CLINICAL STUDY PROTOCOL

Interventional Drug or Biologic

Torsemide comparison with Furosemide for management of patients with stable heart failure

Protocol Number

HIC 2000029589

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Confidentiality Statement:

REVISION HISTORY:

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Synopsis

Primary Objective

The primary objective of this study is to compare the effects of two standard of care loop diuretics (furosemide versus torsemide) on clinical outcomes among patients currently on a stable dose of loop diuretics. All patients will be followed for one year.

Our primary hypothesis is that torsemide will improve clinical outcomes when compared to furosemide.

Secondary Objective (if applicable)

Secondary objectives of this protocol will be to examine the effect of torsemide versus furosemide for the following endpoints:

All-cause mortality or all-cause hospitalization over one year

Total hospitalizations over one year

Change in weight over one year

Study Duration

Subject enrollment is planned to last 4 years. Completion of enrollment, statistical analysis, and publication is planned to be complete within 6 years.

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Study Design

This study will be a randomized, unblinded, two-arm, multi-center clinical trial of patients receiving loop diuretics for treatment of heart failure in an outpatient clinic. This study will serve as additional enrollment for Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORMHF Mechanistic Sub-Study (HIC 2000025867) which is currently only enrolling patients admitted to the hospital for worsening heart failure. Thus allowing for expanded enrollment into HIC 2000025867 with a more diverse group of heart failure patients. Participants will be co-enrolled into this study and HIC 2000025867.

Patients will be randomized 1:1 to either oral torsemide OR oral furosemide (dosing at discretion of local provider with dose equivalency guidance provided). This study will include stable subjects seen at the outpatient setting. The initial and follow-up dosing of torsemide and furosemide will be at healthcare provider discretion, with the following conversion provided as a guide: 1 mg torsemide to 2-4 mg oral furosemide. For instance, a patient would receive torsemide 20mg or furosemide 40-80 mg. Providers will be asked to document their planned initial dose and dosing frequency of torsemide and furosemide

Randomization will occur within thirty days after the consent process and at the discretion of the healthcare provider and research team. Following randomization, the study medication is expected to constitute the oral diuretic therapy for one year. Patients will be prescribed the randomized study medication on the day of randomization.

Dose adjustments will be at the discretion of the treating healthcare provider(s) with strategies in place to maintain prescription of and adherence to the randomized medication. All patients will have 30-day, and 12-month post-randomization phone contacts for assessment of vital status, interval hospitalizations, concomitant HF medications, adherence, and weight.

To achieve these goals, we propose a multi-center 125-patient study that will also co-enroll into Transform Ancillary (HIC 2000025867) a mechanistic sub-study of this study and TRANSFORMHF.

Number of Study Sites

Three

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Study Population

The population will enroll participants that are being treated in YNHH outpatient clinics for heart failure. Eligible patients will be under the care of Yale cardiologists or heart failure clinicians at an outpatient clinic. The diagnosis of heart failure utilized will be the responsibility of the treating clinician.

Number of Participants

The overall enrollment goal for all sites is 125 participants. The enrollment goal for the University of Utah is 25 participants. The enrollment goal for Yale University is 100 participants.

Primary Outcome Variables

All-cause mortality

Secondary and Exploratory Outcome Variables (if applicable)

All-cause mortality or all-cause hospitalization over one year

Total hospitalizations over one year

Change in weight

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1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to (International Conference on Harmonisation-Good Clinical Practice) ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

2 Background

2.1.1 Preclinical Experience

Preclinical and clinical data support the benefits of torsemide over furosemide. Compared with furosemide, torsemide has increased bioavailability and a longer half-life with

maintained absorption in the setting of oral intake.1 Torsemide also has beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular remodeling and natriuretic peptide levels.2-6 Several small studies of torsemide vs. furosemide and two recent meta-analyses suggest a substantial decrease in heart failure morbidity and potentially mortality with torsemide compared to furosemide 7,8-10.

2.1.2 Clinical Experience

Background/prevalence of research topic

Nearly 7 million Americans are affected with heart failure (HF), and its prevalence is expected to increase to nearly 10 million by 2030.11 At age 40, an American's lifetime risk of developing HF is 1 in 5.11 HF causes tremendous morbidity and mortality, with over 1 million hospitalizations in the U.S. each year and with HF listed on 1 in 9 death certificates respectively.11 While HF is generally regarded as the inability of the heart to pump sufficient blood, on a population level, congestion is the primary driver of symptoms leading to hospitalization.12-15

Strategies to treat and prevent fluid/sodium retention have not changed significantly since the 1960's with the introduction of loop diuretics. Despite the fact that loop diuretics are central to our therapy in HF, they are paradoxically one of the least well-studied classes of HF medications.

Torsemide has theoretical pharmacokinetic (PK) advantages to furosemide: Furosemide is currently the mostly commonly prescribed loop diuretic but it has erratic absorption, with bioavailability reported to range from 10%. to 100%.**16,17** Additionally, even if total absorption is constant, the peak serum concentration can vary widely based on the prandial and clinical status of the patient**18,19** Since, loop diuretics require a minimal threshold concentration to induce natriuresis, even with identical bioavailability, slow absorption can limit the time above the renal threshold and result in minimal natriuresis. Importantly, the variability in absorption occurs both on an inter- and intra-patient level. For instance, factors such as a large meal (i.e., sodium load) or bowel edema (i.e., progressive volume retention) can adversely alter furosemide PK parameters, when it is most important the diuretic is effective. Unlike furosemide, torsemide has consistent bioavailability of >80% and absorption kinetics are reproducible and typically approximate that of an intravenous diuretic.**18,19**Torsemide also has a significantly longer half-life in HF (~6 hours) compared to furosemide (~2.7 hours).**17** The major reason that once daily furosemide is not effective as an antihypertensive is due to post diuretic sodium retention. When a short half-life diuretic (i.e., furosemide) wears off, the kidney is left unchecked to reabsorb sodium, and the quantity of excreted sodium during diuresis equals the quantity of sodium reabsorbed after the diuretic is cleared, resulting in no net loss of sodium. Given that torsemide has predictable bioavailability, absorption kinetics, and a relatively long half-life, the hypothesis follows that it could offer more consistent and superior control of volume status, thus improving outcomes such as death and rehospitalization.

The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines indicate that the optimal use of diuretics is the cornerstone of any successful approach to the treatment of heart failure.20 However, in light of the lack of an adequately powered study, there is insufficient evidence to conclude that torsemide should be recommended over furosemide in the management of heart failure.

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3 Rationale/Significance

3.1 Problem Statement

As heart failure cases continue to grow exponentially, patients are routinely placed on furosemide as a first line therapy, potentially delaying treatment with a more effective medication (Torsemide) to relieve their fluid congestion and help prevent further sequela of heart failure.

3.2 Purpose of Study/Potential Impact

This study is designed to be a prospective, randomized, comparative-effectiveness study to definitively compare torsemide with furosemide in heart failure patients. It is meant to serve as additional enrollment in Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study (HIC 2000025867) to broaden the heart failure population to include those that are more stable in their treatment. Patients will be coenrolled into this study and HIC 2000025867.

3.2.1 Potential Risks

This study will evaluate oral torsemide versus oral furosemide in patients with heart failure. Both torsemide and furosemide are currently used in routine clinical practice and are recommended by the current ACC/AHA heart failure guidelines. We therefore do not anticipate that participation in this study will be associated with increased risks beyond that of standard heart failure therapy.

Furosemide: Risks include hepatic encephalopathy, oral and gastric irritation, cramping, pancreatitis, diarrhea/constipation, jaundice, increased liver enzymes, nausea, vomiting, anorexia, systemic vasculitis, tinnitus and hearing loss, leukopenia, thrombocytopenia, anemia, photosensitivity, drug rash, orthostatic hypotension, increase in cholesterol and triglyceride serum levels, hyperglycemia, restlessness, glycosuria, urinary bladder spasm, hyperuricemia, thrombophlebitis, severe anaphylaxis, interstitial nephritis, pruritis, paresthesias, headache, dizziness, vertigo, blurred vision, muscle spasm, fever, weakness.

Torsemide: Risks include headache, excessive urination, dizziness, rhinitis, asthenia, diarrhea, ECG abnormality, cough Increase, constipation, nausea, leucopenia, thrombocytopenia, anemia, increase in liver transaminases, thiamine (B1) deficiency, hypotension, hypokalemia, hypomagnesemia, Hypocalcemia Hyperchloremic alkalosis, Hyperglycemia, Hyperuricemia Hyponatremia, Arthralgia, Dyspepsia Sore Throat, Myalgia Chest Pain, Insomnia Edema, Nervousness, Pancreatitis, Abdominal pain, Paresthesia, Confusion, Visual impairment, Loss of appetite, Stephens- Johnsons Syndrome), Photosensitivity (sensitivity to light), Pruritis(itchy), Acute urinary retention (urine in your bladder that you have not been able to pass), Tinnitus (ringing in your ears), Hearing loss, Severe renal impairment (loss of kidneys full ability to filter wastes and excess fluids from your blood, which are then excreted in your urine).

Data collection: We anticipate minimal risk related to collection of data from the clinical record, including paper charts, EMR, physical exams, and blood and urine samples. We also anticipate minimal risk associated with data entry into the electronic database, which is password-protected and stored on a secure server.

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Urine collection for pregnancy test: There are virtually no risks to the patient related to urine collection.

Minimizing Risks

Furosemide and Torsemide: Both diuretics are currently used in routine clinical practice and are recommended by the current ACC/AHA heart failure guidelines. We therefore do not anticipate that participation in this study will be associated with increased risks beyond that of standard heart failure therapy.

Data collection: Identifying data will be available only to the study PI and study coordinator, and will be used only to facilitate medical record review, and prevent duplicate screenings of patients while looking for subjects to enroll in the study. All data sheets, electronic data entries, and laboratory samples will be labeled with a unique identifier code. These numbers will be unique to the patient and will be the common link between specimens and the data. No identifying data will be reported to the public or in any publications that may result from this research.

Urine collection for pregnancy testing: There is virtually no risk to the patient related to urine collection.

3.2.2 Potential Benefits

The drugs in this study are already used to treat heart failure and clinicians can prescribe either of these medications outside of this study. Therefore, this study will not directly benefit our subjects. However, it may help researchers learn about which diuretic is better at treating heart failure. The results of this study may benefit heart failure patients in the future.

3.2.3 Alternatives

Subjects can choose not to participate and continue receiving standard care from their treatment team.

3.2.4 Payments for Participation (Economic Considerations)

Subjects will be compensated 25 dollars for the first study visit and randomization. For each of the phone calls they will be compensated 10 dollars each, for a total study compensation of 45 dollars.
Payment will be in the form of a Bank of America prepaid card. No additional compensation will be given for transportation or parking.

3.2.5 In Case of Injury

a. Will medical treatment be available if research-related injury occurs? Yes.

b. Where and from whom may treatment be obtained? Patient's medical provider.

c. Are there any limits to the treatment being provided? Unknown.

d. Who will pay for this treatment? Patient's own insurance.

e. How will the medical treatment be accessed by subjects? Through standard contact with their health care provider.

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4 Study Objectives

4.1 Hypothesis

Our primary hypothesis is that torsemide will improve clinical outcomes when compared to furosemide in a nonacute heart failure patient population.

4.2 Primary Objective

The primary objective of this study is to compare the treatment strategy of torsemide versus furosemide on clinical outcomes after one year, among a more stable heart failure population. All patients will be followed for a up to one year. Outcomes will be collected at thirty (+2/-2) days and one year (+2/-2 days).

Secondary Objectives (if applicable)

Other secondary objectives of this protocol will be to examine the effect of torsemide versus furosemide for the following endpoints:

- All-cause mortality or all-cause hospitalization over one year
- Total hospitalizations over one year
- Change in weight over one year

4.3 Exploratory Objectives (if applicable) N/A

5 Study Design

5.1 General Design Description

Study Design

This study will be a randomized, unblinded, two-arm, multi- center clinical trial of patients receiving loop diuretics for treatment of heart failure in an outpatient clinic. This study will serve as additional enrollment for Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study (HIC 2000025867) which is currently only enrolling patients admitted to the hospital for worsening heart failure. Thus allowing for expanded enrollment into HIC 2000025867 with a more diverse group of heart failure patients. Participants will be co-enrolled into this study and HIC 2000025867.

Patients will be randomized 1:1 to either oral torsemide OR oral furosemide (dosing at discretion of local provider with dose equivalency guidance provided). This study will include stable subjects seen at the outpatient setting. The initial and follow-up dosing of torsemide and furosemide will be at healthcare provider discretion, with the following conversion provided as a guide: 1 mg torsemide to 2-4 mg oral furosemide. For instance, a patient would receive torsemide 20mg or furosemide 40-80 mg. Providers will be asked to document their planned initial dose and dosing frequency of torsemide and furosemide Randomization will occur within thirty days after the consent process and at the discretion of the healthcare provider and research team. Following randomization, the study medication is expected to

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constitute the oral diuretic therapy for one year. Patients will be prescribed the randomized study medication on the day of randomization.

Dose adjustments will be at the discretion of the treating healthcare provider(s) with strategies in place to maintain prescription of and adherence to the randomized medication. All patients will have 30-day and 12-month post-randomization phone contacts for assessment of vital status, interval hospitalizations, concomitant HF medications, adherence, quality of life, and symptoms of depression.

5.1.1 Study Date Range and Duration

Participants will be enrolled for a period of one year and enrollment is planned to last 4 years. Completion of enrollment, statistical analysis, and publication is planned to be complete within 6 years.

5.1.2 Number of Study Sites

Three

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

All-cause mortality at one-year. This will be assessed at 30 days, and one year.

5.2.2 Secondary Outcome Variables (if applicable)

- All-cause mortality or all-cause hospitalization over 12 months
- Total hospitalizations over 12 months
- Change in weight

5.3 Study Population

The study will be enrolling participants from YNHH outpatient clinics, or the Yale Transitional Care Clinic. Eligible patients will have a diagnosis of heart failure and have a continued need for diuretic treatment as an outpatient. The diagnosis of heart failure utilized will be the responsibility of the treating clinician. Patients will be approached by study personnel as listed in the IRB which can include doctors, cardiac surgeons, residents, fellows, nurse practitioners, physician assistants, research assistants and registered nurses. All patients approached will be 18 years or older and capable of providing written, informed consent. The selection criteria below were designed to be inclusive and representative of the broad heart failure population in routine clinical practice

Recruitment Methods

5.3.0 Number of Participants

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The target enrollment for this study will be 125 participants across all sites.

Inclusion/ Exclusion Criteria

Inclusion

1) Patients with a diagnosis of heart failure and who have been on a stable dose of a diuretic for at least 30 days.

2) Plan for a daily outpatient oral loop diuretic regimen with anticipated need for long term loop diuretic use
3) ≥ 18 years of age
4) Signed informed consent

Exclusion Criteria

1) End-stage renal disease requiring dialysis therapy
2) Inability or unwillingness to comply with the study requirements
3) History of heart transplant or actively listed for heart transplant
4) Implanted left ventricular assist device or implant anticipated <3 months
5) Pregnant or nursing women or women who are trying to conceive
6) Malignancy or other non-cardiac condition limiting life expectancy to <12 months
7) Known hypersensitivity to furosemide, torsemide, or related agents

6 Methods

6.1 Treatment

This will be an unblinded, two-arm randomized outpatient clinical trial comparing oral torsemide and oral furosemide.
Prior studies have suggested oral torsemide has a relative potency 2-4 fold greater than oral furosemide per mg. The initial and follow-up dosing of torsemide and furosemide will be at healthcare provider discretion, with the following conversions provided as a guide: 1 mg oral torsemide = 2- 4 mg oral furosemide 1 mg oral or intravenous bumetanide = 40 mg oral furosemide.

Prior to randomization, the starting dose of furosemide and torsemide will be documented by healthcare providers, with the intent that providers will initially order this dose of study medication after randomization. Patients will receive the randomized medication to be started the day of randomization (if they have not yet taken their current loop diuretic) or the following day. The randomized study medication dose adjustments will be at the discretion of the treating healthcare provider(s) with strategies in place to maintain adherence (if possible) to the randomized medication.

6.1.1 Identity of Investigational Product

FDA Approved oral Furosemide (Lasix)

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FDA approved oral Torsemide (Demadex)

6.1.2 Dosage, Administration, Schedule

The participant's treating healthcare provider is responsible for dosage and the medication schedule.

6.1.3 Method of Assignment/Randomization

Among those meeting eligibility criteria, and after they are consented; the participants will be randomized in a 1:1 fashion to one of two treatment groups. Anticipated initial daily dosing regimens for oral torsemide and oral furosemide will be recorded by the study team for each patient prior to randomization. Patient treatment assignment will be generated using a simple randomization scheme (i.e. no stratification) given the open-label nature of the intervention to limit the potential bias due to predictable treatment assignment.

At the time of randomization, the following baseline characteristics should be documented: age, sex, race, ethnicity, ejection fraction (most recent by any modality), concomitant HF medications and other key baseline variables. Following randomization, study team will identify the treatment assignment and confirm with the patient and the treatment team the outpatient loop diuretic prescription and accessibility.

6.1.4 Blinding and Procedures for Unblinding

As this is a pragmatic trial with an objective primary endpoint, this study will be unblinded for patients, managing clinicians, and the study team.

6.1.5 Packaging/Labelling

After randomization, the participants will receive a prescription for the randomized medication through their treating healthcare provider. This prescription can be filled though the participants standard of care pharmacy.

6.1.6 Storage Conditions

N/A

6.1.7 Concomitant therapy

There are no restrictions for concomitant therapy.

6.1.8 Restrictions

If after consent, the treating healthcare provider deems that the patient should not be randomized, at that time the patient would be considered a screen failure. If after randomization the participant's randomized study medication is changed for any reason, the participant will be asked to continue with the follow up phone calls at thirty (+2/-2) days and one year (+2/-2) days.

6.2 Assessments

Participants of this trial will be called at the end of thirty (+2/-2) days and at one year (+2/-2 days) to obtain subjective and objective data including how they are feeling, compliance to

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their randomized study medication, if they have had any recent hospitalizations, and what their current weight is.

6.2.1 Efficacy

Participants of this trial will be called at the end of thirty (+2/-2) days and at one year (+2/-2 days). During the two phone calls they will be asked how are they feeling, if they are still taking their randomized medication, if not why was it changed, and what their current weight is. If the participant is not able to be reached after three attempts, this information will be recorded from their EMR.

6.2.2 Safety and Pregnancy-related policy

For participants under the age of 65 years old that have not had a documented hysterectomy, a point of care urine test will be performed prior to randomization. If the participant tests positive for pregnancy, they will be withdrawn from the study.

6.2.3 Adverse Events Definition and Reporting

Data Safety Monitoring Plan: We believe this study presents greater than minimal risks to participants, as furosemide and torsemide used routinely are standard of care therapy.

- The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency quarterly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.
- The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.
- This protocol presents greater than minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated but may occur. In the unlikely event that such events occur, Reportable Events [which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related] or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator.

- If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
- For multi-site studies for which the Yale PI serves as the lead investigator:
    - How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

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Adverse events and unanticipated problems will be recorded and reported in accordance with local institutional and IRB policies.

- What provisions are in place for management of interim results?

  Given the observational nature of this study, no interim data analysis is planned.

- What will the multi-site process be for protocol modifications?

  Modifications will be assessed for relevancy to the clinical site and for their impacts on the study design. When necessary, protocol modifications will be submitted in accordance with local IRB policy.

Definitions

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An AE or suspected adverse reaction is considered “serious” (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Severity

Adverse events will be graded according to [name grading scale, e.g. CTCAE v5.0]. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially

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lifethreatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.]

Relationship to Investigational Product

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- 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.

Expectedness

The Principal Investigator will be responsible for determining whether an 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.

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Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated but may occur. In the unlikely event that such events occur, Reportable Events [which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related] or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator.

6.2.4 Pharmacokinetics (if applicable)

N/A

6.2.5 Biomarkers (if applicable)

N/A

6.3 Study Procedures

1. Enrollment: Patients that meet inclusion/exclusion criteria will be approached during their visit at YNHH outpatient clinics or in the TCC. If they agree to participate, the patient will sign an Informed Consent form prior to any study procedures taking place.
2. Prior to randomization and small urine sample will be collected from any female participant who is under the age of 65 and has not had a hysterectomy. A point of care urine test will be performed.
3. After consenting and the point of care urine test the participant will be randomized to one of the two loop diuretic treatment groups.
4. The study team will work with the treating healthcare provider to ensure that the participant receives a prescription for their randomized therapy.

6.3.1 Study Schedule

Once the participant is consented and after a negative point of care urine pregnancy test (as explained in 6.3), they will be randomized to one of the two treatment groups. Assessments of primary and secondary outcomes will occur as follows:

- 30 (±2) days: Patients will be contacted to document vital status, medication adherence, concomitant HF medications, weight change, and to capture hospitalization information.
- 12 months (±2 days): Patients will be contacted to document vital status, medication adherence, concomitant HF medications, weight change, and to capture hospitalization information.

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6.3.2 Informed Consent

Proper written, informed consent and HIPAA authorization will be obtained prior to patient participation in this trial. The overall protocol (including objectives, procedures and duration), potential risks and benefits, voluntary nature and ability to withdraw will be discussed with each patient. The patient will be given a copy of the IRB-approved ICF to review and will have all questions answered before being asked to sign the informed consent form (ICF). Verification of comprehension of the consent will be obtained by asking the subject to describe in their words the purpose and risks of the study. The patient will be instructed that his or her care will not be affected by his or her decision to participate, or not. If the patient voluntarily agrees to participate in the trial, he or she will be asked to sign the ICF. The original ICF will be kept with the study documents and a copy will be made for the patient's chart. The subject will be given a signed copy of the ICF and HIPAA authorization form. All study subjects will be 18 years or older, with the capacity and ability to provide informed consent, thus making parental or surrogate permission not applicable.

Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Based on treating clinicians' recommendations regarding appropriate patients who have agreed to be approached about a potential research study will be screened within EPIC for study eligibility, including mental status and ability to provide informed consent. Study coordinators will confirm with the patient's provider that the patient has the requisite ability and capacity to give informed consent prior to approaching the patient regarding the study. If at any time during the study there is concern regarding a patient's mental status, study staff will both notify the patient's RN and provider, and reevaluate whether the patient is still appropriate for participation in the study. After the study objectives and procedures are explained to the subject, they will be asked to describe in their words what the purpose and risks of the study. are.

6.3.3 Screening

Potential subjects will be identified by study coordinators in conjunction with treating clinicians by screening the EMR of patients with a clinical diagnosis of HF receiving outpatient loop diuretics. Patients whose providers feel they are appropriate for the study will be approached. Pursuant to HIPAA regulations, a log of disclosures of protected health information for recruitment/screening purposes will be kept.

Any participant that has a positive point of care urine pregnancy test will be withdrawn from the study. Any participant that becomes pregnant during the study will be withdrawn from the study. Any participant that has their randomized study medication changed over the course of the year will be asked to continue with their study participation.
Participants will have the option to select whether they are interested in hearing about future heart failure studies. Locating stable heart failure patients who are on a stable dose of loop diuretics can be difficult, and the inclusion/ exclusion criteria aligns with the majority of our ongoing and future research projects.

6.3.4 Enrollment

The PI or study coordinators will first approach the treating clinician (e.g. physician, nurse practitioner, or physician's assistant) regarding possible involvement in the study. If the

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provider feels the patient is appropriate for the study, the participant will be approached and then asked if they would like to participate. The study team always asks permission from the treating healthcare provider to enroll and randomize a participant.

Participants who meet all eligibility for enrollment will be approached by trained study coordinators either in-person during a clinic visit or by phone / SMS / E-mail. Study coordinators will provide a brief description of the study and confirm eligibility.

Eligible patients who have been missed during an in-clinic visit will be contacted by one of the study coordinators by phone. This may be via a phone call or, if unable to reach the patient, via text messaging and/or via e-email through a MyChart message. The following text messaging script will be sent to an eligible patient:

> "You have been selected by your Yale physician to participate in our Yale Heart Failure 'TRANFORM' Study. If eligible, you will be:
>
> - Compensated for your time
> - Helping us determine the most beneficial diuretic treatment to offer HF patients
>
> We need your help! A study team member will be reaching out shortly to provide you with more information. If you have any questions, you can also respond to this text."

The following MyChart message will be sent:

> "If you attend one of Yale's Congestive Heart Failure Clinics and are at least 18 years of age with heart failure and taking a loop diuretic such as Furosemide or Torsemide, you may be eligible to participate in a free and confidential research study investigating the use of loop diuretics in heart failure. If you enroll, you will be compensated up to $850 for your time and participation. To learn more or see if you are eligible to participate, click on "I am interested" or call the Yale Heart Failure Study line at 203-737-6226.
>
> No action by you is required. You may ignore this message or click "not interested." Thank you very much for considering being a part of research at Yale.
>
> To learn more about future research opportunities, you may also create a volunteer profile through the "Research Tab" in MyChart.
>
> To opt-out of all future research communications, please call the Yale Clinical Trials Office at 1-877-978-8343 and select option 3."

During an enrollment phone call, the coordinator will discuss the study and instruct the patient through the enrollment process outlined above. The patient will access our study website through a link that will be sent to them via email, text message, or other electronic means acceptable to the potential enrollee,

Informational issued flyers will also distributed to Yale Cardiology clinics. Patients who are interested in participating in the research study will be able to contact the research team with the number provided to receive more information.

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Enrollment and randomization will take place after a patient has been seen by their healthcare provider in the outpatient setting. Thus, the patient's healthcare provider will have assessed the patient's clinical status and will be able to determine their eligibility and suitability for study participation with consideration of the previously defined enrollment criteria (see section 5.3.0). The study team will contact the providers of potential patients who have been identified via screening of the electronic medical record either in advance of the patient's scheduled clinic visit or in the clinic at the time of the patient's visit. The details of the study and enrollment criteria will be discussed with the provider in order for the provider to make an informed decision of the patient's suitability for the study. Patients whose provider feels they are not appropriate for the study will not be approached for enrollment into the study.

6.3.5 On Study Visits

Randomization

- Prior to randomization any female participant that is 65 years old or younger, who has not had a hysterectomy, will be asked to produce a small urine sample that will only be used for a point of care pregnancy test.
- After confirmation from the treating healthcare provider that the participant is safe to randomize, the potential doses for furosemide and torsemide will be collected.
- The participant will be randomized in a secure database (Yale REDCap). After randomization, the treating healthcare provider and the participant will be notified of the treatment assignment.
- The treating healthcare provider will be asked to place an order for the assigned treatment therapy.
- The study team will ensure that the randomized study medication has been prescribed and that the participant has been able to attain the medication from their pharmacy.

6.3.6 End of Study and Follow-up

The participant will be called at 30 days (+2/ -2 days) to assess for any adverse events, to see how they are feeling, their current weight, if they are still taking the randomized study medication, and any hospitalizations during the study period. If the participant is unable to be reached by phone (after three attempts) the study team will conduct a medical record review to assess for the participant's health status and obtain the required data.
The final phone call will take place one year from randomization (+2/-2 days) to assess for any adverse events, to see how they are feeling, their current weight, if they are still taking the randomized study medication, and any hospitalizations during the study period. If the participant is unable to be reached by phone (after three attempts) the study team will conduct a medical record review to assess for the participant's health status and obtain the required data.

6.3.7 Removal of subjects

Participants will be withdrawn from the study if:

- Tests positive for pregnancy prior to randomization.
- Becomes pregnant while on study.

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- Significant study intervention non-compliance is observed.
- Any clinical adverse event, 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 participant.
- Disease progression which requires discontinuation of the study intervention occurs.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Continuation of Drug Therapy After Study Closure: Both possible randomized treatments are standard of care therapy. While the participant will no longer be required to take the study medication as part of the study, it will be at the discretion of their treating healthcare provider whether to continue the patient on the randomized treatment.

6.4 Statistical Method

Statistical Design

This will be a randomized, parallel-arm, controlled trial. Randomization will occur at the patient level with no blocks of stratification. Treatment factor will include two levels: furosemide vs torsemide.

This study will serve as additional enrollment for the “Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study” (HIC 2000025867), which is currently only enrolling patients admitted to the hospital for worsening heart failure. Thus, the present study will allow for expanded enrollment into HIC 2000025867 with a more diverse group of heart failure patients. Therefore, sections 6.4.1. to 6.5.10 were based on the “CardioRenal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic SubStudy” (HIC 2000025867).

6.4.1 Sample Size Considerations

The present study is thought to potentially be part of the “ToRsemide compArisoN with furoSemide FOR Management of Heart Failure” (TRANSFORM-HF, NCT03296813). For that study, sample size was estimated as 721 events (approximately 6000 patients) assuming a hazard ratio of 0.80 and a power of 85%. Given that it is unlikely that the present study will enroll so many patients, and patients enrolled in the present study will also be coenrolled in the “Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study (HIC 2000025867)”, we calculated sample size based on the later study (see below).

In the “Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study (HIC 2000025867)” , the endpoint change in plasma volume has the largest number of causal inputs and thus will be expected to drive the sample size requirement. The change in plasma volume in real world hospitalized patients undergoing several days of IV diuresis was reported by Miller and Mullan to be on average -0.5L, with a standard deviation of 0.8L.41 Notably, the vast majority of those patients were discharged with a substantially expanded blood volume, leaving room for additional improvement in TRANSFORM-HF.41 The correlation between pre and post treatment blood volumes was high at r=0.87 (personal communication with Dr. Miller). A clinically relevant difference in the current proposed study would be a ≥300cc change in plasma volume. Of note, this small magnitude of change is similar to that observed in patients that hemoconcentrate, a finding associated with

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improved survival.42-47 The test related coefficient of variation of plasma volume determined by I-131 albumin is small (~2%) and the within subject correlation of serial plasma volume measures before and after treatment is high (i.e., r>0.9 is expected in this study).48 Given that the present study will include stable outpatients, we expect the standard deviation in blood volume from randomization to 30 days will be significantly less than the 0.8L seen in the acute hospitalized setting where a much greater degree of treatment heterogeneity exists. As such, with a sample size of 125 patients (62 per group) we will have >80% power to detect a difference in mean changes between groups of >26.5% between groups. (Calculated using PASS version 15.0.5 using Tests for Two Groups of PrePost Scores with an assumed correlation of r=0.9 within subject, an alpha of 0.05 using a twosided, two sample t-test).

6.5 Planned Analyses

6.5.1 Primary Objective Analysis

The statistical comparison of the two randomized arms with respect to the primary endpoint will be a time-to-event analysis, and therefore will be based on the time from randomization to mortality. The Cox proportional hazards regression model will be the primary tool to analyze and assess outcome differences between the two treatment arms. A hazard ratio and 95% confidence interval for summarizing the difference in outcomes between the two treatment arms will be computed using the Cox proportional hazards regression model.

Covariates in the primary model will include the randomized treatment, age, sex, ejection fraction category, and loop diuretic treatment prior to index hospital admission.

6.5.2 Secondary Objectives Analyses

The analyses for the time-to-event secondary endpoints will be similar to those outlined for the primary endpoint using the time from randomization through the first occurrence of any component of a specific secondary endpoint (or censoring) as the response variable, and assessing group differences using the Cox proportional hazards model.
With regards to the “Cardio-Renal Effects of Torsemide vs. Furosemide: A TRANSFORM-HF Mechanistic Sub-Study” (HIC 2000025867), treatment factor will include two levels: Furosemide vs Torsemide, and time will be included also as a main factor with two levels: baseline vs end of the intervention. Primary outcome variables (such as plasma volume) will be measured at baseline and at day 30. Repeated measures or “change” parameters will be analyzed via a linear mixed model (LMM) (e.g., to estimate the changes in randomization to day 30 in plasma volume).

6.5.3 Exploratory Objectives Analyses (if applicable)

N/A

6.5.4 Safety

Participants enrolled in this study will receive one of two standard of care therapies for heart failure: furosemide or torsemide. The participant’s treating healthcare provider will be adjusting the dosing based on the participant’s presenting symptoms at their regularly scheduled visits. At any point in time, the treating healthcare provider may stop the randomized therapy for the participant’s well-being if they deem it necessary. We will only be

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monitoring their loop diuretic treatment through phone calls and chart reviews at 30 days and one year.

6.5.5 Analysis of Subject Characteristics

Data that will be collected is: age, race, ethnicity, weight, height, ejection fraction, baseline medications, and past medical history.
Continuous variables will be presented as mean ± standard deviation or median (interquartile range) according to the observed distribution. Between randomized group comparisons of continuous parameters will be analyzed using a student's *t* test with appropriate transformation if required, or with Man-Whitney U test. Categorical variables will be presented with n (%), and they will be analyzed with the chi squared test or Fisher exact test as appropriate.

6.5.6 Interim Analysis (if applicable)

N/A

6.5.7 Health economic evaluation

N/A

6.5.8 Other

N/A

6.5.9 Subsets and Covariates

N/A

6.5.10 Handling of Missing Data

Analysis of survival data as time-to-event allows to include all available information. If a patient is lost, his survival will be censored to the last time the patient was contacted.

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Proper written, informed consent and HIPAA authorization will be obtained prior to patient participation in this trial. The overall protocol (including objectives, procedures and duration), potential risks and benefits, voluntary nature and ability to withdraw will be discussed with each patient. The patient will be given a copy of the IRB-approved ICF to review and will have all questions answered before being asked to sign the informed consent form (ICF). Verification of comprehension of the consent will be obtained by asking the subject to describe in their words the purpose and risks of the study. The patient will be instructed that his or her care will not be affected by his or her decision to participate, or not. If the patient voluntarily agrees to participate in the trial, he or she will be asked to sign the ICF. The original ICF will be kept with the study documents and a copy will be made for the patient's chart. The subject will be given a signed copy of the ICF and HIPAA authorization form. All study subjects will be 18 years or older, with the capacity and ability to provide informed consent, thus making parental or surrogate permission not applicable.

Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Based on treating clinicians' recommendations regarding appropriate patients who have agreed to be

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approached about a potential research study will be screened within EPIC for study eligibility, including mental status and ability to provide informed consent. Study coordinators will confirm with the patient's provider that the patient has the requisite ability and capacity to give informed consent prior to approaching the patient regarding the study. If at any time during the study there is concern regarding a patient's mental status, study staff will both notify the patient's RN and provider, and reevaluate whether the patient is still appropriate for participation in the study. After the study objectives and procedures are explained to the subject, they will be asked to describe in their words what the purpose and risks of the study are.

ETHICS AND GOOD CLINICAL PRACTICE
This study must be carried out in compliance with the protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1) ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6) 1996.
2) US 21 Code of Federal Regulations Title 45 Part 46 Protection of HumanSubjects dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Participating investigators agree to adhere to the instructions and procedures described in the protocol. This protocol was designed to conform to principles of Good Clinical Practice and investigators agree to adhere to these principles.

Non-English Speaking Subjects: N/A. Only English-speaking participants will be enrolled.

Patients will be compensated for completion of the study visit and phone calls. Patients completing all required visit and phone calls will receive a total of up to $45 for completion.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.
The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.
A study closure report will be submitted to the IRB after all research activities have been completed.
Other study events (e.g. data breaches, protocol deviations) will be submitted per [insert institution's] IRB's policies.

7.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into REDCap and OnCore data bases. No direct subject identifiers will be entered into REDCap data base.
Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a secure database.

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7.4 Deviations/Unanticipated Problems

If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by the PI in accordance with the policy and procedures in place for reporting.

7.5 Data Collection

Name, address, telephone number, MRN, medical history, date of birth, age, sex, allergies, current and past medications or therapies, family medical history, information from a physical examination (ex: BP, heart rate, respiratory rate and temperature), results of blood and urine tests, pathology tests (biopsies), results of imaging tests (ex: x-rays, CT scans, MRI scans, or ultrasound) will be collected.

Data will be collected from the EMR, and the participant themselves. Data will be recorded in electronic databases (REDCap & OnCore), stored in password-protected software on a secure server. Each subject's samples will be given a unique study ID number and cryovials will be labeled with barcodes. There will be no PHI or information directly linking the patient to these samples. Subjects' clinical data will be stored on password-protected software maintained on a secure server. A "linker file" with PHI will be maintained on a separate, password-protected system, which only the study PI and study coordinator will have access to.

After study enrollment is complete continued analysis of data will be undertaken, and thus destruction of identified data is not planned until completion of all analyses.

7.6 Data Quality Assurance

All study team members are trained and certified in GCP and HIPPA regulations and are required to annual renew their trainings. Systematic data verification is in place within the study team to ensure accurate data collection. Standard operating procedures (SOP)'s are routinely used for each protocol and throughout the laboratory to ensure accurate processing and collection.

7.7 Study Records 7.8 Access to Source Documents

The source documents that will be collected during this study include: A patient contact form, phone call follow-up at thirty-day CRF and phone call follow-up at one year CRF. All source documents will be stored in a locked file cabinet within a locked facility that is only accessed by the study staff. Information from source documents will be collected and stored on secure data base REDCap. This information will be assigned a study code before it is shared with study collaborators.

7.9 Data or Specimen Storage/Security

Name, address, telephone number, medical record number (MRN), medical history and allergies, current and past medications and therapies, information from a physical examination (ex: BP, heart rate, respiratory rate and temperature), family medical history, results of blood, urine and imaging tests (ex: x-rays, CT scans, MRIs, or ultrasound) and

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pathology tests (biopsies), DNA, RNA, tissue and blood. The patients' entire medical record will be reviewed.

Digital data will be stored in a secured server.

Data collected by the PI and other study personnel listed in this protocol will be distributed for secondary research purposes only after the recipient investigator has obtained HIC approval for the proposed research objective, received an exemption or determination by the HIC the study is not considered human subject research. Data will be distributed for research projects of the same nature and similar purpose specified in this protocol, as agreed to by the subjects by signing the compound informed consent and HIPAA authorization form upon enrollment to the study. The PI is responsible for receiving appropriate attestation by recipient investigators prior to permitting access to the database for activities considered preparatory to research.

Data collected during the research study will be shared with other investigators for research projects of the same nature and similar purpose specified in this protocol, as described above. Researchers may still use the data that was collected before the subject withdrew permission/authorization in order to complete the research that has already commenced. All data retained and not yet used for research purposes will be destroyed upon receiving notice of a subject's withdrawal of permission for continued use of their data.

The PI will ensure participants' anonymity is maintained. Each participant is assigned a unique study identification number and is tracked through this number. Participants' clinical data will be entered into password-protected software and stored on a secure server. A log of participants' names, participant ID numbers and pertinent registration information (ex: address, phone number and emergency contact information) is maintained on a password protected computer, to allow re-identification of participants when necessary. This will be maintained by the PI and will not be shared.

7.10 Retention of Records

After study enrollment is complete continued analysis of data will be undertaken, and thus destruction of identified data is not planned until completion of all analyses.

7.11 Study Monitoring

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency quarterly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

7.12 **Data Safety Monitoring Plan**

Greater than Minimal Risk Data and Safety Monitoring Plan (DSMP) Personnel responsible for the safety review and its frequency: The PI will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including

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when re-approval of the protocol is sought). During the review process, the PI will evaluate whether the study should continue unchanged, require modification &/or amendment, or close to enrollment. Either the PI or the IRB, have the authority to stop or suspend the study or require modifications.

The overall risk associated with the proposed study is deemed greater than minimal for the following reasons: We believe this study presents greater than minimal risk with the randomization of furosemide or torsemide because although both medications are standard of care treatments for heart failure, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of firsthand experience with the proposed study methods. The study poses minimal risk from the data collection, as all data will be collected and stored in password protected data bases and all research personnel have been trained in appropriate data collection and storage.

7.13 Study Modification

Consistent review of the protocol and study procedures will be conducted on a frequent basis, depending on the need of the study team or if new information has been obtained. Based on this the protocol will be modified on an as needed basis.

7.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), 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

7.15 Study Completion

Once enrollment has been completed or at the end of the four-year planned enrollment the study team will notify the IRB of their plans to close enrollment. Upon completion of data analysis the study team will again notify the IRB of its plans to close the study.

7.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review

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committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.
All investigators will follow the applicable conflict of interest policies.

7.17 Funding Source

Departmental

7.18 Publication Plan

Subject enrollment is planned to last 4 years. Data analysis will occur after study completion. Completion of enrollment, statistical analysis, and publication is planned to be complete within 6 years

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8 Appendices

Appendix #	Title	Section	Topic

No appendices are included

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9 List of Tables

No tables are included in this version

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