# Registry Of Best Up-titration STrategies in acute Heart Failure (ROBUST-HF): a registry of post-acute heart failure management

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**20 October 2023**

## Protocol Approval

**Protocol Title:** Registry Of Best Up-titration STrategies in acute Heart Failure (ROBUST-HF): a registry of post-acute heart failure management

**Protocol Version and Date:** Version 1.1 dated 20 October 2023

**Sponsor Name:** Heart Initiative

This protocol has been approved by

**Study Principal Investigator**

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Signature: Alexandre Mebazaa

Date of Signature: Oct 21, 2023

**Medical Monitor**

Name: Gad Cotter, MD

Title and Affiliation: CEO, Momentum Research Inc.

Signature: Gad Cotter

Date of Signature: 21-Oct-2023

**Sponsor**

Name: Beth A. Cotter-Davison, PhD

Title and Affiliation: President, Heart Initiative

Signature:

Date of Signature: 20Oct2023

## Site Investigator Protocol Signature Page

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**Sponsor Name:** Heart Initiative

**Declaration of Investigator:**

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date of Signature: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION:

| Affected Section(s) | Summary of Revisions Made | Rationale |
|---|---|---|
| All | Updated protocol version number and date. | N/A |
| 3, 4.1, 5, 7.1 | Removed requirement for registry participants to have been followed up at least once within 2 weeks post discharge. | The change allows inclusion of patients with delayed or no post discharge follow-up, and, thus, a more comprehensive description of the care of patients following discharge from an admission for AHF. |
| 18 | Added doses for SGLT-2 inhibitors canagliflozin, ertugliflozin, and sotagliflozin. | Doses are now provided for additional SGLT-2 inhibitors available on the market. |

# 1 CONTENTS

## 2 ABBREVIATIONS

| | |
|---|---|
| ACC | American College of Cardiology |
| ACEI | Angiotensin converting enzyme inhibitor |
| AE | Adverse event |
| AHA | American Heart Association |
| AHF | Acute heart failure |
| ALT | Alanine transaminase |
| ARB | Angiotensin receptor blocker |
| ARNI | Angiotensin receptor-neprilysin inhibitor |
| AST | Aspartate aminotransferase |
| BB | Beta-blocker |
| CI | Confidence interval |
| CV | Cardiovascular |
| DCC | Data coordinating center |
| EC | Ethics committee |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| EQ-5D | EuroQuol 5-dimension |
| ESC | European Society of Cardiology |
| GDMT | Guideline-directed medical therapy |
| GPP | Good Pharmacoepidemiology Practices |
| HF | Heart failure |
| HFA | Heart Failure Association |
| HFSA | Heart Failure Society of America |
| HFWG | Heart failure working group |
| ICH | International Committee on Harmonization |
| IRB | Institutional review board |
| IV | Intravenous |
| JVP | Jugular venous pulse |
| LVEF | Left ventricular ejection fraction |
| MRA | Mineralocorticoid receptor antagonist |
| NT-proBNP | N-terminal pro B-type natriuretic peptide |
| NYHA | New York Heart Association |
| PASCAR | Pan-African Society of Cardiology |
| PI | Principal investigator |
| PTCI | Percutaneous transluminal coronary intervention |
| QoL | Quality of life |
| RASI | Renin-angiotensin system inhibitor |
| SAE | Serious adverse event |
| SCC | Study coordinating center |
| SGLT-2 | Sodium-Glucose Cotransporter-2 |
| VAS | Visual analog scale |

# 3 SYNOPSIS

| | |
|---|---|
| Study Title | Registry Of Best Up-titration STrategies in acute Heart Failure (ROBUST-HF): a registry of post-acute heart failure management |
| Funder(s) | Grants from biopharmaceutical companies to Heart Initiative |
| Study Rationale | Results of recent studies suggest that initiation and dose optimization of neuroendocrine modulators around the time of discharge from a hospitalization for acute heart failure (AHF) can improve patient prognosis. STRONG-HF showed that rapid up-titration of renin-angiotensin inhibitor (RASI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) to full optimal doses within 2 weeks post-discharge from a hospital admission for AHF, using frequent safety assessments, significantly reduced the 180-day risk of HF readmission or death and significantly increased 90-day quality of life regardless of left ventricular ejection fraction (LVEF). Recent studies have also shown that initiation of angiotensin-receptor neprilysin inhibitor (ARNI) and SGLT-2 inhibitors close to the time of discharge regardless of LVEF, and iron supplementation where indicated, improve patient outcomes. However, studies have shown that pre- and post-discharge up-titration of guideline-directed medical therapy (GDMT) is not common and is limited by lack of post-discharge follow-up of patients after an AHF admission.<br><br>In this retrospective observational registry, ROBUST-HF, medical records will be reviewed and patients will be identified who were discharged at least 6 months prior to data review from an admission for AHF on sub-optimal doses of oral heart failure medications. These patients' records will be reviewed and data collected describing their HF status and treatment during the admission and their post-discharge care including the management of their oral HF medications and frequency and content of post-discharge assessments and clinical outcomes through 6 months post discharge. |
| Study Objective(s) | Describe the post-discharge care including GDMT up-titration of patients with AHF in multiple countries and sites, inclusive of number of post-discharge visits and their timing, care providers conducting those visits, medications prescribed to patients, follow-up exams including labs and their relationships to GDMT up-titration and outcomes during the first 6 months post-discharge. |
| Study Design | Retrospective multinational, multicenter, observational registry of patients discharged from a hospital admission for AHF who were not previously treated with optimal doses of guideline-directed medical therapy (GDMT) for HF. |

| | |
|---|---|
| Participant Population<br><br>key criteria for Inclusion and Exclusion: | Adult patients discharged at least 6 months prior to data review from a hospitalization for acute heart failure who, at the time of discharge, were not treated with optimal doses of oral medications for HF including renin-angiotensin system inhibitors (RASI), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA) or sodium glucose co-transporter inhibitors (SGLTI) despite no obvious contraindications.<br><br><u>Inclusion criteria:</u><br><br>1. Discharged from a hospitalization for acute heart failure (with evidence of diagnosis by dyspnea at rest and pulmonary congestion on chest X-ray or lung ultrasound) at least 6 months prior to data review (qualifying admission).<br>2. During the qualifying admission<br>A. All measures within 24 hours prior to discharge of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.<br>B. The last measurement during the hospital admission prior to discharge of serum potassium ≤ 5.0 mEq/L (mmol/L) and of NT-proBNP > 1,600 pg/mL or BNP > 400 pg/mL.<br>C. At admission and at the time of discharge being prescribed: none to < ½ the optimal dose (see section 18) of 2 of the following 4 categories of oral HF medications: (1) RASi [angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI)], (2) BB, (3) MRA, (4) SGLT inhibitor.<br><br><u>Exclusion criteria:</u><br><br>1. Age < 18.<br>2. Myocardial infarction, unstable angina or cardiac surgery, or percutaneous transluminal coronary intervention (PTCI), within 1 month prior to the qualifying admission for AHF.<br>3. At the time of the qualifying admission for AHF, known presence of any severe valvular stenosis or regurgitation, or any valvular disease in need of surgical correction.<br>4. Last measurement during the qualifying hospital admission of eGFR < 30 mL/min/1.73m$^2$ or history of dialysis.<br>5. Enrolled in a clinical study that mandated a schedule of follow-up visits for heart failure, or assessments or treatment for heart failure. |
| Number of Participants | Up to 5000 patients in up to 60 countries in Europe, the United States, Asia, Africa, and Latin America, with up to 300 sites globally |

| | |
|---|---|
| Study Duration | Each participant's data will be collected from discharge to 6 months post discharge.<br><br>The entire registry is expected to remain open approximately 4½ years. |
| Data Collected | In the registry information will be collected as follows:<br><br>1. Details on the AHF admission including patient characteristics, laboratory exams (natriuretic peptides, creatinine, potassium), and HF medications prescribed.<br><br>2. Information regarding post-discharge outpatient visits through 6 months post-discharge including timing relative to discharge, location, provider of health care during visit, assessments performed (HF symptoms and signs, laboratory evaluations including natriuretic peptides, creatinine, and potassium), and HF medications prescribed.<br><br>3. Details, as available, on any visits with other healthcare providers, readmissions, emergency department admissions, or death. |
| Statistical and Analytic Plan | Summaries of results for individual institutions and aggregated over sites, e.g., by country and region as well as across the entire registry may be done periodically during the life of the registry.<br><br>Analyses will be done to describe the patients' characteristics and treatment during hospitalization for AHF, and their post-discharge care through 6 months. Cumulative 6-month risks of death and HF readmission will be estimated. |

# 4 BACKGROUND INFORMATION AND RATIONALE

## 4.1 INTRODUCTION

This document describes a multicenter, international retrospective observational registry of patients discharged from a hospital admission for acute heart failure (AHF). Patients will be identified through a review of patient medical records who were discharged at least 6 months prior to data review who were not treated with optimal doses of oral medications for HF including renin-angiotensin system inhibitors (RASI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and SGLT-2 inhibitors.

## 4.2 RELEVANT LITERATURE AND DATA

The morbidity and mortality after an AHF event is extremely high with 6-month mortality of about 10% and readmission or death over 25%, very similar to the short-term outcomes of the most severe oncological diseases (Mamas 2017). But while an oncological patient with the same disease severity would have been seen frequently and given complex therapy regimens, HF patients are sent home with almost no follow-up and on suboptimal therapy. For example, an analysis of patients discharged from an admission for acute decompensated heart failure in cardiology and geriatrics departments in the greater Paris university hospitals found that only 72% of patients had a post-discharge outpatient visit within 3 months, with an average time to first visit of 45 days (Laveau 2017).

The 3-6 month period following an admission for acute heart failure (AHF) is a critical opportunity to intervene. During and after an AHF admission, patients have neuroinflammatory activation associated with adverse outcomes (Davison 2021). Novel therapies such as SGLT-2 inhibitors (Bhatt 2021; Voors 2022) and angiotensin receptor-neprilysin inhibitors (ARNI) [Morrow 2019], and rapid up-titration of established HF therapies (RASI, beta-blockers, and MRA) [Mebazaa 2022] that have been initiated close to discharge have been shown to reduce outcomes such as death and readmission by 25-40%.

In the STRONG-HF study, renin-angiotensin inhibitor (RASI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) were up-titrated to half optimal doses just prior to discharge, with up-titration to full optimal doses at 2 weeks post discharge. Safety was evaluated at each visit prior to each potential up-titration and 1 week following each up-titration – for a total of 5 visits within 3 months post discharge – through physical examination of signs and symptoms of HF, vital signs including blood pressure and heart rate, and laboratory measures of potassium, NT-proBNP, and eGFR. This rapid up-titration just prior to discharge from and early after a hospital admission for acute heart failure (AHF) was associated with a significantly reduced risk of readmission for heart failure or death by 180 days (15.2% vs 23.3% in usual care, $p=0.0021$) and significantly increased quality of life (QoL) (90-day mean change in EQ-5D VAS of 10.72 vs 7.22 points in usual care, $p<0.0001$). The effect of this high intensity care strategy was evident in patients regardless of LVEF (Mebazaa 2022). Results of three reasonably sized randomized controlled trials suggest that intensified follow-up visits alone, without up-titration of medications to maximally tolerated doses, do not affect readmission or death (Jaarsma 2008; Van Spall 2019; Logeart 2022).

Few patients in STRONG-HF were treated with ARNI, SGLT-2 inhibitors, or iron. Recent evidence from the PIONEER study showed that in-hospital initiation of ARNI was safe and reduced NT-proBNP more than enalapril; the 8-week risk of cardiovascular (CV) death or HF readmission was 9.2% vs 15.2% with enalapril – a 42% relative reduction (Morrow 2019). Results of the SOLOIST study showed that the SGLT-1/2 inhibitor sotagliflozin reduced the 6-month risk of CV death or HF readmission by about 26% (Bhatt 2021). The EMPULSE study showed that the SGLT-2 inhibitor empagliflozin improved quality of life within 90 days (Voors 2022). In both studies patients were enrolled regardless of LVEF and there was no interaction between treatment effect and LVEF. The AFFIRM-HF study showed that in iron deficient patients with LVEF < 50%, intravenous ferric carboxymaltose reduced the 6-month risk CV death or HF readmission by a relative 18% (Ponikowski 2020). Taken together, these results suggest that ARNI , beta-blockers, MRA, and SGLT-2 inhibitors, and iron supplementation where indicated, When not available, a simple strategy of ACEi or ARB, BB, and MRA was effective in the STRONG-HF study. These should be given in maximal doses simultaneously in addition to diuretics (Cotter 2022).

The main barriers to implementation of this new approach are related to two main issues: first, the need for successive visits during the first weeks after discharge including lab work, and, second, the need to acquire skills to safely up-titrate oral HF medications during the rapid up-titration phase. Clinical inertia combined with no structured follow-up after an AHF admission discharge (Butler 2021) lead to a lack of up-titration of GDMT during and after an AHF admission. Therefore, it would be of interest to determine whether early post-discharge follow-up is associated with more GDMT up-titration and whether this pattern persists if patients are then seen more often in the outpatient setting and its relationship to outcomes.

# 5 OBJECTIVES

The main aim of the ROBUST-HF registry is to describe the post-discharge care, including GDMT up-titration, of patients with AHF in multiple countries and sites, inclusive of number of post-discharge visits and their timing, care providers conducting those visits, medications prescribed to patients, follow-up exams, inclusive of labs, and their relationship to GDMT up-titration and outcomes during the first 6 months post-discharge.

# 6 REGISTRY DESIGN

## 6.1 RESEARCH DESIGN

This is a retrospective, multinational, multicenter, observational registry of patients discharged from a hospitalization for AHF who were not previously treated with optimal doses of GDMT for HF. Investigators at participating centers will review patients' medical records to identify patients who were discharged at least 6 months prior to data review and who meet all eligibility criteria. Investigators will enter data abstracted from eligible patients' medical records (see section 8.3) into the ROBUST-HF registry database.

## 6.2 REGISTRY SITES AND NUMBER OF PARTICIPANTS

The registry will be conducted in up to 60 countries in Europe, the United States, Asia, Africa, and Latin America, with up to 300 sites globally, for inclusion of up to 5000 total participants.

## 6.3 REGISTRY DURATION

Each patient's data will be collected retrospectively for the period between hospital discharge and 6 months following hospital discharge, after which time no additional information will be collected. Data collection is anticipated to begin in third quarter 2023 and to continue for approximately 4.5 years.

## 6.4 MULTI-SITE RESEARCH LOGISTICS/COMMUNICATION PLAN

### 6.4.1 STUDY LEADERSHIP

The study leadership will comprise two committees:

1. Executive committee – this will include 2 representatives from the US HFSA; two representatives of the European ESC HFA, one representative each of the Asian Pacific Society of Heart Failure, African PASCAR, and South America; the 3 principals of the STRONG-HF study; with additional members as deemed necessary throughout the study.
2. Steering committee – this will include one representative from each participating country, preferably the head of the country HFA/HFWG. In the USA, the US HFSA may designate 10 regional HF leaders to participate in the steering committee.

Each of these committees will meet periodically during the course of the study.

### 6.4.2 STUDY COORDINATION

Momentum Research Inc. in Durham, NC will serve as the Study Coordinating Center (SCC). The SCC will assure that all sites have the most recent protocol version, that all required approvals have been obtained, and that investigators have been trained with respect to registry procedures. The SCC will notify participating sites of any problems that may arise, availability of interim results, and closure of the registry.

# 7 PARTICIPANT SELECTION

## 7.1 INCLUSION CRITERIA

Patients admitted for acute heart failure at least 6 months prior to data review who were not treated with optimal doses of oral medications for HF including renin-angiotensin system inhibitors (RASI), beta-blockers (BB), and mineralocorticoid receptor antagonists (MRA), who met all the inclusion criteria and none of the exclusion criteria will be enrolled.

<u>Inclusion criteria:</u>

1. Discharged from a hospitalization for acute heart failure (with evidence of diagnosis by dyspnea at rest and pulmonary congestion on chest X-ray or lung ultrasound) at least 6 months prior to data review (qualifying admission).
2. During the qualifying admission:
   A. All measures within 24 hours prior to discharge of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.

B. The last measurement during the hospital admission prior to discharge of serum potassium ≤ 5.0 mEq/L (mmol/L) and of NT-proBNP > 1,600 pg/mL or BNP > 400 pg/mL.
C. At admission and at the time of discharge being prescribed: none to < ½ the optimal dose (see section 19) of 2 of the following 4 categories of oral HF medications: (1) RASi [ angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI)], (2) BB, (3) MRA, (4) SGLT inhibitor.

### 7.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this registry:

1. Age < 18.
2. Myocardial infarction, unstable angina or cardiac surgery, or percutaneous transluminal coronary intervention (PTCI), within 1 month prior to the qualifying admission for AHF.
3. At the time of the qualifying admission for AHF, known presence of any severe valvular stenosis or regurgitation, or any valvular disease in need of surgical correction.
4. Last measurement during the qualifying hospital admission of eGFR < 30 mL/min/1.73m$^2$ or history of dialysis.
5. Enrolled in a clinical study that mandated a schedule of follow-up visits for heart failure, or assessments or treatment for heart failure.

## 8 REGISTRY PROCEDURES

### 8.1 RECRUITMENT OF PARTICIPANTS

Participating centers will be identified by representatives of regional heart failure professional societies (e.g., Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology), or Executive or Steering Committee members. Participating investigators will identify eligible patients who were hospitalized for AHF in their institutions.

### 8.2 DATA COLLECTION

#### 8.2.1 DATA COLLECTION SCHEDULE

All data will be collected from the medical record. Data needed to confirm study eligibility are required to be collected for each included patient. Data for each post-discharge visit through 6 months post-discharge, and clinical outcomes should be recorded to the extent available. Data will be entered by the investigator or their designee into an eCRF.

| Data Collected | During AHF admission | Each Outpatient Visit | Outcomes through 6 Months |
|---|---|---|---|
| Registry Eligibility Criteria | X | | |
| Demographics | X | | |
| Medical history | X | | |
| Healthcare provider, setting | X | X | |
| Medications for heart failure | X | X | |
| Physical assessment of heart failure signs and symptoms | X | X | |
| Vital signs | X | X | |
| Laboratory test results, including natriuretic peptides, creatinine, potassium | X | X | |
| Re-hospitalization* | | | X |
| Death† | | | X |

*Including timing of admission and discharge, primary reason for admission

†Including timing of death, primary cause of death

#### 8.2.1.1 SCREENING AND INCLUSION

Medical records will be reviewed for patients who were discharged from a hospital admission for AHF at least 6 months prior to data review. Each eligible patient's data will be collected through 6 months after discharge from the hospitalization. To be eligible for inclusion in the registry, a chest X-ray or lung ultrasound documenting pulmonary congestion must have been performed during the hospitalization. Vital signs, and local laboratory measures of serum potassium, eGFR and NT-proBNP or BNP prior to discharge must also be available. The patient's medical history regarding significant pulmonary disease, renal disease, or history of dialysis, and oral HF medications at admission and at discharge should be reviewed.

#### 8.2.1.2 OUTPATIENT VISITS FOR HEART FAILURE

To the extent possible, data for every post-discharge outpatient visit for heart failure through 6 months post-discharge will be collected. Visits include any encounter with the patient including, for example, face-to-face (home or clinic) visits, remote (telemedicine) visits, urgent outpatient clinic visits, emergency department visits, and phone calls by any healthcare provider including, for example, physician, physician assistant, nurse. Data will be collected for each visit describing the setting and provider, doses of oral HF medications prescribed, and other medications prescribed. Any assessment of HF signs and symptoms, vital signs, or laboratory tests that were performed will also be captured.

#### 8.2.1.2.1 CLINICAL OUTCOMES THROUGH 6 MONTHS

The patient's medical record should be reviewed for any re-hospitalizations and death between hospital discharge and 6 months post-discharge. If the patient was lost to follow-up prior to 6 months post-discharge, this will be recorded.

### 8.2.2 DATA TO BE COLLECTED

#### 8.2.2.1 DEMOGRAPHICS AND MEDICAL HISTORY

Information regarding the patient's demographics and medical history will be obtained through review of the patient's medical record for relevant conditions present prior to the qualifying admission. Demographic information to be recorded includes the patient's age, sex at birth, race and ethnicity (where permitted to be recorded), and health insurance coverage.

#### 8.2.2.2 QUALIFYING HOSPITALIZATION FOR HEART FAILURE

Information regarding the hospitalization for heart failure which qualified the patient for inclusion in the registry will be collected, as available. Data collected will include the length of the hospital stay; time spent in acute care units; vital signs, laboratory values, and clinical assessment of HF signs and symptoms at admission, during the admission, and at discharge, and medications and other therapies administered before admission, at admission, and during the admission.

#### 8.2.2.3 MEDICATIONS FOR HEART FAILURE

Medications for heart failure prescribed just prior to anticipated hospital discharge and at each post-discharge outpatient visit through 6 months will be collected. Information will include medication name and dose. Use of ACEI, ARB, ARNI, BB, MRA, SGLT-2 inhibitors, loop diuretics as well as IV iron will be assessed.

#### 8.2.2.4 PHYSICAL ASSESSMENTS INCLUDING VITAL SIGNS

Any reported vital signs including body weight, systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation will be collected at admission and discharge and at each post-discharge outpatient visit. Any clinical assessment of signs and symptoms of HF (NYHA classification, orthopnea, peripheral edema, rales, JVP) will be collected at admission and discharge, and at each post-discharge outpatient visit.

#### 8.2.2.5 BLOOD TEST RESULTS INCLUDING NATRIURETIC PEPTIDES

Results available for the following local laboratory tests, if performed, will be collected at admission and discharge and at each post-discharge outpatient visit: hemoglobin, white blood cell (WBC) count, WBC differential counts, glucose, sodium, potassium, creatinine, eGFR, blood urea nitrogen, urea, uric acid, AST, ALT, total bilirubin, total cholesterol, iron, iron saturation, ferritin, NT-proBNP or BNP, and troponin I or T.

No materials of human origin (e.g., blood or tissue specimens) are to be collected or stored for this study.

#### 8.2.2.6 CLINICAL OUTCOMES

Detail regarding any death or re-hospitalization that occurs through 6 months post discharge will be collected. An overnight stay in the hospital will be considered a hospitalization. (Stays of

shorter duration can be reported as outpatient visits.) The primary reason for the rehospitalization and the primary cause of death will be selected by the investigator from pre-defined lists in the eCRF. The choices for primary cause of death are largely consistent with ACC/AHA Clinical Data Standards for cardiovascular endpoints in clinical trials (Hicks 2015). The investigator-reported rehospitalization reasons and causes of death will not be adjudicated.

# 9 DATA MANAGEMENT AND QUALITY PLAN

## 9.1 DATA DE-IDENTIFICATION

Patients' data will be pseudonymized. The registry will not include the participant's contact or identifying information. Direct patient identifiers such as social security number or medical record number will not be collected. Rather, individual participants and their research data will be identified by a unique study identification number. The study participant's contact information, and linkage to the participant's study identification number, will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, Institutional policies, or sponsor requirements.

## 9.2 DATA CONFIDENTIALITY, STORAGE, AND RETENTION

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their designates. This confidentiality is extended to cover results of testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. Patients have the right to control the use and disclosure of their information. The site investigator will keep paper and electronic records of patients' medical records that include basic personal information such as name, contact details, age, sex, race, height and weight, medical history, and clinical data collected as part of the patient's medical care. The patient has the right to access, through the site investigator, all the information collected about them and ask for corrections if applicable.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or EC, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients included in this registry. The clinical study site will permit access to such records. All personnel accessing patients' records are required to respect their confidentiality.

Study patient research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center (DCC) at Momentum Research Inc. Access to the EDC system will be carefully controlled by the DCC, and data will be protected through electronic security measures including firewalls, restricted access, and encryption technology. After 5 years following closure of the registry, data will be de-identified and stored indefinitely as directed by the Sponsor. Only de-identified data will be shared with

institutions or individuals not employed by or contracted to the Sponsors, the Data Coordinating Center or the Study Coordinating Center.

### 9.3 DATA QUALITY

Data will be entered by study site staff into an eCRF. Quality checks to be performed including edit checks and manual review will be described in a Data Management Plan. Data will be reviewed centrally; sites may be monitored at random or for cause, and source document verification may be performed. A Clinical Monitoring Plan will describe processes for site selection, site initiation, interim monitoring, and site closeout.

### 9.4 DATA SHARING

Individual patient data required to reach aims in an approved proposal, after de-identification, will be made available to investigators whose proposed use of the data has been approved by the study's Executive Committee. Proposals may be submitted up to 36 months after study completion and should be directed to the study's Principal Investigator.

## 10 STATISTICAL CONSIDERATIONS

Analyses summarizing an individual institution's data will be performed, as well as summaries of results aggregated over sites, e.g., country, region. Summaries of results across the entire registry may be done periodically during the life of the registry. A detailed Statistical Analysis Plan describing these reports will be prepared separately.

### 10.1 SAMPLE SIZE DETERMINATION

Up to 5000 patients are to be enrolled in the registry. The final registry sample size may change depending on ease of enrollment, data availability, and progress towards study goals. The total sample size should provide fairly precise estimates of the proportions of patients prescribed full optimal doses of oral HF medications. In STRONG-HF, 55%, 49.3%, and 83.8% of patients in the high intensity care group were on full optimal doses of RASI, beta-blocker, and MRA, respectively, at day 90 (approximately 90 days after discharge). With 3000 patients, using a large sample normal approximation, the 95% confidence interval (CI) for these proportions would be ± 1.8%, 1.8%, and 1.3%, respectively.

Similarly, the total sample size will allow precise estimation of 6-month risks of clinical outcomes. The risk of death or HF admission was 15.2%, and of death was 8.5%, by 180 days in the high intensity care group of STRONG-HF. With 3000 patients, the 6-month risk of the composite endpoint can be estimated with a 95% CI of ± 1.3%, and the risk of death ± 1%, using a large sample normal approximation.

### 10.2 ANALYSES TO ADDRESS MAIN AIMS

To describe the post-discharge care of patients admitted to hospital for acute heart failure, the following descriptive analyses will be performed:

- Characteristics of patients enrolled including demographics, general and heart failure medical history, pre-admission and discharge HF medications, vital signs and laboratory findings

- HF medications prescribed at discharge from the qualifying hospitalization for HF (proportion of patients on medications in each of the four classes at discharge), and latest HF meds prescribed reported by 3 and 6 months with respect to optimal doses (proportions of patients on <½, ½-<full and ≥ full optimal doses of medication in each class at 2 weeks, 1 month, 3 months, and 6 months post discharge). The association between medication doses prescription and number and type of visits performed after the AHF discharge.
- Time from discharge from the qualifying HF hospitalization to first post-discharge visit; number of post-discharge outpatient visits through 3 and 6 months and their timing (the proportions of patients with follow-up visit within 1 week, 2 weeks, 1 month, 3 months, and 6 months post discharge), types of visit (urgent/emergent, clinic/home/hospital/office visit, phone call), care providers (non-physician v physician, specialty of physician, training of non-physician), labs (e.g., potassium, eGFR, NT-proBNP or BNP) done, clinical assessment of congestion done (i.e., proportion of post-discharge visits where NT-proBNP or BNP measured, other labs measured, vital signs measured, clinical assessments of congestion done).
- 6-month outcomes including 6-month cumulative risks of death, CV death, re-hospitalization, CV re-hospitalization, HF re-hospitalization, and various composite outcomes (e.g., first HF re-hospitalization or CV death). The association of these adverse outcomes with medication prescription rates and visits density between discharge and 6-months post discharge.

# 11 POTENTIAL RISKS AND BENEFITS

## 11.1 POTENTIAL BENEFITS

This study does not include any protocol-specified alterations to the treatment or medical care of patients included in the registry. Patient management is at the discretion of the participant's care providers. Participating in the registry may heighten the awareness of the patient's care providers to adherence to guideline-directed care including rapid optimization of HF medications under intensive post-discharge care. Thus, the post-discharge prognosis of future patients might be improved as a result.

## 11.2 POTENTIAL RISKS

No specific treatments or care are mandated by this study. Inclusion in the registry may involve the risk of accidental disclosure of the patient's personal data.

## 11.3 MITIGATION OF RISKS

Provisions to protect the privacy of participants' data are described in sections 9.2 and 11.4.

## 11.4 PROVISION TO PROTECT THE PRIVACY INTEREST OF REGISTRY PARTICIPANTS

All precautions will be taken to make sure that only authorized individuals will be accessing participant research records. The collection of sensitive information about participants is limited to the amount necessary to achieve the aims of the research registry, so that no unneeded

sensitive information is being collected. Section 9.2 details processes for maintaining data confidentiality.

# 12 SAFETY CONSIDERATIONS

## 12.1 MEDICAL MONITORING

The Medical Monitor will review accumulating data and will alert the site investigator if any patient-related safety concerns are evident in the data collected.

# 13 ETHICAL CONSIDERATIONS

## 13.1 ETHICS COMMITTEES OR INSTITUTIONAL REVIEW BOARDS

The protocol and request for waiver of patient informed consent will be submitted to the Institutional Review Board (IRB) or Ethics Committee (EC) for review and approval. Approval of both the protocol and waiver of consent must be obtained before any patient data are included in the registry.

## 13.2 ETHICAL CONDUCT OF THE STUDY

This document is a protocol for a human research registry. This registry is to be conducted in accordance with the protocol, and according to Guidelines for Good Pharmacoepidemiology Practices (Public Policy Committee ISoP 2016), and in accordance with applicable country and local regulations and EC/IRB policies and procedures. Appropriate approvals must be obtained from the IRB or EC before any patient data are included in the registry.

# 14 FUNDING SOURCE

ROBUST-HF will be funded by grants to Heart Initiative from biopharmaceutical companies.

# 15 PARTICIPANT STIPENDS OR PAYMENTS

Patients will not be reimbursed for their inclusion in the registry.

# 16 PUBLICATION PLAN

Every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers by contacting the study's principal investigator.

A publication committee consisting of several investigators and Sponsor representative(s) will solicit input and assistance from other investigators and will collaborate with authors and the Sponsor as defined in the Publication Charter. Membership on the committee does not guarantee authorship on any given publication; individual authors must meet established criteria for authorship.

Investigators will not publish study results from their institution prior to publication of the main manuscript for the study.

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# 18 APPENDIX: OPTIMAL DOSES OF HEART FAILURE MEDICATIONS

| Medication generic name | Half dose | Full dose |
|---|---|---|
| **MRA** | | |
| Eplerenone | 25 mg q.d. | 50 mg q.d. |
| Spironolactone | 25 mg q.d. | 50 mg q.d. |
| **Beta-blocker** | | |
| Bisoprolol | 5 mg q.d. | 10 mg q.d. |
| Carvedilol | 12.5 mg b.i.d. | 25 mg b.i.d. |
| Metoprolol succinate extended-release tablet | 100 mg q.d. | 200 mg q.d. |
| Nebivolol | 5 mg q.d. | 10 mg q.d. |
| Atenolol | 50 mg q.d | 100 mg q.d |
| Betaxolol | 10 mg q.d | 20 mg q.d |
| Metoprolol tartrate | 50 mg b.i.d | 100 mg b.i.d |
| **ACEi** | | |
| Captopril | 25 mg t.i.d. | 50 mg t.i.d. |
| Enalapril | 10 mg b.i.d. | 20 mg b.i.d. |
| Lisinopril | 17.5 mg q.d. | 35 mg q.d |
| Ramipril | 2.5 mg b.i.d. or<br>5 mg q.d. | 5 mg b.i.d. or<br>10 mg q.d. |
| Trandolapril | 2 mg q.d. | 4 mg q.d. |
| Perindopril | 4 mg q.d. | 8 mg q.d. |
| Fosinopril | 20 mg q.d | 40 mg q.d |
| Zofenopril | 15 mg b.i.d | 30 mg b.i.d |
| **ARB** | | |
| Candesartan | 16 mg q.d. | 32 mg q.d.. |
| Valsartan | 80 mg b.i.d. | 160 mg b.i.d. |
| Losartan | 75 mg q.d. | 150 mg q.d. |
| Irbesartan | 150 mg q.d | 300 mg q.d |
| Telmisartan | 15 mg q.d | 30 mg q.d |
| Olmesartan[1] | 20 mg q.d. | 40 mg q.d. |
| Azilsartan Medoxomil | 40 mg q.d | 80 mg q.d |
| **ARNi** | | |

| Medication generic name | Half dose | Full dose |
|---|---|---|
| Sacubitril/valsartan (Entresto™) | 49/51 mg b.i.d. | 97/103 b.i.d. |
| **SGLT-2 Inhibitor** | | |
| Dapagliflozin | 5 mg q.d. | 10 mg q.d. |
| Empagliflozin | 5 mg q.d. | 10 mg q.d. |
| Canagliflozin | 150 mg q.d. | 300 mg q.d. |
| Ertugliflozin | 7.5 mg q.d. | 15 mg q.d. |
| Sotagliflozin | 200 mg q.d. | 400 mg q.d. |