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

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## Protocol Signature Page

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

**Protocol Version/Date:** *TBD*

**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 the Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date of Signature: _____

# 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 | 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 acute heart failure (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 evidence also suggests 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 prognosis.<br><br>In this prospective registry of patients not treated with optimal doses of oral HF medications being discharged from an admission for AHF, ROBUST-HF, data will be collected describing 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) | 1. Describe in a multi-national multi-site registry the post-discharge care of patients with AHF, 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 NT-proBNP and finally outcomes during the first 6 months post-discharge.<br>2. Provide professional education and resources for physicians to accelerate the initiation and up-titration of evidence-based, guideline-directed medical therapies in appropriate patients following AHF hospitalization.<br>3. Provide hospitals and country leaders information on patterns of care for patients discharged from an admission for acute HF by summarizing and providing benchmark data reports. |
| Study Design | Prospective, multinational, multicenter, observational registry of patients being discharged from a hospital admission for AHF who were not previously treated with optimal doses of guideline-directed medical therapy (GDMT) for HF. |

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| Subject Population<br><br>key criteria for Inclusion and Exclusion: | Patients admitted for acute heart failure for at least 72 hours who are 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 meet all inclusion criteria and none of the exclusion criteria will be enrolled.<br><br><u>Inclusion criteria:</u><br><br>1. Admitted to the hospital for acute heart failure (diagnosed by dyspnea at rest and pulmonary congestion on chest X-ray or lung ultrasound) more than 72 hours prior to enrolment.<br>2. All measures within 24 hours prior to enrolment of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.<br>3. The last measurement during the hospital admission prior to enrolment of serum potassium ≤ 5.0 mEq/L (mmol/L).<br>4. The last measurement during the hospital admission prior to enrolment of NT-proBNP > 1,500 pg/mL<br>5. At admission and at the time of enrolment being prescribed: (1) none to < ½ the optimal dose (see section 19) of renin angiotensin system inhibitor (RASi) - angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), AND (2) none to < ½ the optimal dose of beta-blocker (BB), AND (3) none to ≤ ½ the optimal dose of mineralocorticoid receptor antagonist (MRA).<br>6. Written informed consent to participate in the study.<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 enrolment.<br>3. Presence at enrolment of any severe valvular stenosis or regurgitation in need of surgical correction.<br>4. Last measurement during the hospital admission prior to enrollment of eGFR < 30 mL/min/1.73m$^2$ or history of dialysis.<br>5. Currently enrolled in a clinical study that mandates a schedule of follow-up visits for heart failure, or particular assessments or treatment for heart failure. |
| Number Of Subjects | 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 |

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| Study Duration | Each subject's participation will last for a period of 6 months following hospital discharge.<br><br>The entire study is expected to last approximately 4½ years. |
| Study Phases<br><br>Site Education<br><br>Screening<br><br>Observational Period<br><br>Follow-Up | Site Education: Prior to enrolling any patients in the registry, and thereafter throughout the registry professional education regarding most recent guideline directed medical therapy and safety assessments/patient monitoring based on both national and international guidelines and recently published manuscripts will be provided to each participating investigator.<br><br>Screening: Investigators will identify eligible subjects who are hospitalized for AHF in their institutions. Screening for eligibility will be done and informed consent will be obtained just prior to anticipated hospital discharge.<br><br>Observational Period: Data will be collected regarding all outpatient visits for HF, rehospitalizations for HF, and death through 6 months post discharge.<br><br>Follow-up: At 6 months or early study discontinuation (e.g., due to death), patients will be contacted by phone to assess vital status (dead or alive), the occurrence of any re-hospitalizations, and prescribed HF medications. |
| Data Collected | In the registry information will be collected as follows*:*<br><br>1. Details on the AHF admission prior to enrolment inclusive of baseline characteristics, first laboratory exams, last laboratory exams prior to enrolment including NT-proBNP, creatinine, and potassium, medications before admission, at admission, during admission, and at enrolment.<br><br>2. Discharge from the hospital – date, time, medications prescribed, last laboratory tests available including NT-proBNP, creatinine, and potassium disposition.<br><br>3. All post-discharge outpatient visits through 6 months inclusive of timing, location, provider of health care during visit, physical examination inclusive of HF symptoms and signs, laboratory evaluations including NT-proBNP, creatinine, and potassium, medications prescribed, disposition.<br><br>4. At 6 months – details on any readmissions, death, visits with other healthcare providers, emergency department admissions, and prescribed HF medications. |

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| Statistical And Analytic Plan | Patients will be enrolled into the registry in each site in at least two blocks. Each block within site will represent a period of 4 months during which at least 15 patients will be enrolled. After the end of the 4-month enrolment period and after the enrolled patients have been followed for 6 months, data from these patients will be summarized and presented to the site. Following discussions with the sites, a second period of 4 months during which an additional at least 15 patients will be enrolled will be undertaken. Once the last patient in this enrolment period has reached 6 months follow up, data will be again summarized and presented to the site for discussion.<br><br>Summaries of results across the entire registry may be done periodically during the life of the registry. |
| Data And Safety Monitoring Plan | A Medical Monitor will review accumulating patient data and will alert the site principal investigator of any concerns regarding patient safety. |

# 4 BACKGROUND INFORMATION AND RATIONALE

## 4.1 INTRODUCTION

This document describes a multicenter, international research registry of patients who are about to be discharged from a hospital admission for acute heart failure (AHF). Patients will be enrolled who are 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 or 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.

Both issues may relate to a lack of clear acceptance and communication of patients' risk of adverse outcomes after an AHF admission. In line with other trials and registries, the STRONG-HF study has shown that the risk of dying after an AHF admission is approximately 10% at 6 months, and repeat admission or death, denoting disease progression, occur in a quarter of the patients under usual care. This risk can be reduced by a third within half a year, by rapid up-titration of GDMT. However, for this to occur, both physicians and patients need to become cognizant of the significant adverse outcomes of AHF, which mirror those of significant oncological disease, and accept both the need for frequent post-discharge outpatient visits and the occurrence of some adverse events while medications are up-titrated in a manner that may prevent disease progression. Without a recognition of the seriousness of AHF, physicians and patients may prescribe and take medications in a way that minimizes their adverse effects rather than aiming for maximally tolerated doses.

The cost of additional outpatient visits in some healthcare systems may also be a consideration and might be mitigated by modifying the approach taken in the STRONG-HF study, in which physicians (mostly cardiologists), physically assessed patients at 5 post-discharge visits within 3 months. Adapting the approach, for example by utilizing providers other than heart failure specialists or cardiologists, such as nurses, or some combination of telemedicine with laboratory analyses, might make implementation more feasible in some settings.

# 5 OBJECTIVES

The registry has three main aims:

1. Describe in a multi-national multi-site registry the post-discharge care of patients with AHF, 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 NT-proBNP and finally outcomes during the first 6 months post-discharge.
2. Provide professional education and resources for physicians to accelerate the initiation and up-titration of evidence-based, guideline-directed medical therapies in appropriate patients following AHF hospitalization.
3. Provide hospitals and country leaders information on patterns of care for patients discharged from an admission for acute HF by summarizing and providing benchmark data reports.

# 6 REGISTRY DESIGN

## 6.1 RESEARCH DESIGN

This is a prospective, multinational, multicenter, observational registry of patients admitted to hospital more than 72 hours for AHF who were not previously treated with optimal doses of GDMT for HF. Prior to enrollment of patients in the registry, participating investigators will be trained with respect to best practices for management of GDMT. Patients at participating centers who meet all eligibility criteria will be enrolled at least 72 hours following admission to hospital for AHF, and data regarding the patient's characteristics and the initial hospitalization will be collected. Data including examinations, blood test results, and prescribed medications will be collected for each post-discharge outpatient visit through 6 months post-discharge. Detail regarding any death or re-hospitalization through 6 months will be collected. Patients will be contacted by phone at 6 months to assess vital status, the occurrence of any rehospitalizations, and prescribed HF medications.

### 6.1.1 STAGES OF REGISTRY

Patients will be enrolled into the registry in each site in at least two blocks. Each block within site will represent a period of 4 months during which at least 15 patients will be enrolled. After the end of the 4-month enrolment period and after the enrolled patients have been followed for 6 months, data from these patients will be summarized and presented to the site. Following discussions with the sites (see below), a second period of 4 months during which an additional at least 15 patients will be enrolled will be undertaken. Once the last patient in this enrolment period has reached 6 months follow up, data will be again summarized and presented to the site for discussion.

### 6.1.2 EDUCATION OF SITES

Professional education regarding effective implementation of most recent guideline-directed medical therapy will be carried out, both before the initiation of a site and during the study, as well as after all patients in the first enrolment period and second enrolment period have reached 6 months follow-up and the data summarized and presented to the site. Efforts would include site-level discussions, country-level meetings/teleconferences and global meetings/teleconferences. Educational efforts will be aimed at providing the most up to date cardiovascular science and guidelines and best practice sharing to facilitate the transfer of knowledge into practice; as well as highlighting performance gaps and providing strategies to improve that performance driving to improving patient outcomes.

## 6.2 REGISTRY SITES AND NUMBER OF SUBJECTS

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 a total enrollment of up to 5000 subjects.

## 6.3 REGISTRY DURATION

Each patient will remain active in the registry for a period of 6 months following hospital discharge, after which time no additional information will be collected. Enrollment in the registry is anticipated to begin in third quarter 2023 and to continue for approximately 3 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, with additional members as deemed necessary throughout the study, and the 3 principals of the STRONG-HF study .
2. Steering committee – 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 SUBJECT SELECTION

## 7.1 INCLUSION CRITERIA

Patients admitted for acute heart failure for at least 72 hours who are 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 meet all the inclusion criteria and none of the exclusion criteria will be enrolled.

<u>Inclusion criteria:</u>

1. Admitted to the hospital for acute heart failure (diagnosted by dyspnea at rest and pulmonary congestion on chest X-ray or lung ultrasound) more than 72 hours prior to enrolment.
2. All measures within 24 hours prior to enrolment of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.

3. The last measurement during the hospital admission prior to enrollment of serum potassium ≤ 5.0 mEq/L (mmol/L).
4. The last measurement during the hospital admission prior to enrollment of NT-proBNP > 1,500 pg/mL
5. At admission and at the time of enrolment being prescribed: (1) none to < ½ the optimal dose (see section 19) of renin angiotensin system inhibitor (RASi) - angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), AND (2) none to < ½ the optimal dose of beta-blocker (BB), AND (3) none to ≤ ½ the optimal dose of mineralocorticoid receptor antagonist (MRA).
6. Written informed consent to participate in the study.

## 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 enrolment.
3. Presence at enrolment of any severe valvular stenosis or regurgitation in need of surgical correction.
4. Last measurement during the hospital admission prior to enrollment of eGFR < 30 mL/min/1.73m$^2$ or history of dialysis.
5. Currently enrolled in a clinical study that mandates a schedule of follow-up visits for heart failure, or particular assessments or treatment for heart failure.

## 7.3 CONSENT PROCEDURES

Consent forms describing study in detail including study procedures, and risks are given to the participant and written documentation of informed consent is required prior to enrolling the subject in the registry.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)- or Ethics Committee (EC)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to enrollment in the registry. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the

form signed, before any of the participant's data are entered into the registry. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

# 8 REGISTRY PROCEDURES

## 8.1 SPECIFIC TRAINING

The STRONG-HF study combined rapid up-titration of oral HF medications in three classes (RASI, BB, and MRA) with frequent visits to monitor patient safety. All three classes of medications were to be up-titrated to half optimal doses just prior to anticipated hospital discharge and to full optimal doses at 2 weeks if the patient's clinical status and laboratory results indicated that it was safe to do so. Investigators will be trained with respect to the need for close post-discharge monitoring of patients, and guidelines permitting the safe, rapid initiation and up-titration of contemporary four pilar GDMT that includes ARNI, (ACEi/ARB when ARNI) is not feasible, BB, MRA and SGLT2 inhibitors (Cotter 2022).

## 8.2 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 subjects who are hospitalized for AHF in their institutions. Recruitment strategies may vary among institutions.

## 8.3 DATA COLLECTION

### 8.3.1 DATA COLLECTION SCHEDULE

Data needed to confirm study eligibility, and written informed consent, are required to be collected for each participating patient. At each post-discharge visit, any changes in medications used to treat HF and patient outcomes in terms of readmission and death must be recorded; additional data (physical assessment, vital signs, laboratory results) should be recorded to the extent available. Data will be entered by the investigator or their designee into an eCRF.

| Data Collection SCHEDULE | Data Source | Enrollment (at least 72 hours after admission) | Discharge | Each Outpatient Visit | 6-Month Follow-up |
|---|---|---|---|---|---|
| Inclusion and Exclusion Criteria | Medical record | X | | | |
| Informed Consent | Original signed document | X | | | |
| Demographics | Patient reported and | X | | | |

| | | | | | |
|---|---|---|---|---|---|
| | medical record | | | | |
| Medical history | Patient reported and medical record | X | | | |
| Healthcare provider, setting | Investigator reported and medical record | X | X | X | |
| Medications for heart failure | Investigator reported and medical record | X | X | X | X |
| Physical assessment of heart failure signs and symptoms | Investigator reported and medical record | X | X | X | |
| Vital signs | Investigator reported and medical record | X | X | X | |
| Blood and urine test results, including NT-proBNP | Investigator reported and medical record | X | X | X | |
| Re-hospitalization* | Investigator and patient reported and medical record | | | X | X |
| Death† | Investigator reported and medical record | X | X | X | X |

*Including date and time of admission and discharge, primary reason for hospitalization

†Including date and time of death, primary cause of death

#### 8.3.1.1 SCREENING AND ENROLLMENT

Patients should be enrolled within 72 hours of hospital admission. To determine study eligibility, a chest X-ray or lung ultrasound, must have been performed. Vital signs, and local laboratory measures of serum potassium within 24 hours prior to enrollment, eGFR at the time of

enrollment, and NT-proBNP at enrollment must have been taken. The patient's medical history should be reviewed for significant pulmonary disease, renal disease, or history of dialysis and oral HF medications at admission and at enrollment should be reviewed. The date and time that informed consent was obtained (see section 14.3) will be considered the date and time of enrollment in the registry. Patient contact information (e.g., phone numbers, email address, street address) and alternative contacts (e.g., relative, friend, primary care physician) should be noted in the patient's record.

#### 8.3.1.2 OUTPATIENT VISITS FOR HEART FAILURE

To the extent possible, data for every post-discharge outpatient visit for heart failure 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 death or rehospitalization will also be captured. Any assessment of HF signs and symptoms, vital signs, or laboratory tests that were performed will also be captured.

##### 8.3.1.2.1 6-MONTH FOLLOW-UP

At 6 months following discharge, the patient's medical record should be reviewed for any unreported outpatient visits for HF, changes in oral HF medications, or lab results, re-hospitalizations and death. A phone call to the patient, or alternate contact(s), will be made to determine vital status (dead or alive), and to inquire about any rehospitalizations and current use of oral HF and other medications. If the patient is lost to follow-up, this will be recorded.

### 8.3.2 DATA TO BE COLLECTED

#### 8.3.2.1 DEMOGRAPHICS AND MEDICAL HISTORY

Detailed information regarding the patient's demographics and medical history will be obtained through review of the patient's medical record and patient interview for relevant conditions present prior to Screening. Demographic information to be recorded includes the patient's age, sex at birth, race and ethnicity (where permitted to be recorded), and socioeconomic status indicators including but not necessarily limited to education level, household income, and health insurance coverage.

#### 8.3.2.2 INITIAL HOSPITALIZATION FOR HEART FAILURE

Information regarding the hospitalization for heart failure during which the patient was enrolled will be collected. Data collected will include the admission and discharge dates; time spent in acute care units; vital signs, laboratory values, and clinical assessment of HF signs and symptoms at admission, at enrollment, and at discharge, and medications administered before admission at admission, and at enrollment, and medications and other therapies administered during the admission.

#### 8.3.2.3 MEDICATIONS FOR HEART FAILURE

Medications for heart failure prescribed just prior to anticipated hospital discharge, at each post-discharge outpatient visit through 6 months, and at 6 months follow-up 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.

#### 8.3.2.4 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, at enrollment 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, at enrollment and discharge, and at each post-discharge outpatient visit.

#### 8.3.2.5 BLOOD TEST RESULTS INCLUDING NT-PROBNP

Results available for the following local laboratory tests, if performed, will be collected at enrollment 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, urinary albumin and creatinine or any other blood and urine tests performed. NT-proBNP may be measured using either a lab analyzer or point-of-care device.

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

#### 8.3.2.6 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 SUBJECT COMPLETION OR EARLY WITHDRAWAL

### 9.1 INVESTIGATOR WITHDRAWAL OF SUBJECTS

Patients with whom the investigator loses contact will not be withdrawn from the study but will be considered as having missing data. If the investigator re-establishes contact, or learns of the patient’s death, after 6 months post discharge but prior to closure of the registry, data may be collected regarding the patient’s status up to 6 months post discharge.

### 9.2 SUBJECT REQUEST FOR WITHDRAWAL FROM REGISTRY

Patients wishing to withdraw their data from the research registry will be directed to contact the site principal investigator. From the point of withdrawal, no further data will be collected from the patient or their medical records. However, any data collected up to the point of withdrawal will be maintained for integrity of the research registry. Patients will be made aware of their rights in the consent form.

### 9.3 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN SUBJECTS

Patients who request withdrawal or who are withdrawn by the site PI from the registry will have their data maintained in the research database up to the point of withdrawal. This data will be included in subsequent analysis.

## 10 DATA MANAGEMENT AND QUALITY PLAN

### 10.1 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.

### 10.2 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 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.

All research activities will be conducted in as private a setting as possible.

Participants have the right to control the use and disclosure of their information. The site investigator will keep paper and electronic records of participants' 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 participant's medical care. The participant 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 participants in this study. The clinical study site will permit access to such records. All personnel accessing participants' records are required to respect their confidentiality.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center (DCC). 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.

### 10.3 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.

### 10.4 DATA SHARING

Individual participant 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.

## 11 STATISTICAL CONSIDERATIONS

Analyses summarizing an individual institution's data will be performed, and feedback provided to the participating center, after the first wave of patients has completed 6-months post discharge follow-up and may include 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.

### 11.1 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 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. 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.

### 11.2 ANALYSES TO ADDRESS FIRST AIM

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

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

- Description of the HF meds prescribed at discharge, and latest HF meds prescribed reported by 3 and 6 months with respect to optimal doses.
- Description of time to first post-discharge visit, number of post-discharge outpatient visits through 6 months and timing, 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) done, clinical assessment of congestion done.
- Description of 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).

### 11.3 ANALYSES TO ADDRESS THIRD AIM

Feedback for quality improvement may be based on quality indicators, including*:*

- Proportion of patients with follow-up visit within 1 week, 2 weeks, 1 month, 3 months, and 6 months post discharge,
- time from discharge to first visit,
- number of follow-up visits within 3 months post discharge,
- proportion of patients on medications in each of the four classes at discharge,
- 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,
- proportion of post-discharge visits where NT-proBNP measured, other labs measured, vital signs measured, clinical assessments of congestion done.

## 12 POTENTIAL RISKS AND BENEFITS

### 12.1 POTENTIAL BENEFITS

This study does not include any protocol-specified alterations to the treatment or medical care of registry participants. 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 the patient and future patients might be improved as a result.

### 12.2 POTENTIAL RISKS

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

### 12.3 MITIGATION OF RISKS

Provisions to protect the privacy of participants' data are described in sections 10.2 and 12.4.

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

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

information is being collected. Section 10.2 details processes for maintaining data confidentiality.

# 13 SAFETY CONSIDERATIONS

## 13.1 ADVERSE EVENT REPORTING

The ICH guideline on clinical safety data management definitions and standards for expedited reporting (E2A) defines an adverse event (AE) as an untoward medical occurrence in a patient administered a pharmaceutical product, whether or not the occurrence is related to or considered to have a causal relationship with the treatment, although the precise definition of an adverse event may vary according to institution or authority. A serious AE (SAE) is an event that results in death, is life threatening (an event in which the patient was at risk of death at the time of the event), requires or prolongs inpatient hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly. Important medical events may also be considered serious when, based on medical judgment, they may jeopardize the person exposed and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., death or prolonged hospitalization).

This registry is not following patients that have been exposed to a specified biopharmaceutical product or device. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including serious adverse events) these will be reported by the investigator to the IRB or Ethics Committee in accordance with the processes required by the IRB or Ethics Committee(s) that approved the research.

The investigator should report any AE with a reasonable possibility of being causally related to a drug to the company that manufactures the product or to the competent authority according to their normal practice for marketed products.

## 13.2 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.

# 14 ETHICAL CONSIDERATIONS

## 14.1 ETHICS COMMITTEES OR INSTITUTIONAL REVIEW BOARDS

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) or Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

## 14.2 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. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review

Board (IRB) or Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

### 14.3 PATIENT INFORMED CONSENT

Patients will be informed and consent will be obtained prior to enrollment in the registry as described in Section 7.3.

Patients will consent to the initial research purpose and use of registry data, and will consent to subsequent use of registry data by the Sponsor and clinical researchers for the same or different research purposes.

## 15 FUNDING SOURCE

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

## 16 SUBJECT STIPENDS OR PAYMENTS

Participants will not be reimbursed for their participation in the registry.

## 17 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 be 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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# 19 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 | 25 mg b.i.d. | 50 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** | | |

| | | |
|---|---|---|
| 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. |