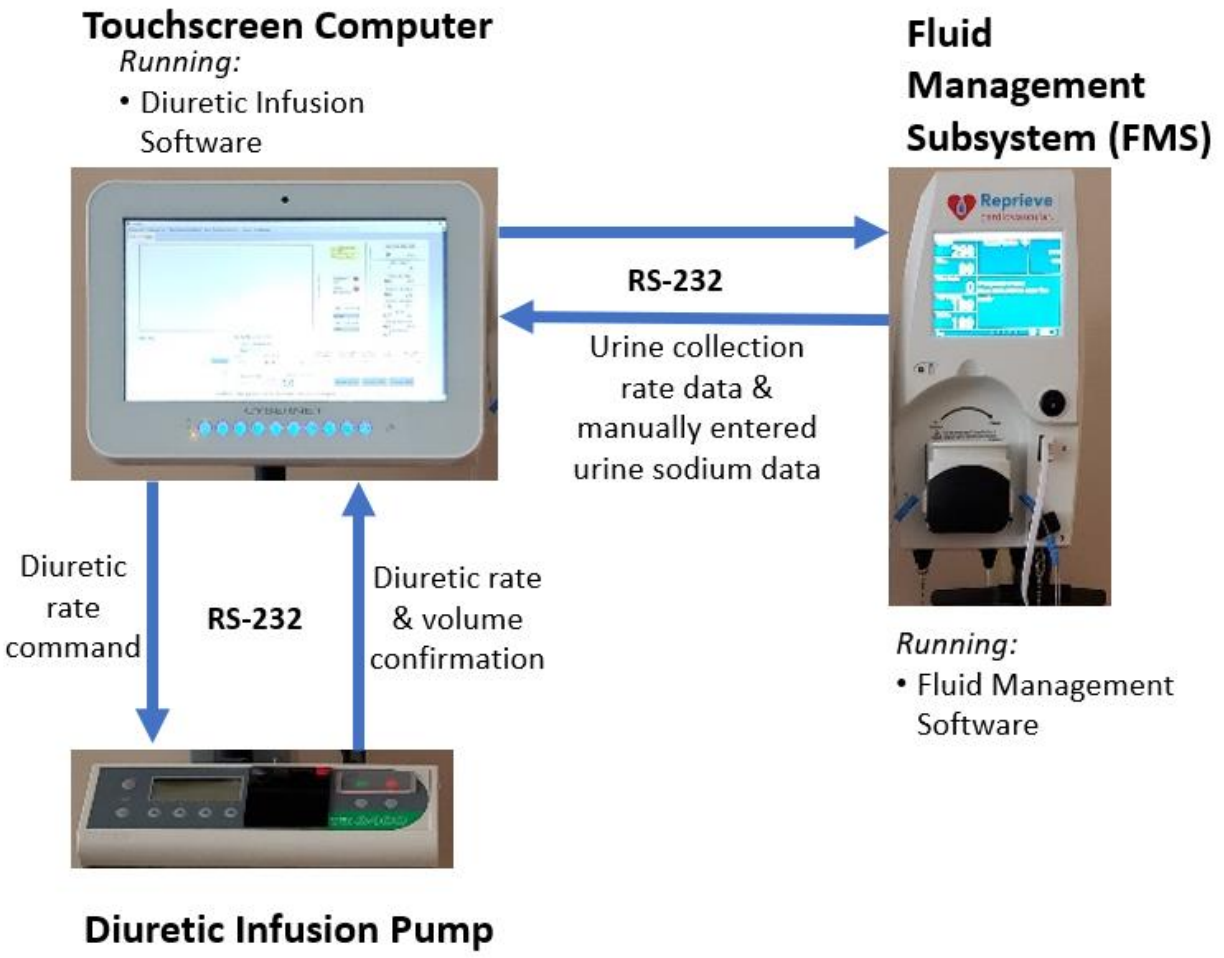

Figure 2: Reprieve DMS Block Diagram

As shown above, the Touchscreen Computer receives urine output rate data and the manually entered urine sodium concentration from the FMS, and this data is used to generate the desired diuretic rate, which is then sent to the Diuretic Infusion Pump. The Touchscreen Computer does not control the operation of the FMS as the control of saline infusion is performed independently by the FMS. The health care professional starts and stops saline infusion, and enters urine sodium concentration directly on the control panel of the FMS.

A detailed description of the hardware components and software is provided in the owner's manual.

4.2 RISK/BENEFIT ASSESSMENT

4.2.1 KNOWN POTENTIAL RISKS

The risks associated with the use of peripheral IV catheter and Foley catheter with the Reprieve Decongestion Management System are expected to be similar to other procedure utilizing these catheters. There are also risks associated with over-hydration and under-hydration along with the risks associated with loop diuretic therapy for ADHF patients.

"Over-hydration" has a range of potential causes, including insufficient diuretic dosing, excess saline infusion, and hypotension/low intravascular volume. "Under-hydration" also has a range of potential causes, including excess diuretic dosing, insufficient saline infusion, and a rapid increase in diuresis. The risks of each are identified in more detail below:

Risks of under-hydration:

- Low urine production
- Symptomatic hypovolemia/hypotension
- Electrolytic Imbalance including hyponatremia and hypokalemia
- Abnormal laboratory values
- Dizziness and headaches
- Muscle cramps
- Ototoxicity
- Renal compromise/acute kidney injury
- Arrhythmia

Risk of over-hydration:

- Increased urination
- Symptomatic hypervolemia/hypertension
- Worsening pulmonary function
- Electrolytic imbalance
- Renal compromise
- Arrhythmia

General risks associated with Reprieve DMS:

- Allergic reaction/hypersensitivity to medication, or device materials
- Complications at IV/vascular catheter insertion sites, e.g., bruising, hematoma, pain, bleeding
- Device malfunction or breakage
- Extravasation/Infiltration at IV/vascular catheter insertion sites
- Infection (IV/vascular catheter insertion site or Foley catheter) or sepsis
- Injury or trauma to the bladder or urethra
- Hemorrhage or bleeding
- Embolism
- Fever
- Hematuria
- Hemodynamic compromise
- Myocardial infarction

- Pain/discomfort
- Pulmonary edema
- Worsening heart failure or low cardiac output
- Anemia
- Death

General risks associated with Study Participation:

- Increased risk of infection or blood loss due to increased blood draws

Complications may occur at any time during the procedure, post-procedure, or follow-up period. The above risks may require intervention to address the condition. There may also be other risks that are unforeseen at this time.

There may also be side effects associated with the standard of care diuretics used in conjunction with the Reprieve Decongestion Management System, i.e., furosemide. Refer to relevant drug package insert for full details.

4.2.2 POTENTIAL PRODUCT BENEFITS

The investigational system has been designed to provide rapid fluid removal in ADHF patients. The following potential benefits associated with the Reprieve-DMS study may include, but are not limited to, greater procedural efficiency, improved clinical outcomes, as well as enhanced scientific understanding of ADHF treatment:

Potential Procedural Benefits:

- Personalized diuretic dosing: Today's initial loop diuretic dosing is typically set based on a simple multiple of the home diuretic dose. The Reprieve DMS is designed to find the optimal individualized patient diuretic dose through a Dose Finding Phase that determines the continuous IV diuretic dose required to generate sufficient urine production which leads to sustained fluid loss.
- Faster time to optimal diuretic dosing: The Reprieve DMS dose finding algorithm is designed to find the optimal dose within the first hour of therapy, as opposed to the current standard of care where the patient is only assessed by the healthcare professional for dose modification every 24 hours during rounds, thus leading to much slower dose optimization.
- Removal of a higher and clinically significant net volume with the Reprieve-DMS System than with standard of care diuresis alone.
- Greater sodium losses through higher sodium content in the urine. By infusing a volume of saline based on the patient's estimated urine sodium output rate, as determined by the measured urine volume and the manually entered lab measurement of the patient's urine sodium concentration, the Reprieve DMS is designed to prevent the activation of sodium retaining mechanisms. In doing so, the patient's urine sodium content may be higher than that

of patients who are not receiving a saline infusion and has the potential to lead to an increase in the net volume of sodium removed.

- In the situation where the Reprieve DMS is unable to make substantive progress towards decongestion, the system may be able to more quickly identify failure to respond to diuretic therapy. This could lead to earlier escalation of alternative and/or more invasive treatment options to address the patient condition.

Reprieve plans to study how the above procedural benefits translate to better patient outcomes in all enrolled Medicare and non-Medicare patients via the specified secondary endpoints. The pilot trial results will inform the eventual pivotal study design.

Potential Clinical Benefits:

- More rapid resolution of symptoms of shortness of breath
- Improved vital organ function, in particular kidney function, through the delivery of an optimized diuretic dose combined with saline infusion to moderate the kidney's hormonal and mechanical compensatory mechanisms and to prevent diuretic resistance.
- Reduction in hospital length of stay due to a faster time to decongestion.
- Increased home diuretic dosing accuracy by using the therapeutic dose found in the Dose Finding Phase to inform at home diuretic dose.
- Increased home days due to reduced length of stay in the hospital and/or discharge to home vs. higher acuity care locations like SNFs.
- Longer duration benefit (reduced readmissions) based on better hospital decongestion, faster discharge (lower risk of hospital acquired conditions) and optimized home diuretic dosing.

In addition to the above procedural and potential clinical benefits, the study may also provide scientific insights into the following:

- Better understanding of the physiology of diuretic response and diuretic resistance.
- Greater understanding of the role of fluid and salt replacement in diuretic resistance.
- Enhanced fidelity of urinalysis, in both the therapy and control group, may increase understanding of the response of the kidneys of ADHF patients to diuretic therapy.

Ultimately, efficient decongestion may be a pre-cursor to meaningful clinical outcomes like length of stay, home days, and, potentially, lower readmissions and mortality rates for acute decompensated heart failure patients. These clinically significant endpoints have been incorporated into the protocol as ancillary endpoints, and the knowledge gained in the pilot study will be used to inform the design and selection of the pivotal trial endpoints.

4.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is an open label, prospective, randomized controlled pilot study. In all situations, appropriate mitigations have been contemplated and presented as part of the overall study plan. The aim of the study will be to carefully evaluate all aspects of the product and procedure, and all subjects will be closely monitored during treatment and the follow-up period to minimize any untoward risks. Risk mitigation measures include:

- Mitigations for the risk of over-hydration:
    - To mitigate the risk of over-hydration due to over-infusion of saline, the saline infusion algorithm is designed to limit saline infusion to always be less than urine output, as outlined in the IDE, to avoid infusion of more saline than the real-time urine output measurement. In addition, lab urine sodium concentration measurements are performed every time the urine bag is emptied, and the result is used to optimize the rate of saline infusion to prevent over infusion of saline. Other safeguards in the DMS include redundant monitoring of both the urine weight scale as well as saline infusion pump to ensure accurate fluid measurements.
    - To mitigate the risk of over-hydration due to insufficient diuretic dosing, there are system alerts for low urine output.
- Mitigations for the risk of under-hydration
    - If the Reprieve DMS detects prolonged high urine production (see IDE Description for details) it will automatically implement a down-titration of the diuretic dose to prevent potential electrolyte imbalances. In today's standard of care, healthcare professionals may be unaware of high urine production for an extended period of time due to the intermittent nature of manual urine output measurement, thus increasing the potential risk of over-infusion of diuretic.
    - Appropriate saline infusion with the Reprieve DMS system is designed to mitigate the risk of under-hydration.
- The investigators in this study are selected based on their experience in treating patients with Acute Decompensated Heart Failure.
- Investigators and associated study team members will be trained in proper use of the Reprieve Decongestion Management System (DMS) device operation prior to treatment of subjects. Training may include didactic and hands-on training with the DMS.
- Well defined clinical study protocol, including specific inclusion/exclusion criteria to enroll appropriate subjects in the trial.
- Careful monitoring of each patient during the treatment with DMS including serum, hemodynamic and urine value evaluations over the treatment.
- Established thresholds on physiologic status to guide temporary suspension or termination of treatment to stabilize the patient to avoid any untoward event.

- Ongoing monitoring of study data and results, including the use independent committees (i.e., CEC & DSMB).

This benefit-to-risk profile supports the use of the Reprieve Decongestion Management System in an IDE clinical study setting.

5 OBJECTIVES AND ENDPOINTS

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine if the Reprieve DMS can more efficiently decongest ADHF patients in comparison to control therapy without clinically significant acute kidney injury. All study endpoints will be evaluated in two study cohorts (subjects with home dose of ≥ 80 mg of furosemide equivalent and subjects with home dose of <80 mg of furosemide equivalent).

5.2 PRIMARY ENDPOINTS

The trial will employ co-primary endpoints, one for efficacy and one for safety, respectively as defined below:

The primary efficacy endpoint is total urine sodium output at 24 hours post-treatment initiation.

The primary safety endpoint is clinically significant acute kidney injury defined as KDIGO stage 2 or greater AKI [≥ doubling of baseline serum creatinine or use of renal replacement therapy (RRT)], severe electrolyte abnormality (serum potassium <3.0 mEq/L, magnesium <1.3 mEq/L or sodium <135 mEq/L), symptomatic hypotension or hypertensive emergency. For subjects enrolled with baseline sodium levels of ≤135 mEq/L, there needs to be drop of at least 5 mEq/L to be considered against primary safety endpoint. The changes in creatinine and electrolytes will be evaluated from baseline to peak value during the maximum 72-hour study period after randomized therapy initiation. RRT includes hemodialysis, hemofiltration, hemodiafiltration, peritoneal dialysis, and kidney transplant. Isolated ultrafiltration without dialysis will not be considered RRT. Hypertensive emergency is defined as blood pressure than 180/120 mmHg with end-organ damage. Symptomatic hypotension is defined as sustained hypotension (<80 mmHg systolic) with corresponding symptoms that require an intervention (i.e., fluid bolus or vasoactive medication).

5.3 SECONDARY ENDPOINTS

5.3.1 SECONDARY EFFICACY ENDPOINTS

- ***Net Fluid Loss*** at end of randomized therapy.
- ***Time on IV loop diuretic*** Defined as the time from initiation of randomized therapy to last dose of IV loop diuretic administered for ADHF.

5.3.2 SECONDARY SAFETY ENDPOINTS

The assessment of all Device and Procedure related AEs and SAEs in the study population as determined by an Independent Clinical Events Committee (CEC), as outlined in the committee charter. It should be noted that episodes of hematuria associated with Foley catheter placement that can be adequately managed will not be included as a secondary safety endpoint, since this is an anticipated adverse event commonly associated with Foley placement. Also, small to moderate sized bumps in creatinine have consistently been shown to have limited prognostic significance, are not associated with true renal injury and generally signify more complete decongestion [30,31].

5.3.3 ANCILLARY ENDPOINTS

All of the following non-powered ancillary endpoints will be objectively reported.

- ***Home days***: Defined as the number of days alive and at home (e.g., without a visit to an emergency room, unscheduled clinic visit or acute care facility, skilled nursing facility, inpatient rehab) within the initial 90 days after randomization. Increase in number of home days will be considered as a positive outcome.
- ***Length of stay*** Defined as the time from initiation of randomized therapy to discharge. Increase in length of stay will be considered as a negative outcome.
- ***Net fluid loss*** at day 7 or discharge (whichever occurs first), following initiation of randomized therapy. Increase in net fluid loss will be considered as a positive outcome.
- ***Total urine output*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy. A higher urine output will be considered as a positive outcome.
- ***Sodium output*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy (in ODT group total sodium output, in DMS group net to the system). A higher amount of sodium output will be considered as a positive outcome.
- ***Change in Weight*** at the end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy, 7 days and 30 days post-discharge visit. A decrease in weight as it relates to decongestion will be considered as a positive outcome.
- ***Dyspnea VAS*** AUC at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit. A lower score on dyspnea VAS will be considered as a positive outcome.

- ***Change in creatinine based eGFR*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit. A lower eGFR at all these timepoints will be considered as a worse outcome.
- ***Change in NT-proBNP*** at discharge . A higher NT-proBNP is considered as a worse outcome.
- ***Change in RAAS markers:*** Renin, aldosterone, plasma renin activity, measured at discharge . High RAAS markers will be considered as a worse outcome.
- ***Change in serum electrolytes*** at end of randomized therapy, day 7 or discharge (whichever occurs first), following initiation of randomized therapy,7 days and 30 days post-discharge visit.
- ***Time to and total death and rehospitalization:*** through 90 days**.** A lesser time to death and rehospitalization will be considered as a worse outcome, along with total number of deaths and rehospitalizations.
- ***Average rate of weight loss*** during the IV therapy (i.e., initial randomized IV diuretic dose to the cessation of IV therapy) for a maximum of 72 hours after randomized therapy initiation. An increase in the rate of weight loss will be considered as a positive outcome.
- ***Change in KCCQ*** at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. An increase in the KCCQ scores will be considered as a positive outcome.
- ***Change in Dyspnea Score (5 and 7-point Likert scale)*** at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. An improvement in dyspnea scores will be considered as a positive outcome.
- ***Change in Modified Congestion Score*** (based on sum of score for degree of edema, pleural effusion and ascites) at end of randomized therapy, discharge, 7 days and 30 days post-discharge visit. A reduction in congestion scores will be considered as a positive outcome.
- ***Changes in Serum Creatinine and Weight*** at end of randomized therapy. An increase in weight loss without corresponding increase in creatinine will be considered as a positive outcome.
- ***Ototoxicity:*** Shift in audiometry measurements from baseline to discharge and 7 day post-discharge visit, meeting any one of the following:
  - Decrease of 10 dB at 2 consecutive frequencies from 250-8000 Hz, or
  - Decrease of 20 dB at 1 frequency from 250-8000 Hz, or
  - Loss of response at three consecutive test frequencies where responses were previously obtained (where baseline responses are obtained close to the limits of audiometric output and later responses cannot be obtained at the limits of the audiometer).
  - Increase in events of ototoxicity will be considered as a worse outcome.

6 STUDY DESIGN

6.1 OVERALL DESIGN

This is an open-label, prospective, randomized, controlled pilot trial to compare the rate of decongestion for up to 72 hours with the Reprieve DMS compared to control therapy (ODT). ODT is based upon recommendations by the AHA HF Guidelines and the DOSE-AHF clinical trial[32], a landmark clinical trial of diuretic treatment in acute heart failure subjects. However, the final treatment decisions will be made by the physicians based on their medical judgement, patient characteristics and site's standard of care.

The study population is patients with acute decompensated heart failure (ADHF) admitted to the hospital or presenting to the Emergency Department who require decongestion.

A maximum of 100 subjects randomized 1:1 to DMS and ODT will be included in the study. This sample size is considered sufficient to provide meaningful clinical insights at this stage of therapy development. Furthermore, the use of a prospective control cohort receiving optimal diuretic therapy will allow for direct comparison of the safety and performance between DMS and ODT control therapy. A maximum of three roll-ins per site will also be treated with the study device prior to randomization. Sites will be asked to use the roll-in arm of the trial after implementation of the latest version of the study protocol (version 1.6) regardless of previous enrollment activity at their respective sites. The final number of roll-ins will be decided by the sponsor based on site status and experience. In addition, sites will have the opportunity to enroll subjects in an ongoing registry who meet the study criteria but refuse to participate in the trial. A maximum of 20 subjects per clinical site will be enrolled in the registry.

A maximum of twenty-five clinical sites located in the United States and Europe will participate in this study.

This pilot study will prospectively compare decongestive therapy administered by the Reprieve DMS system versus control therapy (ODT). This data will help inform the design and development of future clinical trials of the Reprieve DMS device.

6.2 END OF STUDY DEFINITION

A subject is considered to have completed the study at the time he/she has completed all phases of the study including the last visit (i.e., 90-Day Follow-up visit) shown in Table 1: Schedule of Assessments.

The end of the study is defined as completion of the last visit shown in the Schedule of Assessments in the trial across the enrolled and treated subjects.

7 STUDY POPULATION

Target patients are those with Acute Decompensated Heart Failure admitted to the hospital or presenting to the Emergency Department who require decongestion.

7.1 INCLUSION CRITERIA

Candidates for participation in the study must meet all of the following inclusion criteria.

1. Hospitalized with a diagnosis of heart failure as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema/swelling) AND 1 sign (peripheral edema, ascites, jugular venous distension).
2. ≥10 lb (4.5 kg) above dry weight either by historical weights or as estimated by health care provider.
3. Prior use of outpatient oral loop diuretics within 30 days prior to admission.
4. Patients ≥ 18 years of age able to provide informed consent and comply with study procedures.

7.2 EXCLUSION CRITERIA

Candidates for participation will be ineligible for the study if any of the following exclusion criteria apply:

1. Inability to place Foley catheter or IV catheter or other urologic issues that would predispose the patient to a high rate of urogenital trauma or infection with catheter placement.
2. Hemodynamic instability as defined by any of the following: systolic blood pressure <90 mmHg, use of vasopressors, use of IV inotropes to treat hypotension (systolic blood pressure <90 mm Hg) or suspected/confirmed low cardiac output/shock, mechanical circulatory support, uncontrolled arrhythmias, active severe bleeding, or confirmed or suspected cardiogenic shock. *Note: In the absence of the above conditions, use of inotropes to augment diuresis is permitted.*
3. Dyspnea due primarily to non-cardiac causes (e.g., severe chronic obstructive pulmonary disease or pneumonia).
4. Acute infection with evidence of systemic involvement (e.g., clinically suspected infection with fever or elevated serum white blood cell count).
5. Estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m^2 calculated using the MDRD equation or current use of renal replacement therapy.
6. Significant left ventricular outflow obstruction, uncorrected complex congenital heart disease, severe stenotic valvular disease, infiltrative or constrictive cardiomyopathy, acute myocarditis, type 1 acute myocardial infarction requiring treatment, or any other pathology that, in the opinion of the investigator, would make aggressive diuresis poorly tolerated.
7. Inability to follow instructions or comply with follow-up procedures.
8. Other concomitant disease or condition that investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric, behavioral or cognitive disorders, sufficient to

interfere with the patient's ability to understand and comply with the study instructions or follow-up procedures.

9. Severe baseline electrolyte abnormalities (e.g., serum potassium <3.0 mEq/L, magnesium <1.3 mEq/L or sodium <125 mEq/l). *Note: These are based on baseline/screening labs. Subjects whose electrolyte levels are repleted cannot be reassessed for inclusion in the trial*.
10. Presence of active COVID-19 infection.
11. Enrollment in another interventional trial during the index hospitalization.
12. Inability to return for follow-up study visits.
13. Life expectancy less than 3 months.
14. Women who are pregnant or intend to become pregnant.

7.3 INFORMED CONSENT

7.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Consent materials specifically developed for this clinical study are considered part of the clinical investigational plan.

7.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. Upon reviewing the document, the investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present

throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

Informed consent shall be obtained in writing from the subject or their legally authorized representative and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject, except when special circumstances apply. If during the course of the study assessments, a subject is found not to be eligible for inclusion in the study, the subject or their representative should be notified and the reason for ineligibility documented on the screening log/form.

The general process for obtaining informed consent shall:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process;
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation;
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- Not waive or appear to waive the subject's legal rights;
- Use native non-technical language that is understandable to the subject;
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation;
- Include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process;
- Provide the subject with a copy of the signed and dated informed consent form and any other written information; and,
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

7.4 SCREEN FAILURE

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

7.4.1 SCREENING/ENROLLMENT

The subject is identified at the time of evaluation in the ED or Hospital Ward. If the subject is in ADHF they will be evaluated for their eligibility to enroll in this clinical study based upon the eligibility criteria**.** If a subject qualifies for the study and signs the informed consent, they will be randomized.

7.4.2 SCREEN FAILURE REGISTRY

Subjects who meet all the study criteria but refuse to participate in the randomized clinical trial will be followed in a tandem screen failure registry. These patients will be managed per standard of care and will be followed through 30 days to document safety outcomes. The objective of the registry is to document treatment paradigm and safety outcomes as these subjects get managed by standard practice at the clinical site. An ad hoc analysis will be performed between the subjects randomized to the control therapy and subjects enrolled in the registry.

Each clinical site will enroll a maximum of 20 subjects in the registry.

7.5 RANDOMIZATION PROCEDURE

Subjects will be prospectively randomized into this clinical trial. Randomization will occur only after the subject provides written informed consent for enrollment into the trial, completes all screening procedures, and satisfies the requirements of the study eligibility criteria. Sites will need to document physician assessment of diuretic dosing and any contraindication to the DOSE trial diuretic therapy before a subject can be randomized in the trial. Sites will also need to document the planned dosing in the ODT arm of the trial if the subject is randomized to ODT arm, before the subject is enrolled in the trial. Importantly, should the patient be randomized to ODT this dosing must be utilized for the first 24 hours of the randomized therapy. Subjects will be randomized 1:1 to DMS or ODT and the randomization will be stratified based on site. Further stratification will occur based on home dose such that those < 80 and ≥ 80 mg will be stratified 1:1 to ODT vs Reprieve DMS.

The randomization schedules will be generated in advance by the study statistician or designee using a computerized random number generator. This randomization schedule will be masked to the study subjects, site personnel, and Sponsor. Only the unmasked statistician and designates will be privy to the masked randomization scheme.

Randomization will be accomplished using a secure interactive web-based randomization system (IWRS). Treatment assignment is made only after site verification of proper informed consent execution and study eligibility. The study coordinator or a designee will log into the IWRS and be asked a series of questions verifying that the subject is eligible and informed consent has been obtained prior to receiving the randomization assignment for the subject. A printed copy of the randomization assignment should be maintained in the subject's file. Neither the investigator nor subject shall be blinded to the treatment assignment.

The treatment initiation must happen within 12 hours of randomization. However, sites should randomize the subjects as close as possible to the initiation of therapy.

A Subject is not randomized until the randomization assignment has been dispensed by the system. The web-based system will not provide a randomized study assignment if it cannot confirm that a subject is eligible. If, at any time after randomization, the Subject becomes ineligible or withdraws, the Subject is still considered randomized.

8 STUDY INTERVENTIONS

8.1 REPRIEVE DMS STUDY INTERVENTION DESCRIPTION

The three primary phases of the Reprieve DMS therapy include a rapid dose finding algorithm (to identify the personalized effective diuretic dose), a fluid replacement system (to suppress sodium avidity mechanisms and diuretic resistance), and standardization of the transition from IV to PO diuretic treatment. The system enables these mechanisms through three unique phases:

1) Dose Finding Phase
2) Continuous Infusion Phase
3) Therapy Transition Phase

Each phase is described in detail in the following sections.

8.1.1 DOSE FINDING PHASE

The Reprieve Decongestion Management System (DMS) shall be utilized to maximize fluid removal over a maximum duration of 72 hours. DMS begins by administering IV furosemide to achieve the target urine rate of 525 ml/hr. using an exponentially increasing ramp dose until the target urine rate is met or maximum IV furosemide dose (200 mg) is reached ("Dose Finding Phase").

Figure 3 below details the exponential increase of the Dose Finding Algorithm.

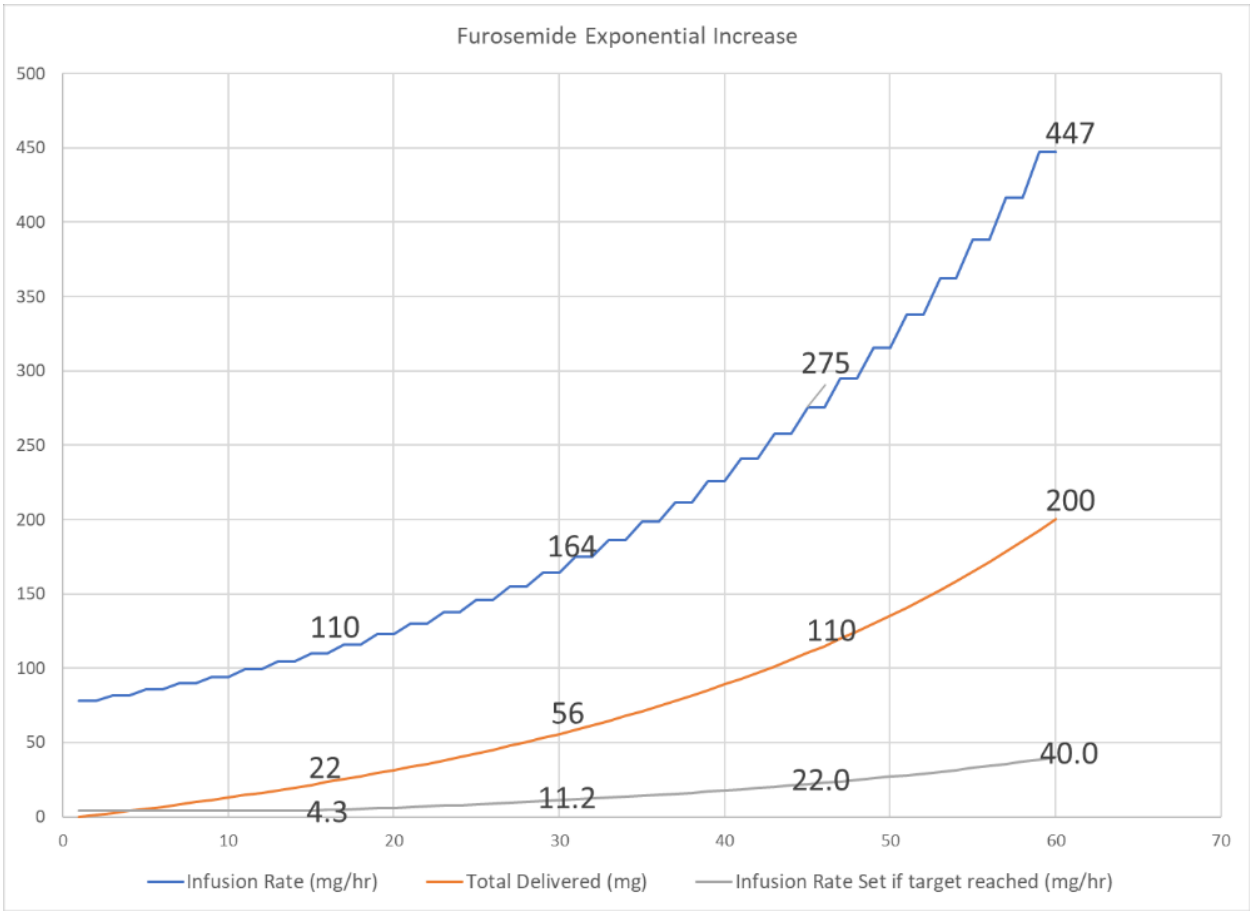

Figure 3: Dose Finding Algorithm

- The top line details the rate of diuretic infusion over the 60 minutes of the Dose Finding Phase. The diuretic rate is increased every two minutes.
- The second line details the total volume of diuretic infused over the 60 minutes of the Dose Finding Phase.
- The third line details the continuous diuretic infusion rate set if the urine output target is reached at that timepoint.

The rate of increase in the diuretic infusion rate during this phase has been designed to approximately double the total volume of diuretic infused every fifteen minutes. This exponential increase was chosen based on the pharmacokinetics of furosemide to approximate the infusion required to acutely cause a serum level of furosemide that generates a urine output above the target urine rate. The largest dose that can be infused by this Dose Finding Algorithm over the 60 minutes of the Dose Finding Phase is 200 mg. If 200 mg are delivered without the patient reaching the target urine output, the algorithm will stop, and the Continuous Infusion Phase will begin (detailed in the next section).

It should be noted that the initial dose finding phase uses a default (isotonic) assumed urine sodium concentration (140 mmol/L) and is not adjusted for the patient's specific urine sodium concentration.

Once the Dose Finding Phase is complete (either due to achievement of the target urine rate or completion of the full diuretic ramp), the system moves into the Continuous Infusion Phase.

Subjects receiving high dose loop diuretic at home (≥ 240 mg furosemide, 3 mg bumetanide, or 60 mg torsemide per 24 hours) must be administered an oral long half-life thiazide/thiazide like diuretic (10mg metolazone, 50mg chlorthalidone, 100mg HCTZ or equivalent) 2 to 12 hours prior to initiating Reprieve therapy.

8.1.2 CONTINUOUS INFUSION PHASE

In the Continuous Infusion Phase, the Continuous Infusion Algorithm sets the continuous diuretic infusion rate to an hourly rate of 20% of the total diuretic infused during the Dose Finding Phase. This rate has been selected based on the pharmacokinetics of furosemide to provide the infusion required to maintain the serum level of furosemide during the continuous infusion phase that generated the urine output above the target urine rate. The minimum continuous infusion rate is 4 mg/hr and the maximum continuous infusion rate is 40 mg/hr. Thus, the system can infuse a minimum daily diuretic infusion of 96 mg (24 hours * 4 mg/hr) and a maximum dose of 1,120 mg (200 mg + 23 hours * 40 mg/hr). The doses used by the system are consistent with the practice that is utilized by our study investigators in their normal course of patient care and are also consistent with doses that have been utilized in several NIH clinical trials (CARESS, ROSE, etc.).

The Continuous Infusion Algorithm delivers a personalized continuous dose of diuretic based on the total dose required to reach the target urine output. If a large volume of diuretic was required to reach the target urine rate, a high continuous infusion rate will be set to maintain the high serum level of diuretic that patient requires to maintain rapid diuresis. If only a small volume of diuretic was required to reach the target urine output rate, the continuous infusion rate will be set to a low rate. In either case, the diuretic infusion is tailored to the patient's individual response.

When therapy begins, during the diuretic Dose Finding Phase, the FMS replaces 100% of the urine measured with an equal volume of normal saline until the patient receives an absolute volume of 250 ml of saline (Initial Fluid Match Volume) or one hour has elapsed, whichever comes first. This one-to-one fluid replacement is intended to increase urine output and deliver an initial bolus of sodium and chloride to stimulate nephron activity without causing additional clinical symptoms of heart failure. Following completion of the Dose Finding Phase and the start of the Continuous Infusion Phase, and once the target Initial Fluid Match Volume of 250 ml has been reached, the FMS controls the saline infusion based on the urine output. The urine collection bag weight (corresponding to the volume of collected urine) is measured continuously, and urine output rate

is calculated every minute. The Fluid Management Software assesses how much saline to infuse every minute during the continuous infusion phase.

Following the start of the Continuous Infusion Phase, each time the FMS alerts the user to a full urine bag, or whenever the healthcare professional chooses to empty the urine bag, the bag is shaken by the healthcare professional to ensure that the contents are mixed, and a urine sample is taken prior to emptying the bag. This sample is sent to the local hospital lab and the urine sodium concentration (mmol/L) is measured. When the result is received, the healthcare professional manually enters the value into the FMS using the touchscreen display. It is recommended that the urine sodium concentration be obtained and entered within two hours of sample collection. The FMS uses these urine sodium values to calculate an adjusted urine output rate, which will be different for each patient. Once the FMS calculates this first adjusted urine output rate, the value is used instead of the measured urine output rate to calculate the rate of saline infusion to maximize diuresis and to prevent over-infusion of saline. Finally, the FMS transfers the adjusted urine output rate to the Diuretic Infusion Software running on the Touchscreen Computer.

The Diuretic Infusion Software uses the adjusted urine output rate to adjust the target urine rate for subsequent suggestions to restart the dose finding algorithm, and to adjust suggestions for therapy escalations described below. Note that the adjusted urine output rate is not used to adjust suggestions to stop therapy.

8.1.3 THERAPY TRANSITION PHASE

At the start of therapy, the treating physician enters an estimate of the volume of fluid to be removed from the patient, the Estimated Excess Fluid Volume. Determination of the Estimated Excess Fluid Volume relies on the healthcare professional's estimation of the patient's dry weight. The treating healthcare professional will estimate dry weight based on their training, clinical experience, the subject's medical records, and discussion with the subject. The Estimated Excess Fluid Volume is used by the Therapy Transition Algorithm to compare to the actual fluid removed from the patient during therapy to determine the percentage of the Estimated Excess Fluid Volume that has been removed. The system expects an update to this estimate approximately every 24 hours of therapy to allow the physician to adjust the estimate as the patient's care progresses.

When the system has completed the Dose Finding Phase and is running in the Continuous Infusion Phase, the system regularly checks the percentage of the Estimated Excess Fluid Volume that has been removed as well as the volume of fluid remaining to be removed. Based on the result and a low urine output signal, one of the following two actions are taken:

- If < 80% of the Estimated Excess Fluid Volume removed AND > 1L of The Estimated Excess Fluid Volume remaining, then start Dose Escalation Algorithm.
- If >80% of the Estimated Excess Fluid Volume removed OR < 1L of The Estimated Excess Fluid Volume remaining, then start Therapy Stopping Algorithm.

The goal of the first rule is if the fluid removed is well below the target, to check if an escalation of therapy is warranted. The goal of the second rule is if the fluid removed is nearing the target, to check if a stopping of therapy is warranted.

8.1.3.1 DOSE ESCALATION

As the system runs in the Continuous Infusion Phase, every minute the Dose Escalation Algorithm checks to see if the system is currently infusing the maximum furosemide dose of 40 mg/hr and if the urine output rate has been below the low urine threshold for the last three hours. If these conditions have been met, and the Estimated Excess Fluid Volume has been updated by the physician within the previous 30 hours, the system alerts the health care professional that urine output is low. In such scenario, an oral/IV thiazide diuretic can be administered to the patient. First dose must use moderate dose thiazide or thiazide like diuretics (either 100mg oral hydrochlorothiazide, 50mg oral chlorthalidone, 10mg oral metolazone, 500mg IV chlorothiazide, or 1000mg oral chlorothiazide) in either group. Investigators can then administer any diuretic at any dose after this initial dose. If the patient is not currently on a thiazide diuretic, there are three possible paths:

- If it is determined that the patient has met stopping criteria, then therapy should be stopped manually.
- A thiazide diuretic may be administered. The low urine alert is cleared, the healthcare professional logs on the DMS that a thiazide was administered, therapy continues in the Continuous Infusion Mode, and the system will wait three hours before restarting the check for low urine output.
- If it is determined that the low urine output reading is incorrect, the healthcare professional can clear the low urine alert, therapy continues in the Continuous Infusion Mode, and the system will wait three hours before restarting the check for low urine output.

The decisions to escalate therapy are always at the discretion of the healthcare professional. This is intended to provide the safest possible therapy to the patient as any increase in the therapy is decided by the healthcare professional who is at the bedside and is able to assess the clinical state of the patient.

8.1.3.2 THERAPY STOPPING ALGORITHM

If the percentage of the Estimated Excess Fluid Volume is greater than 80% **or** there is less than one liter of the Estimated Excess Fluid Volume remaining, the system runs the Therapy Stopping Algorithm.

As the system runs in the Continuous Infusion Phase, every minute the Therapy Stopping Algorithm checks to see if the system is currently infusing the high furosemide dose of 30 mg/hr and if the urine output has been below 325 ml/hr for the last three hours. If these conditions have

been met, the system alerts that the urine output is low, and that the system will stop automatically in one hour. At this stage, there are four possible actions that can be taken:

- Therapy can be stopped immediately.
- If no action is taken, the therapy will stop automatically in one hour.
- If it is believed that the low urine output reading is incorrect, the healthcare professional can clear the low urine alert, therapy continues in the Continuous Infusion Mode, and the system will wait three hours before restarting the check for low urine output.
- The physician can modify the Estimated Excess Fluid Volume such that the remaining fluid to be removed is greater than one liter. The low urine alert will then be cleared, therapy continues in the Continuous Infusion Mode, and the system will wait three hours before restarting the check for low urine output.

The Therapy Stopping Algorithm is designed to stop therapy automatically if the patient's urine output has been low for three hours while on a high continuous dose of furosemide, and the urine output is close to reaching the physician-set Estimated Excess Fluid Volume. At this point the healthcare professional can choose to continue therapy if they feel that the low urine output reading was incorrect or can extend therapy if they feel that the Estimated Excess Fluid Volume is too low and the patient has more fluid to be removed. In all cases, the healthcare professional has control over whether to continue or stop therapy.

8.1.4 OUTPATIENT DOSING IN PATIENTS RANDOMIZED TO DMS

For patients randomized to DMS therapy, the discharge diuretic dose cannot be less than the ramp defined dose. For subjects who present with a high home dose of oral loop diuretics and are treated with thiazide/thiazide like diuretics before DMS therapy, the discharge dose cannot be less than the home dose. The exception to this is if there a strong clinical indication to use a lower dose (i.e., known prior non-compliance, AKI with higher dose, etc.). It is recommended that the ramp defined dose should be transitioned to oral torsemide on a 2:1 basis (i.e., 200mg furosemide = 100mg torsemide). Conversions for oral diuretics should be the following:

	Bumetanide	Torsemide	Furosemide
Intravenous	1 mg	20 mg	40 mg
Oral	1mg	20 mg	80 mg

Torsemide will be given once daily at the ramp defined dose unless one of the following criteria are met, in which case it will be given twice daily:

1. The patient's urine output in the two hours following the ramp was < 1L.

2. The patient has signs or symptoms of continued volume overload (above dry weight, residual edema, etc.)

8.2 OPTIMAL DIURETIC THERAPY (ODT)

Consider best practices of optimal diuretic dosing as demonstrated in recent randomized trials (DOSE[31], ADVOR[32], CLOROTIC[33]). The Reprieve DMS can infuse a maximum dose of 1,120 mg/day of furosemide. It is recommended that subjects randomized to ODT should also not exceed maximum dose of 1,120 mg/day of furosemide

Trial	**Dosing Recommendation**
Dose Trial (High dose Arm)	• 2.5 times their total daily oral loop diuretic dose in furosemide equivalents
ADVOR Trial	• 2 times their home dose + Acetazolamide • Transition to 1 x home dose + Acetazolamide one day after treatment initiation • *Dose of Acetazolamide: 500 mg once daily*
CLOROTIC Trial	• IV furosemide at the same outpatient oral dose by intermittent bolus every 12 hours + Hydrochlorothiazide • After 24-48 hours, physicians can maintain current therapy or increase/decrease dose by 25% based on their medical judgement. • *Dose of hydrochlorothiazide: estimated glomerular filtration rate (eGFR) >50 mL/min: 25 mg daily; 20–50 mL/min: 50 mg daily; and <20 mL/min: 100 mg daily.*

Consideration can be given to use up-front oral long half- thiazide diuretic appropriate adjustment of IV loop diuretic dose in patients receiving high dose loop diuretic prior to enrollment *(≥ 240 mg furosemide, 3 mg bumetanide, or 60 mg torsemide per 24 hours)*

8.3 REPRIEVE DMS AND ODT GROUPS

After 72 hours, any intravenous diuretic treatment in Reprieve DMS, and ODT randomized therapy groups will be performed at the investigator's discretion and is not protocol-driven.

As standard background therapy, all patients must receive 2 g daily sodium diet and a 2 L daily oral fluid intake restriction, in addition to strict fluid input and output recording and daily weights.

The study investigators are allowed to manage subject's other comorbidities, such as hypertension and diabetes, per their standard of care and based on their medical judgement for both Reprieve DMS and ODT groups. All medications and any subsequent changes during trial participation will be documented in the study case report forms.

9 STUDY INTERVENTION SUSPENSION/TERMINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 SUSPENSION / TERMINATION OF STUDY INTERVENTION

9.1.1 TREATMENT SUSPENSION

The DMS or ODT treatment shall be suspended or terminated if any of the following criteria are observed for greater than 15 consecutive minutes:

- Progressive dyspnea or respiratory failure
- Sustained systolic pressure <80mmHg; or
- Symptomatic hypotension; or
- Hemodynamic instability that in the opinion of the investigator requires treatment suspension or termination.
- ≥ doubling of serum creatinine from the baseline value.
- Electrolyte abnormality(s) uncorrectable with standard therapy that in the opinion of the investigator require treatment suspension or termination.
- Increase in serum sodium >12 mmol/L per day.

All of the safety mitigation techniques shall be utilized to ensure safe operation of the Reprieve DMS to optimize diuresis.

9.2 TREATMENT TERMINATION

Therapy with either DMS or ODT will be stopped upon:

- Achieving the patient's optimal volume status per the investigator. Patients' optimal volume status is defined as either euvolemia, or continued hypervolemia but further treatment limited by worsening clinical status (e.g., worsening kidney function or hypotension).
    - Additionally, DMS patients should have urine output of < 325 mL/hr. with either: 1) a non-productive second diuretic ramp (UOP returns to <325/hr. within 3 hours) or 2) the patient is already at maximal furosemide dose.
- Worsening heart failure requiring higher level of HF therapy (e.g., addition of inotropes [only for treatment of hypotension or low cardiac output] aside from dopamine

<5mcg/kg/min, mechanical support, ultrafiltration or renal replacement therapy, mechanical ventilation, etc.).

9.3 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Disease progression which requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The subject wishes to withdraw their consent for participation in the study.

The reason for subject discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF).

9.4 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for follow-up and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study follow-up visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (3 telephone calls and a certified letter to the subject's last known mailing address). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 SCREENING/BASELINE

Screening activities should be performed as close to randomization as possible. All screening activities, with the exception of informed consent and pregnancy test (where applicable), must be repeated if the subject is not randomized within 24 hours of screening.

- Assessment of Eligibility Criteria
- Informed Consent
- Weight assessment
  - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
- *Clinical estimate of excess volume*
- Medical History
- *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)*
- Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
- Pregnancy testing (if applicable)
- Serum Clinical Pathology (Comprehensive metabolic panel, Magnesium)
  - Site will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples. Lab results must be obtained within 24 hours of informed consent.
- Review of concomitant medications, including diuretics
- *Oral diuretic dosing.* Sites will also document the ODT dosing if the subject is randomized to ODT arm.
- Auditory testing
- KCCQ Questionnaire
- Dyspnea score (using 5 and 7-point Likert Scale)

Note: Items in italics must be completed by a physician or another advanced practitioner

10.2 ASSESSMENTS DURING RANDOMIZED THERAPY (REPRIEVE DMS OR CONTROL)

- Initiation of Randomized Treatment (within 60 minutes of start of therapy)
    - Randomization – Randomized treatment must start within 12 hours of randomization.
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium, NT-proBNP, RAAS Markers)
        - Site will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples. Samples for NT-proBNP and RAAS Markers will be processed and sent to a core lab.
        - Serum Sodium level must be monitored every 8 hours if baseline level was 125-130 mEq/l.
    - Urine Sample Collection
        - Sites will process samples for analysis by core lab (Na, K, Cl, Creatinine, Specific gravity, Osmolality)
    - Adverse Event Evaluation
- During Randomized Treatment (whenever the urine bag is emptied)
    - Urine Sample Collection
        - Urine collection and urine sodium analysis will be performed by site's local laboratory.
- During Randomized Treatment (every 12 hours ± 4 hour)
    - Serum Clinical Pathology (Comprehensive metabolic panel, calcium, magnesium)
        - Sites will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples.
    - Fluid Balance (Replacement fluid input, Other IV input, Oral intake, Urine output, other output)
    - Adverse Event Evaluation

- <u>During Randomized Treatment (every 24 hours ± 4 hours)</u>
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - Urine Sample Collection
        - 24-hour urine collection and analysis will be performed by site's local laboratory (Na, K, Cl, Creatinine, Specific gravity, Osmolality).
    - Review of concomitant medications, including diuretics
- <u>During Randomized Treatment (every 24 hours ± 12 hr) – To be conducted by PI/Sub-I</u>
    - Clinical estimate of excess volume
    - Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)
- <u>Post-Randomized Treatment (within 12 hours after treatment end)</u>
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - Fluid Balance (Replacement fluid input, Other IV input, Oral intake, Urine output, other output)
    - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium)
        - Site will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples.
    - Urine Sample Collection
        - Total amount of urine will be collected from last collection time point (e.g., 24-hours during treatment) and within 12 hours after treatment completion. Analysis will be performed by site's local laboratory (Na, K, Cl, Creatinine, Specific gravity, Osmolality).
    - KCCQ Questionnaire

- Dyspnea score (using 5 and 7-point Likert Scale)
- Adverse Event Evaluation
- Review of concomitant medications, including diuretics

Note: These assessments are not required if the subject is discharged within 12 hours of treatment completion. Only discharge assessments must be completed in such a scenario.

- Post-Randomized Treatment (within 24 hours after treatment end) – To be conducted by PI/Sub-I
  - Clinical estimate of excess volume
  - Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)

Note: These assessments are not required if the subject is discharged within 12 hours of treatment completion. Only discharge assessments must be completed in such a scenario.

- Day 7 (± 12 hours) Post-treatment Initiation (Only required if the subject is still hospitalized)
  - Weight assessment
    - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
  - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
  - *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)*
  - Fluid Balance (Replacement fluid input, Other IV input, Oral intake, Urine output, other output)
  - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium)
    - Sites will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples.
  - *Oral diuretic dosing and rationale*
  - Review of concomitant medications, including diuretics
  - Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

- Discharge
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)*
    - Fluid Balance (Replacement fluid input, Other IV input, Oral intake, Urine output, other output)
    - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium, NT-proBNP, RAAS Markers)
        - Sites will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples. Samples for NT-proBNP and RAAS Markers will be processed and sent to a core lab.
    - Urine Sample Collection
        - Sites will process samples for analysis by core lab (Na, K, Cl, Creatinine, Specific gravity, Osmolality).
    - *Oral diuretic dosing and rationale*
    - Auditory testing
    - KCCQ Questionnaire
    - Dyspnea score (using 5 and 7-point Likert Scale)
    - Review of concomitant medications, including diuretics
    - Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

Additional Data Collection: Reprieve DMS Device Log Files

- Reprieve DMS device log files will be submitted to Reprieve Cardiovascular for patients receiving DMS therapy. Log files may be used for characterization of device operation and system diagnostic purposes. No specific pre-defined analysis will be performed on this device log file data.

10.3 ASSESSMENTS POST-DISCHARGE/FOLLOW-UP

- 7 Days Post-Discharge Follow-Up (± 2 Days)
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)*
    - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium)
        - Site will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples
    - Review of concomitant medications, including diuretics
    - *Oral diuretic dosing and rationale*
    - Auditory testing
    - KCCQ Questionnaire
    - Dyspnea score (using 5 and 7-point Likert Scale)
    - Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

- 30 Day Post-Discharge Follow-Up (± 5 Days)
    - Weight assessment
        - Use standing weight using standardized scales. Use of alternate methods (bed scales, etc.) is allowed if it is not possible to obtain standing weights.
    - Hemodynamics (BP (Systolic/Diastolic/MAP), Heart rate, Respiratory Rate, Pulse O_2 Saturation)
    - *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, Pleural Effusion, NYHA Class)*
    - Serum Clinical Pathology (Complete blood count, Comprehensive metabolic panel, Calcium, Magnesium)
        - Site will use site's clinical pathology laboratory (per Institutional methods) for testing serum samples

- Review of concomitant medications, including diuretics
- *Oral diuretic dosing and rationale*
- KCCQ Questionnaire
- Dyspnea score (using 5 and 7-point Likert Scale)
- Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

- 90 Day Post-Discharge Follow-Up (± 5 Days) – Can be conducted over phone
  - Review of concomitant medications, including diuretics
  - Oral diuretic dosing
  - Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

- Unscheduled Visit: In the event the patient presents during the follow-up period outside of the protocol-specified visits, the following minimum information is recommended to be collected, to the extent possible:
  - *Targeted Physical Exam (SOB, Dyspnea VAS, Rales, JVP, Leg Edema, Sacral Edema, Ascites, NYHA Class)*
  - Hemodynamics (manual BP: Systolic/Diastolic, Heart rate, Respiratory Rate, Pulse O_2 Saturation)
  - Review of concomitant medications, including diuretics
  - *Oral diuretic dosing and rationale*
  - Adverse Event Evaluation

Note: Items in italics must be completed by a physician or another advanced practitioner

Any out-of-range lab values for protocol-specified clinical pathology (serum or urine chemistry assays) obtained following randomization should be assessed for clinical significance or not. Clinical significance is defined as any variation in a result that has medical relevance and requires an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an Adverse Event (AE) Case Report Form completed.

10.4 ADVERSE EVENTS (AE)

Throughout the study, the Investigator or designee will determine adverse event (AE) occurrences.

An **Adverse Event** is any undesirable clinical occurrence or change from subject's baseline in a subject regardless of relationship to the device or procedure. Each adverse event is considered to be either anticipated or unanticipated as described below. The site is required to report the classes of Adverse Events that occur in the study, described below.

These events shall also be classified according to the suspected causality by the study Investigator.

Investigational Device/Therapy Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the investigational device and/or therapy received during randomized treatment.

Non-Investigational Device Related Adverse Event: An adverse event which, in the judgment of the Investigator, it is reasonable to believe that the event is associated with an accessory device used during the randomized index treatment procedure and is not specific to the investigational device or therapy use.

Not Related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Unknown: If the Investigator cannot determine the cause of the event, it should be classified as unknown.

10.4.1 UNANTICIPATED ADVERSE DEVICE EFFECT

Any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.4.2 SERIOUS ADVERSE EVENT (SAE)

A **Serious Adverse Event** (SAE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening illness or injury
- Permanent impairment of a body structure or body function
- Inpatient hospitalization or prolongation of existing hospitalization

- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Fetal distress, fetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

10.5 CLASSIFICATION OF AN ADVERSE EVENT

10.5.1 SEVERITY OF EVENT

For adverse events (AEs) the following guidelines will be used to describe severity.

Mild:	Adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with activities of daily living.
Moderate:	Adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to research subject.
Severe:	Adverse event that interrupts activities of daily living, or significantly affects clinical status or may require intensive therapeutic intervention.

10.5.2 EXPECTEDNESS

The investigator, in conjunction with the study sponsor or designee, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

10.6 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At the follow up study visits, the investigator or designee will query the subject about the occurrence of AE/SAEs since the last visit. The occurrence of an adverse event (AE) or serious adverse event (SAE) may also come to the attention of study personnel during interview of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including events not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and recorded as medical history on the applicable CRF and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator or designee is required to complete the adverse event Case Report Form(s) at each study visit, if an adverse event occurs. One adverse event CRF must be completed for each adverse event. The Investigator should report all serious adverse events to the IRB as required per IRB requirements.

All adverse events must be reported to the Sponsor no later than 10 working days of site's first knowledge of the event. Any SAE, UADE or device deficiency must be reported to the Sponsor no later than 72 hours of site's first knowledge of the event.

11 STATISTICAL CONSIDERATIONS

11.1 STATISTICAL OVERVIEW

This is a pilot study designed to primarily assess the safety and efficacy of the Reprieve Decongestion Management System to treat acute decompensated heart failure in patients admitted to the hospital or presenting to the Emergency Department. A target total sample of 100 subjects treated at up to 15 different sites in the United States is expected to provide meaningful data for the design of future trials. Subjects will be randomized 1:1 to DMS or ODT and the randomization will be stratified based on site and planned ODT diuretic dose therapy.

11.2 POPULATIONS FOR ANALYSES

The study population will include subjects with variable home dose of diuretics. All study analysis will be conducted by dividing the subjects in two cohorts; subjects who present with $\leq$ 80 mg of Furosemide equivalent at baseline and subjects who present with >80 mg of Furosemide equivalent dose at baseline. Sponsor will continue to monitor the patients enrolled in both cohorts and make any adjustments as needed to have a balanced cohort.

Intent-to-Treat (ITT)

The Intent-to-Treat population (ITT) will consist of all DMS subjects who have undergone randomization. Subjects in the ITT population in whom the Reprieve Decongestion Management System was connected to the subject but not turned on, will be followed through 30 days for safety purposes. These subjects will not be included in any efficacy endpoint analyses but will be included in a secondary safety analysis. Adverse events will be reported for all ITT subjects through 30 days. Subjects will be analyzed according to the treatment to which they were randomized.

As Treated Population

Subjects will be included in the As Treated Population group if they sign the ICF and the Reprieve Decongestion Management System is connected to the subject and turned on. The As Treated population represents the Primary Safety Analysis population for the study since all of these subjects will have received treatment with the DMS. However, if a subject is identified to not be responding to diuretic treatment after the initial two hours of administration of medication, the subject is deemed to need more aggressive treatment and is therefore withdrawn from the study.

Modified Intent-to-Treat (mITT)

Subjects will be included in the Modified Intent-to-Treat group if they sign the ICF and the Reprieve Decongestion Management System is connected to the subject and turned on and have demonstrated to be a responder to diuretic treatment (average > 50 ml/hour urine production) within the first two hours of therapy.

11.3 STATISTICAL ANALYSES

11.3.1 GENERAL APPROACH

All final study analyses will be performed when all subjects have completed the 90-day follow-up visit. All safety and performance analyses will be performed on the ITT, As Treated and mITT analysis sets.

11.3.2 ANALYSIS OF THE PRIMARY ENDPOINT

Reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to subjects lost to follow-up or noncompliance with required assessments. Any missing data on study endpoints will be described. Study endpoints will be analyzed using all available data. Data will be summarized using descriptive statistics. There are no planned formal statistical analyses. Reprieve is also planning interim looks at the data using the analysis methods mentioned above.

11.3.3 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Data points obtained for individual subjects will be listed by measure and timepoint, as appropriate.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB/EC, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, or FDA, as applicable.

The Sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All patients already enrolled should continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final follow-up visit of the last enrolled patient.

The Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

12.1.1 CONFIDENTIALITY AND PRIVACY

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The principal investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the principal investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

12.1.2 SAFETY OVERSIGHT

The study will utilize an Independent CEC) and DSMB. The CEC will be charged with adjudicating clinical safety events. The main objective of the DSMB is to advise regarding the continued safety of the subjects and those yet to be recruited to the trial; and to ensure the validity and scientific merit of the trial. The details around CEC and DSMB will be documented in the respective charters.

The physician members of the CEC will be responsible for the review and validation of reported adverse events that are related to device and/or procedure along with serious adverse events. The CEC shall classify each of these adverse events based on severity and association to the device and/or procedure. During the review of the events, the CEC shall be blinded to the clinical site as much as possible. A CEC Charter will be developed prior to the start of study enrollment. The Charter shall include consistent definitions for each type of event and shall outline the review process.

In addition, the DSMB shall review aggregate data to monitor overall safety of the study. In this safety monitoring role, prior to enrollment of any subjects, the DSMB will establish in the charter aspects which may include operating procedures and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed study stopping rules. The specific stopping rules shall remain confidential to the sites and Sponsor to minimize bias. Written minutes of all meetings related to monitoring overall safety of the study shall be developed after each meeting and major conclusions (i.e. the assessment for study continuation vs. stopping) shall be documented.

13 SITE/INVESTIGATOR TRAINING

The Sponsor together with CRO will provide training to the investigator and appropriate clinical site personnel. Training is designed to ensure uniform data collection and protocol compliance. Study initiation visits to review the clinical protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, methods for soliciting data from alternative sources, review of clinical assessment of excess volume (including JVP), review of medical therapy for heart failure, and schedules for follow-up with study site personnel will be reviewed. This initiation/ training is aimed to take place at the same time as device/procedure training. Training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this trial are trained.

14 MONITORING

It is the responsibility of Reprieve to ensure proper monitoring of this trial. Participating sites will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. Monitoring visits may be conducted both on site and remotely, primarily to ensure the safety and well-being of the subjects is preserved, as well as to assess study site progress periodically, the investigator's adherence to the CIP, regulatory compliance, maintenance of records and reports, and review and verification of source documents against subject CRFs in accordance to the study-specific monitoring plan. Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring visits will also be used to verify that data submitted on case report forms are complete and accurate with respect to the subject clinical records and to verify device accountability. Sites should provide appropriate access to the source data. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur via a risk-based approach as outlined in the Monitoring Plan.

The progress of the trial will be monitored by:

• On-site or remote review, as deemed appropriate by Reprieve and as described in the monitoring plan

• Telephone communications between the site personnel (e.g., investigator, trial coordinator) and trial monitors

• Review of eCRFs and the associated clinical records

• Review of regulatory documents

Upon study completion, Site Closeout Visits will be conducted as outlined in the Monitoring Plan.

Monitoring and monitoring oversight will be provided by Syntactx, LLC (4 World Trade Center, 150 Greenwich Street, 44th floor, New York, NY 10007). Prior to the first site activation, a monitoring plan will be established outlining the above activities, as well trial materials to be supplied to sites, the process for corrective and preventive actions and Investigator disqualification procedures.

15 REGULATORY AGENCY INSPECTION

If an investigator is contacted by a regulatory agency regarding this study, the investigator will notify the Sponsor or its designee immediately. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The investigator must provide the Sponsor or designee with copies of all correspondence that may affect review of the current trial (e.g., Form FDA 483, Inspectional Observations and Warning Letters). The Sponsor may provide needed assistance in responding to regulatory audits.

16 DEVICE AND DATA HANDLING/STORAGE

16.1 INVESTIGATIONAL DEVICE ACQUISITION AND ACCOUNTABILITY

The investigational system includes the Reprieve Decongestion Management System Console as well as the disposable items (IV administration set and Urine Bag). All components of the system will be distributed by the study sponsor, Reprieve Cardiovascular, Inc. Access to investigational product shall be controlled and the investigational product shall be used only in the clinical investigation and according to this Clinical Investigational Plan (CIP). The sponsor shall keep records to document the physical location of all investigational product from shipment of investigational product to the investigational sites until return or disposal. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational product, which shall include:

- the date of receipt
- identification of each investigational product (batch number/serial number or unique code)
- the expiry date, if applicable
- the date or dates of use
- subject identification
- date on which the investigational product was returned, if applicable, and
- the date of return of unused or expired investigational product, if applicable.

16.2 DATA HANDLING AND RECORD KEEPING

16.2.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Each participating site will maintain appropriate medical and research records for this trial, in compliance applicable regulations and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), the sponsor's designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial.

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Electronic Case Report Forms are used for the collection and recording of data at all Investigative Centers. Investigators are responsible for the timely completion and updating the case report forms.

Incoming data are reviewed to identify inconsistent or missing data and adverse events. Data issues will be addressed via data queries within the data management system with the investigative Centers and/or during site visits. All hard copy forms and data files will be secured to ensure confidentiality.

Development of the primary database for the study will be performed by CRO, a designee of the Sponsor. CRO will also be responsible for the verification, validation and quality control of the database and confirming the overall integrity of the data.

Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study patient's medical records that corroborate data collected on the CRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study investigator, study name, patient number assigned and a statement that consent was obtained.

- Dated and signed notes from each study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).
- Information related to adverse events.
- Study patient's condition upon completion of or withdrawal from the study.
- Discharge summaries/procedure reports.

16.2.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

17 INVESTIGATOR RECORDS

Investigators will maintain complete, accurate and current study records. Records shall be maintained during the clinical study and for two years (or as required by Sponsor/Regulators after the later of the date on which the study is terminated or completed, or the date the records are no longer required to support FDA approval of the device). Investigator records shall include the following materials:

- Correspondence: Documentation of all verbal and written correspondence with FDA, the Clinical Monitor, the independent physician adjudicator, and other investigators regarding this clinical study or any subject enrolled therein.
- Subject Records: Signed informed consent forms, copies of all completed Case Report Forms and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50) or 45 CFR part 46, as applicable.
- Clinical Investigational Plan/Protocol: A current copy of the Clinical Study Protocol including Instructions for Use of the device system and blank case report forms.
- Ethics Committee (EC)/Institutional Review Board (IRB) Information: All information pertaining to IRB/EC review and approval of this clinical study including a copy of the IRB/EC letter approving the clinical study, a blank informed consent form approved by the IRB/EC, and certification from the IRB/EC Chairman that the IRB/EC complies with FDA regulations (21CFR, part 56)/regulatory body regulations, and that the IRB/EC approved the clinical study protocol based on the Report of Prior Investigations.

- Investigator Agreements: Copies of signed Investigator, Co-investigator and Sub-Investigator Agreements with accompanying curriculum vitae.
- Other: Any other records that may be required by applicable state or federal laws.

18 INVESTIGATOR REPORTS

The PI is responsible for signing of all electronic CRFs (e-CRF) and adverse event reporting to IRB per local requirements (see table 10-2). If based on reported information, any action is taken by an IRB with respect to the study, the information must be forwarded to the sponsor.

The PI is responsible for the preparation and submission of the reports cited in the following table. Reports must be prepared in a complete, accurate and timely manner. These reports may be subject to inspection and copying by regulatory authorities and sponsor, and the retention requirements described above for Investigator Records. In addition to the reports listed in the following table, relevant regulatory authorities or the reviewing IRB may request reports pertaining to any aspect of the clinical study.

Table 2: Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator for	Time of Notification
Enrollment Notification	Sponsor	Within 48 hours of procedure
Case Report Forms	Sponsor	Within 14 working days of the corresponding study visit
Adverse Event	Sponsor and IRB (as required)	No later than 10 working days of knowledge
Serious Adverse Event	Sponsor and IRB (as required)	Immediately, but no later than 72 hours of knowledge
Unanticipated Adverse Device Event	Sponsor and IRB (as required)	Immediately, but no later than 72 hours of knowledge
Patient Death	Sponsor and IRB (as required)	Immediately, but no later than 72 hours of knowledge
Withdrawal of IRB/EC	Sponsor	Within 48 hours of knowledge
Medical Emergencies	Sponsor and IRB (as required)	Immediately, but no later than 72 hours of knowledge
Other information upon the request of Sponsor, EC/IRB, and/or FDA/applicable regulatory authority	As appropriate	As requested

19 SITE AND INVESTIGATOR SELECTION

The Sponsor selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. Investigational sites will be selected using combined current assessments of site and investigator qualifications. Following factors will be considered in selecting a site to participate in the trial:

- Dedicated heart failure program.
- Qualified investigators in terms of education, training and experience to conduct the trial in patients with ADHF.
- Availability of a qualified investigator for all trial-related medical decision, to adequate supervise the trial, and to protect safety and welfare of the subjects.
- Dedicated research staff with time and availability for the conduct of the study.
- Adequate facilities and equipment to support trial-related activities.

Following information will be collected from the study investigators prior to their participation in the trial.

- Investigator's curriculum vitae.
- A statement of the investigator's relevant experience, including the dates, location, extent, and type of experience
- If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
- A statement of the investigator's commitment to:
    - Conduct the investigation in accordance with the agreement, the investigational plan, and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA.
    - Supervise all testing of the device involving human subjects.
    - Ensure that the requirements for obtaining informed consent are met.
- Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement.

Study investigator must prior any updated information to the Sponsor if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

20 PROTOCOL DEVIATIONS

An investigator is not allowed to deviate from the CIP/Protocol if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Under emergency circumstances, deviations from the CIP/Protocol to protect the rights, safety and well-

being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB/EC as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study patient who does not meet all the inclusion/exclusion criteria specified in the protocol or missed study visits without documentation. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, applicable regulations, Good Clinical Practices, and any conditions of approval imposed by their IRB.

All deviations are reviewed and assessed for their impact on subject safety by the Sponsor or designee. The PI and study staff are responsible for knowing and adhering to their IRB reporting requirements.

The protocol deviations for this protocol consist of, but are not limited to the following:

- Failure to obtain patient's informed consent prior to any study-related activities
- Failure to conduct protocol required clinical follow-ups
- Failure to conduct protocol required clinical follow-ups within time windows; and
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviations may result in termination of the site's study participation. Subjects enrolled at these sites will continue to be followed per the clinical protocol.

21 STUDY AUDIT(S)

The auditing of clinical investigation systems shall be conducted in accordance with the sponsor's written procedures or specific plan on what to audit, how to audit, the frequency of audits and the form and content of audit reports.

The sponsor's audit plan and procedures for a clinical investigation audit shall be guided by the importance of the clinical investigation, the number of subjects in the clinical investigation, the type and complexity of the clinical investigation, the level of risk to the subjects and any identified problem(s). The audit results shall be documented and communicated to relevant parties, if applicable.

22 PUBLICATION AND DATA SHARING

This study will be conducted in accordance with the following publication and data sharing policies and regulations: Trial Information and the Clinical Trials Registration and Results

Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in a peer-reviewed journal(s).

The Sponsor manages its clinical studies in an ethical and rigorously scientific manner, working with leading experts in the field, to demonstrate the benefits, risks, and value of the Reprieve Decongestion Management System clearly and publicly to caregivers and study patients alike. The sponsor accepts the obligation to facilitate publication of medically important clinical data in a timely, objective, accurate, and balanced manner, regardless of the outcome of this trial. To ensure that an accurate record of the study data is presented to the public, the Sponsor understands the need to allow sufficient time, for careful preparation, analysis, interpretation, and review of study data and reports prior to their dissemination.

23 ABBREVIATIONS

ADE	Adverse Device Event
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
Cl	Chloride
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRO	Clinical Research Organization
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy

CVP	Central Venous Pressure
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DMS	(Reprieve) Decongestion Management System
DNVR	Desired Net Rate of Volume Removal
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Form
ED	Emergency Department
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGTP	Gamma-Glutamyl-Transpeptidase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HF	Heart Failure
HR	Heart Rate
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IL-18	Interleukin-18
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISOC	Independent Safety Oversight Committee
ITT	Intention-To-Treat
IV	Intravenous

JVP	Jugular Venous Pressure
K	Potassium
KIM-1	Kidney Injury Molecule-1
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-To-Treat
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
Mg	Magnesium
Na	Sodium
NAG	N-acetyl beta-D-glucosaminidase
NCT	National Clinical Trial
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NT-proBNP	N-terminal pro b-type natriuretic peptide
ODT	Optimal Diuretic Therapy
PA	Pulmonary Artery
PI	Principal Investigator
POC	Point of Care
QA	Quality Assurance
QC	Quality Control
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOA	Schedule of Activities
SOC	System Organ Class

SOP	Standard Operating Procedure
TRUP	Target Rate of Urine Production
UADE	Unanticipated Adverse Device Effect
UF	Ultrafiltration
UOP	Urine Output
US/USA	United States / United States of America

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