Manual of Operations
Addendum to the LIFE Study

Entresto™ (**L**CZ696) **I**n Advanced Heart **F**ailur**e**

Version 2: May 15, 2019

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1 LIFE INTRODUCTION & CONTACTS

The purpose of the LIFE Addendum is to describe the study-specific operational plan and procedures to comply with the LIFE protocol and HFN Network policies and procedures generally outlined in the HFN Site Manual of Operations.

1.1 DCRI Coordinating Center Team

Name	Role	E-Mail	Phone
Pamela Monds	Project Leader	pamela.monds@duke.edu	(919) 668-8695
Teresa Atwood	Lead Clinical Research Associate	teresa.atwood@duke.edu	(919) 668-8841
LaGia Davis	Clinical Research Associate	lagia.davis@duke.edu	(919) 668-8748
Matt Baum	Clinical Research Associate	matt.baum@duke.edu	(919) 668-7809
Alexa Winston	Clinical Trials Assistant	alexa.winston@duke.edu	(919) 668-8806
Medical Monitor	DCRI_HFN_Clinical_Helpline@dm.duke.edu		(919) 970-4433
Trevorlyn Haddock	Safety Surveillance	trevorlyn.haddock@duke.edu	(919) 668-8552
Tracey Adams	Data Management	tracey.e.adams@duke.edu	(919) 668-8059
HFN RightFax #:	hfn.rightfax@dm.duke.edu		(919) 668-9871

1.2 Core Laboratories

Biomarker and Biorepository - University of Vermont, Dr. Russell Tracy
360 South Park Drive
Colchester, VT 05446
Rebekah Boyle- Project Manager
Office: 802-656-8938
Email: rebekah.boyle@med.uvm.edu

Please refer to the core lab specific Blood Processing MOP for further requirements and details.

1.3 InForm EDC (eCRF)

Questions regarding technical problems using the eCRF or to reset your password:
U.S. 1-866-999-DCRI [3274]
E-mail: edchelp@dm.duke.edu
Coverage: 6am to 12am Monday through Friday
Questions regarding data entry, queries, etc., contact your site CRA (contact information listed above in section 1.1).

1.4 Almac/WebEZ

Almac Clinical Technologies Helpline 1-800-923-3209

1.5 HF Network Clinical Helpline

Sites are encouraged to call the Clinical Helpline to seek assistance on unclear issues that arise, after consultation with your site PI/Investigator, when applying the protocol specified research plan to specific patients. Use of the Clinical Helpline is especially important before the randomization of a patient with any question regarding eligibility and when a patient is considering discontinuing the study for any reason.

The HFN Clinical Helpline is for questions related to:

- Enrollment
- Urgent clinical questions related to patients and the trial (most should be addressed initially by the site PI)
- Unblinding
- Discontinuations

The HFN Clinical Helpline is not for questions related to:

- Operational or procedural questions re: an HFN trial or Core Lab
- Re-supply orders should not go through the clinical helpline. Study Coordinators should contact the DCRI Coordinating Center (CC) or logon to the HFN website for site materials.

A physician will be available 24 hours a day to answer urgent questions about recruitment, enrollment, and patient management by calling the HFN Clinical Helpline at DCRI_HFN_Clinical_Helpline@dm.duke.edu (email preferred) or 1(919)970-4433 (pager). For non-urgent or general questions please contact your CRA.

HFN Fellows, will take the role as the Medical Monitor on the HFN Clinical Helpline. Study Coordinators should email the HFN Fellows if they do not receive a call back after paging the helpline. When placing a call to the HFN Clinical Helpline: listen carefully to the instructions on the phone. The prompter will either say a) enter your call back number or b) note the telephone number to call (cell phone). **It I important to listen to the whole message**, do not punch a number in right away or the message will not be delivered. If the Study Coordinator still does not receive a response from the Medical Monitor, then CC Site Management should be contacted.

2 HF NETWORK CLINICAL SITE ACTIVATION PROCESS

Site activation by the CC will occur once the following has been completed:

- Site contract has been executed
- Regulatory documents are complete and approved by CC (refer to table 1)
- Study/Protocol training has been completed by PI & Primary Study Coordinator (minimum)
- Inform and WebEZ Training completed by those requiring access
- Study drug & Core Lab supplies have been received
- Site Initiation Phone Visit Conducted (and any required action items closed)

All HF Network and study specific site manuals, documents and tools will be provided by the CC. Additional copies or resupply requests are available via the HFN website Resupply Request Form under the study folder on the HFN website at www.hfnetwork.org. Please review and organize all study specific materials and required documents prior to the Site Initiation Phone Visit with the CC. Please refer to the HFN MOP for details regarding preparation for patient enrollment.

Upon review and approval of the above required documents, along with completion of appropriate protocol training, the CC will notify each site PI, study coordinator, and other appropriate personnel of approval to initiate study enrollment. This notification should be filed in the regulatory binder as documentation of the date in which the site was activated.

TABLE 1 - Documents for Completion by each Clinical Site to be collected: (Please refer to the regulatory document completion guidelines provided with the regulatory packet for start-up documents.)

1.	Study Site Staff Delegation and Signature Log (SDSL)	Sites send to the DCRI project team at start-up. The SDSL is a living document and should be updated upon changes in personnel at site. The original is maintained at the site.

2.	Investigator CV / Bio sketch	RCC PI and site PI must provide current CV. Site sends to the DCRI project team prior to activation.
3.	Medical License	RCC PI and site PI must be current and available to the DCRI project team prior to activation
5.	COI Form	RCC PI and site PI listed on the SDSL must sign a COI at the start of the study and update it annually or upon change in COI status.
7.	Federal Wide Assurance (FWA) Number	FWA Number is updated according to the expiration date. Sites send to the DCRI project team prior to activation and as needed according to expiration date.
8.	Copy of IRB Approval for Protocol & Informed Consents	IRB approval must be updated yearly. Sites send IRB approvals and Informed Consents to the DCRI project team prior to activation and throughout study as IRB renewal and amendment approval is obtained. The CC will review and approve all ICFs prior to submission to their local IRBs.
9.	Documentation of Human Subject Protection Training	This documentation is required for all key personnel listed on the SDSL. Sites send documentation to the DCRI project team prior to activation and provides updates to the form when new key personnel are added.
10.	Signed Contract with CC	Each enrolling site in the U.S. needs an executed contract prior to activation.
11.	Protocol Training	Training certificates for each individual person(s) that attend DCRI training sessions will be provided by the DCRI project team. The PI and SC (at minimum) must receive protocol training prior to activation. Ongoing training and training of all other study personnel or new study personnel must be documented at the site.
12.	InForm Training	Each site user requiring access including the PI must complete InForm training.
13.	Almac IXRS/WebEZ	Each site user must attend a training session or review the WebEZ guide and send a signed copy of the site personnel training log or equivalent document to DCRI for access to WebEZ.

A change in study PI requires the collection of new or updated documents including CV, Medical License, updated ICF(s), IRB approval/acknowledgement, site delegation log, and contract amendment.

Additionally, evidence of qualifications including any licensures or credentials and documented protocol training for those listed on the SDSL should be maintained on file at the site.

3 SCREENING PROCEDURES

3.1 Screening/Recruitment Plan

A protocol specific Recruitment Plan will be completed by each enrolling site to define strategies to increase protocol awareness, delegate personnel and adequate resources, identify competing studies and prioritization plans, and list potential recruitment barriers and actions to mitigate barriers. This plan will be reviewed and discussed during the site initiation phone visit. Based on recruitment, it is expected that PI and study team will review the effectiveness of their plan on a periodic basis throughout the study and update strategies as needed to meet the HFN recruitment goal of 1 subject per month.

3.2 Pre-Screening Log (for non-consented subjects)

Sites are to maintain a record of subjects screened but not consented for the study. This screening log data will be entered by the site into SharePoint or the screening logs can be sent to the CC on a weekly basis at the beginning of the study, and then at minimum, monthly, as specified by the CC. Screening log data includes: date of prescreening, failed code(s), reason description, and chart status of failed. Note: All consented subjects will be entered into WebEZ and InForm.

3.3 Consent

Informed consent will be obtained as required by the local institutional review boards. Written informed consent must be obtained from the patient prior to beginning any activities that are not part of the patient's routine care. Patients should be encouraged to have supportive family member(s) and other advocates present during the consent process. Additionally, they should be given full access to all physicians involved in their care to aid in their deliberation on trial entry. Patients should be informed that their consent can be withdrawn at any time and for unstated reasons. All subjects will receive a copy of the signed informed consent and contact numbers for the research team in the event of questions or to report any concerns related to the study.

It is important to assess and rule out all inclusion/exclusion criteria prior to consent, in order to avoid unnecessary activities and/or screen failures.

Master Subject Log
Per GCP, sites will maintain a log of all subjects who signed informed consent along with their study ID, name, and medical record number. This information is confidential and should be files in a secure location.

4 SCREENING/VISIT 0 (Enrollment)

Patients with an advanced HFrEF and LVEF≤ 35% are screened for entry criteria.

Patients meeting screening eligibility criteria will be approached regarding participation in this study. Potentially eligible research participants will be identified by investigators reviewing the patients' medical records. The primary physician will be contacted with full explanation of the protocol and consultation regarding the suitability of the patient. If the primary physician agrees, patients will be approached for study participation. Suitable candidates will be approached by investigators (or their designee) regarding the study and be provided with detailed study information. After eligibility criteria has been confirmed, patients will undergo the consent process and written informed consent will be obtained prior to any study specific procedures and a copy of the consent form provided to the research participants.

Pocket Reference Cards will be provided with inclusion/exclusion criteria. This reference card also includes the study flow diagram and the schedule of activities table which will be a useful reference at the time of each patient assessment.

All subjects who sign informed consent will be screened in WebEZ and assigned a Subject ID (please refer to the WebEZ Manual on the HFN website), complete baseline assessments, and provided detailed instructions on screening procedures.

Please note that **V1/Run-in Start** visit must be within 7 days of **V0/Screening**. The rationale for the 7 day window is patient safety - before starting drug, the goal is to make sure that labs/clinical assessment done at screening are very representative of current patient status. The longer the gap between the patient being deemed eligible at V0/Screening and run-in beginning, the higher the chance of an interval change in status (e.g., worsening

kidney function) that would make us not want to start run-in. Please contact that HFN Clinical Helpline for guidance if this window cannot be met, as the patient may need to be screen failed and rescreened. For this reason, we recommend you specifically confirm the subject's availability for this visit as part of the inclusion for "ability to comply with study procedures" prior to completing the consent/enrollment process (i.e., hold off on obtaining written consent/enrolling & screening until this visit window can be met).

Study assessment and procedures include*:

- Complete Medical History, documented history of HF visits (inpatient and outpatient) within 6 months and Medication Review
- Physical exam including height, weight, SpO2, and orthopnea
- NYHA class assessment
- Confirmation of ejection fraction (EF) ≥35% within the last 12 months
- KCCQ
- Local laboratory testing, including complete chemistry panel: sodium, potassium, Chloride, CO2/bicarbonate, Total Calcium, Magnesium, BUN, Creatinine.
- Serum pregnancy test on all woman of childbearing potential
- Discontinue ACEI 36 hours prior to the start if the run-in phase, if applicable

*V0/Screening & visit assessments are expected to be conducted on the day of consent. However, for this visit only, standard of care labs are accepted up to 7 days prior to screening for outpatients and 24 hours prior for in-patients.

5 RUNIN/VISIT 1 (Begin run-in phase)

Visit should take place within 7 days of the screening/visit 0. This visit will begin the 3-7 day run-in period. All subjects will be administered LCZ696 50 mg po BID (At least 6 doses of the1 tablet BID). For those subjects taking ACEI prior to the run-in period, ensure that the ACEI has been discontinued and last dose of ACEI was ≥ 36 hours prior to the first dose of LCZ696.

Study assessment and procedures include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Local laboratory testing, including the following:
  - Sodium
  - Potassium
  - Chloride
  - CO2/bicarbonate
  - Total calcium
  - Magnesium
  - Blood Urea Nitrogen (BUN)
  - Creatinine
- Adverse event monitoring

For subjects who are stable and for whom lab results have been reviewed, the SCREEN/Visit 0 and RUNIN/Visit 1 may be combined at the investigator's discretion as long as the investigator ensures the 1st dose of LCZ696 is > 36 hours after last ACEI dose (if applicable).

All subjects will receive written dosing instructions and a screening diary to record doses taken during the run-in phase. IRB approval is required for all subject documents/materials

prior to distribution to participants. For hospitalized subjects, investigators and study staff should review medical records to ensure compliance with administration of the run-in test doses per the protocol.

After completion of this visit and the test dose phase, subjects will complete Study Visit 2 where the study doctor determines if they were able to tolerate LCZ696.

6 RANDOMIZATION/Visit 2 (End of Run-in/Begin Randomization)

V2/End of Run-in and Randomization visit is 3-7 days post V1. In the event the subject cannot return to the clinic within the 7 days, the subject should continue to take the open label study drug until V2. V2 assessments should be conducted on the day of the visit. Run-in tolerability will be evaluated based on Investigator review of these assessments and either screen failed or passed accordingly.

If pass/tolerated, the subject can be randomized. If failed, screen failure status must be updated in WebEZ.(refer to the WebEZ Guide for detailed instructions). Per the protocol, subjects will need to be followed via telephone to assess clinical stability/safety for two weeks post last dose of study drug.

All eligible subjects who tolerate* the run-in phase of LCZ696 will be randomized at Study Visit 2 following the below assessments:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Local laboratory testing, including the following*:
  - Sodium
  - Potassium
  - Chloride
  - CO2/bicarbonate
  - Total calcium
  - Magnesium
  - Blood Urea Nitrogen (BUN)
  - Creatinine
- Core laboratory testing (Cystatin C, BNP/NT-proBNP)**
- Adverse event monitoring

*Note: Investigator review of local lab results prior to randomization is important to ensure that the run-in was safely tolerated (e.g., evaluate for newly worsening creatinine or hyperkalemia) by the patient and that randomization is appropriate. Failing to review labs may put the subject at increased safety risk and could unnecessarily result in premature study drug discontinuation/subject withdrawal which impacts endpoint collection.

**Biomarker compliance is critical for the primary analysis of LIFE.

A Randomization Worksheet with evidence that the patient meets inclusion/exclusion criteria and a signed Informed Consent Form should be completed prior randomization.

Subjects will be randomized 1:1 to two treatment groups LCZ696 or valsartan. Randomization should occur immediately following the end of the run-in phase. If the subject cannot return to the clinic within 7 days of starting the run-in phase, the subject should continue to take LCZ696 po BID until the randomization visit and site personnel should notify the CC.

Subjects will be randomized by using WebEZ's randomization system. For detailed instructions on randomization procedures, please refer to the WebEZ User Guide.

Following randomization, study staff will notify the IP contact via order by a study clinician to dispense the assigned study drug kit (low dose or high dose kits) depending on previous ACEI or ARB medication dosage or lab test results. Study staff will educate the subject on how to take and store the medication and to document their study drug doses and other important medication changes in the diary provided by the CC. Study staff will reinforce the importance of taking medication from both bottles (active and placebo) and returning all bottles at the next in-clinic visit for the investigator and study staff to assess dosing compliance.

Randomized subjects will receive the first dose of study drug as follows:

- For subjects not previously taking ACEI or ARB, previously taking ACEI or ARB at a low dose, or participants who have an eGFR < 30 mL/min/1.73m², the starting dose of valsartan will be 40 mg po BID and the starting dose of LCZ696 will be 50 mg po BID.
- For subjects taking an ARB at greater than low dose†, the starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID.
- For subjects taking an ACEI at greater than low dose, the ACEI will be withheld for ≥ 36 hours prior to randomization. The starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID.

*At Investigator discretion, study drug may be started at the low dose (LCZ696/placebo 50 mg po BID or valsartan/placebo 40 mg po BID) if there are any concerns regarding tolerability at the 100 mg / 80 mg dose.

All subjects will receive the following documents or materials at Study Visit 2:

- A patient wallet card to present to a hospital, emergency room or urgent care facility following randomization into the trial
- Study Drug Regimen Instructions
- Participant Diary to document study drug dosing following randomization
- An HFN Tote Bag – to transport study materials/supplies
- An HFN Sharpie Pen – to record date each foil packet is opened

IRB approval is required for all subject documents/materials prior to distribution to subjects.

Study staff will define optimal times and phone numbers for the protocol specified phone contacts to encourage compliance with study procedures. Reminders will include study drug dosing and use of the diary, plans for future study visits and the reminder to bring back study drug for compliance assessments.

7 FOLLOWUP EVALUATIONS

Follow-up visits and associated assessments should be conducted for randomized subjects based on the corresponding number of weeks post V2.

Clinic Visit 3, 4, 5, 7, and 10

Patients will complete in-clinic visits at 4, 8, 12 and 24 weeks after randomization. Two and four weeks after randomization (clinic visits 3 and 4) are dose titration visits. The Investigator will ascertain if the study medication is well tolerated. If tolerated, study treatment will be titrated up (doubled at each visit) to the target dose of 200 mg LCZ696 (two 100 mg LCZ696 and two placebo tablets po BID) or Valsartan 160 mg (two 80 mg valsartan and 2 placebo tablets po BID).

Study staff will educate the subject on the following:

- How to take and store the medication
- How to document their study drug doses and other important medication changes in the diary provided by the CC.
- Reinforce the importance of taking medication from both bottles (active and placebo)
- Importance of returning all bottles and completed diary to all study visits

Study staff will complete drug accountability activities at each visit to assess patient compliance and clarify any discrepancies with the subject. Patient re-education will be provided, as needed, to maintain and/or improve compliance (significant concerns should be addressed with Investigator).

For hospitalized subjects, investigators and study staff should review medical records to ensure compliance with administration of the study medication doses per the protocol.

The following procedures will be performed:

- Interim History and Medication Review
- Physical Examination (except visit 5)
- Local laboratory testing, including the following:
  - Sodium
  - Potassium
  - Chloride
  - CO2/bicarbonate
  - Total calcium
  - Magnesium
  - Blood Urea Nitrogen (BUN)
  - Creatinine
- Core Laboratory Testing (BNP/NT-proBNP) (including Cystatin C at visits 4, 5, 7, and 10)
- AE Monitoring
- Adherence and tolerance assessment
- KCCQ (visits 4, 7, and 10)

Phone Visit 6, 8, and 9

Study staff will contact the patient by telephone at 10, 16 and 20 weeks after randomization ($\pm$ 5 days) to assess dosing compliance with study drug and inquire about applicable adverse events and events of interest. The patient will be reminded to take the study medication and the date and time of their next study in-clinic visit.

Study staff will contact the patient by telephone at 26 weeks after randomization to inquire about applicable adverse events and events of interest.

Unscheduled Visits

If the Investigator determines that a participant should be brought to the clinic to be evaluated for a potential change in study drug dose between scheduled study visits, an “unscheduled visit” should be done. Study drug dose changes will be recorded in the eCRF.

Assessments expected at this visit include:

- Interim history
- Review of medications
- Physical examination
- Local laboratory testing, including the following:
  - Sodium

- Potassium
- Chloride
- CO2/bicarbonate
- Total calcium
- Magnesium
- Blood Urea Nitrogen (BUN)
- Creatinine

- Adverse event monitoring

8 Biomarker Sample Compliance

The primary objective of LIFE is to evaluate the effects of sacubitril/valsartan (LCZ696) compared to valsartan on the proportional change from baseline for NT-proBNP levels at 2, 4, 8, 12, and 24 weeks. Given the importance of NT-proBNP values to the primary analysis, diligence in collecting all samples from baseline through week 24 is critical.

Study teams must ensure that the processes for systematically collecting all samples are done and quality improvement processes are in place to ensure steps are taken to meet the primary objectives of the LIFE study. This could include revising local operating procedures to identify time points, collection methods, processing, storage, packaging and shipping of LIFE samples. Instructions as outlined in the LIFE Biomarker Core Lab Manual should followed and regularly reviewed for compliance.

9 STUDY DRUG

9.1 Study Drug

In order to maintain the study blind, study drug will be administered in a double-dummy design, where subjects will take both active drug (either LCZ696 or valsartan) and placebo. Subjects will take LCZ696 plus placebo or valsartan plus placebo twice daily by mouth, according to the Dosing Guidelines.

9.2 Study Drug Dispensing

Drug distribution will be managed by the CC in collaboration with Almac. Upon site activation, sites will receive an initial supply of blinded study drug kits (containing both active and placebo tablets) and resupplied as needed until completion of enrollment. At enrollment, the pharmacy or IP contact at each site will provide the study personnel with sufficient study drug supply to permit twice daily dosing as prescribed by their study doctor. The study drug will be self-administered in the outpatient setting. Please refer to the LIFE Pharmacy Manual and LIFE Kit Dispending Guidelines for additional details.

9.3 Dosing Guidelines

The study will begin with the 3-7 day run-in period in which all subjects will be administered LCZ696 50 mg po BID. For those subjects taking ACEI prior to the run-in period, the first dose of LCZ696 will be held ≥ 36 hours after last ACEI dose.

Subjects tolerating the LCZ696 in the run-in period will be randomized to either LCZ696 or valsartan. Doses will be assigned in the following fashion:

If previously taking no ACEI/ARB, low-dose ACEI/ARB†, or eGFR < 30 ml/min/1.73m^2

- LCZ696 50 mg po plus placebo BID or valsartan 40 mg po plus placebo BID

If previously taking greater than low dose ACEI/ARB†

- LCZ696 100 mg po plus placebo BID or valsartan 80 mg po BID plus placebo

Two weeks after randomization, upward dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID or valsartan 160 mg po BID. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.

Two weeks after the prior dose titration visit and four weeks after randomization, further dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID or valsartan po 160 mg BID. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose. The total duration of study drug treatment will be 24 weeks.

† Low dose is defined as 24 hour dose of ≤ 10 mg lisinopril, ≤ 5 mg Ramipril, ≤ 50 mg Losartan, ≤ 10 mg Olmesartan, or other dose equivalent.

At designated visits, subjects will be resupplied using WebEZ. Subjects may also be resupplied with a low dose kit at any time during the study if needed for tolerance. For detailed instructions on resupply procedures, please refer to the Almac User Guide and LIFE Kit Dispending Guidelines.

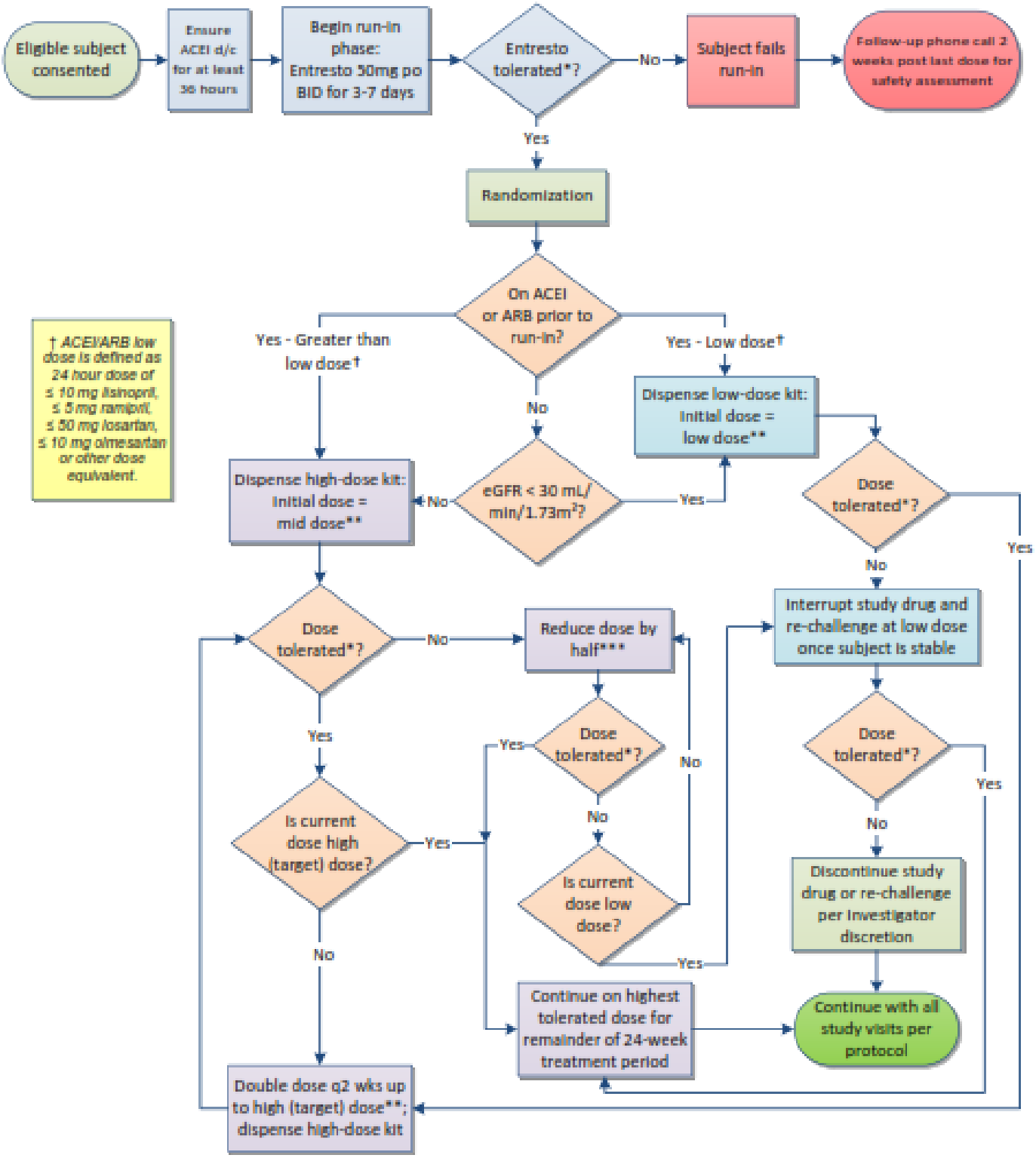
Subjects will discontinue the study medication when they return to Study Visit 10 (24 weeks +/-5 days).

9.4 Study Drug Interruption

If a subject should stop taking the study medication for any reason before completing the 24 weeks of study drug dosing, an attempt should be made to restart the study drug at the last tolerated dose when the subject is stable, per physician discretion. If the treating physician decides to stop study medication and start the patient on an ACEI, then a 36 hour wash-out period is required after the last dose of study drug before starting the ACEI. All subjects will complete all study assessments through study visit 11, regardless of whether they have received the full 24 weeks of study drug treatment.

Please see below for the HFN-LIFE Study Drug Dosing Flow sheet

HFN-LIFE Study Drug Dosing Flowsheet



*"Tolerated" for this study is defined as SBP > 90 mmHg, creatinine (Cr) ≤ 2.0 mg/dL, and no symptoms of hypotension.

** Study Drug: Low dose = 1 tab from each bottle in low-dose kit po BID
Mid dose = 1 tab from each bottle in high-dose kit po BID
High (target) dose = 2 tabs from each bottle in high-dose kit po BID

*** If subject was on high dose, reduce to mid dose. If subject was on mid dose, reduce to low dose (dispense low-dose kit.)

9.5 Drug Storage, Accountability and Destruction

9.5.1 Storage

Store at 20-25°C (68-77°F) with excursions between 15°C and 30°C (59°F and 86°F) are permitted. All other excursions should be immediately reported to the CC . Protect from moisture. Investigators should ensure proper storage conditions and record and evaluate the temperature. Study drug should be stored in a locked and secure environment.

9.5.2 Drug Accountability

All study drug shipments received at the site must be accounted for in written documentation and maintained by the investigator. Forms to record receipt and dispensing of study medication will be provided prior to the initial shipment of the study drug. A copy of the completed study drug accountability record will be provided to the CC as part of the study closeout activities.

9.5.3 Site Drug Accountability Log (DAL)

The Drug Accountability Log (DAL) is used to document dispensation of all kits received: when a shipment of drug is received, when study drug is dispensed, when drug is lost/damaged, when drug is returned and/or destroyed. The site should initial by each entry.

After a patient is dispensed study drug, the **Drug Accountability Log** or equivalent document should be completed. The subject number, amount of study drug, date dispensed, and amount and date returned must be documented on the subject drug accountability log (SDAL).

The following study drug records should be maintained by the designated site personnel:

- All study drug shipment invoices
- All IXRS confirmations documenting allocation for each subject number
- Study Drug Accountability Logs or equivalent
- Subject Specific Accountability Logs for study drug return and compliance assessment

Subjects should be reminded to return all unused study drug at the next study visit. At each visit, study drug counts should be completed and compared to the subject diary for consistency to assess and document subject compliance. All efforts should be made to have study drug returned.

9.5.4 Destruction

Study drug should not be destroyed until written authorization is obtained from the CC. Once authorization is received, partially used and unused study drug should be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure. A copy of the drug destruction SOP should be maintained in the pharmacy section of the Regulatory Binder. Study drug destruction should be documented in the comments section of the Drug Accountability Log.

9.5.5 Randomization, Stratification and Blinding

Subjects will be consented and enrolled at the Screening Visit (V0). This will be followed by a run-in phase (V1). Subjects who successfully tolerate the study drug during the run-in phase will be randomized at Visit 2. Subjects will be randomized in a 1:1 allocation ratio using a permuted block design with stratification based on the clinical center and atrial fibrillation status. This will ensure relatively equal distribution of subjects to each arm within each site.

9.5.6 Unblinding

Unblinding should be a very rare occurrence. The investigative sites will be given access to the treatment code for their participants for emergency unblinding ONLY by contacting the medical monitor at the CC. Decisions about un-blinding will be made at the discretion of the site PI and the CC Medical Monitor. Randomization data are kept strictly confidential, accessible only to authorized persons until the time of unblinding.

9.5.7 Concomitant Medications

Subjects should be treated with standard HF strategies (diuretics for congestion, blood pressure control and heart rate control if subject is in atrial fibrillation) as per recommended guidelines. Subjects may not take ARBs (other than blinded study drug) during the study, and ACE inhibitors and direct renin inhibitors are prohibited during the study.

10 SCHEDULE OF ASSESSMENTS and PATIENT FOLLOW-UP

Visit number	0	1	2	3	4	5	6	7	8	9	10	11	
Time of Visit	Enrollment	Run-in*	1st dose	Dose titration (2 weeks)	Dose titration (4 weeks)	8 weeks	10 weeks	12 weeks	16 weeks	20 weeks	24 weeks	26 weeks	Unscheduled Visit for dose adjustment
Inclusion/Exclusion criteria	x		x										
Information & Informed consent	x												
Physical examination	x	x	x	x	x			x			x		x
KCCQ questionnaire	x				x			x			x		
Dispense study medication		x[1]	x	x	x	x		x			x		x
Laboratory test (routine)+	X^	x	x	x	x	x		x			x		x
Laboratory test (core)			x[2]	x[3]	x[2]	x[2]		x[2]			x[2]		
Adverse events		x	x[4]	x	x	x	x	x	x	x	x		x
Telephone follow-up							x		x	x			
Telephone Safety Assessment												x	

* The Screening visit and Visit 1 may be combined at the investigator's discretion for subjects who are stable and for whom lab results have been reviewed as long as the investigator ensures the 1st dose of LCZ696 ≥ 36 hours after last ACEI dose (if applicable). If not combined, Visit 1 should take place within 7 days of the Screening Visit

\+ Local lab tests include the following: Sodium, Potassium, Chloride, CO2/Bicarbonate, Total Calcium, Magnesium, BUN, Creatinine

^ For Screening/Study Visit 0 only - Standard of care labs are acceptable, using results within 24 hours prior for hospitalized patients and within 7 days prior for outpatients.

[1] Open-label LCZ696 (50 mg po BID) during run-in phase

[2] BNP, NT-proBNP and Cystatin C

[3] BNP and NT-proBNP only

[4] Run-in failure patients should be contacted approximately 2 weeks after their last dose of study drug.

10.1 Patient Discontinuations

It is expected that every attempt is made to have the subjects complete all study treatment, assessments, evaluations and lab work per protocol. If the patient states that they no longer want to participate in the study, please clarify exactly what aspects of the study the subject wishes to discontinue. It is expected that the Study Coordinator notify and involve their PI/Investigator in these decisions:

- If a patient request to stop study drug and/or intervention – clarify if they will continue to complete all other study assessments.
- If a patient request to stop study assessments and/or clinic visits – clarify if they will allow you to continue to follow via phone, contacting their physician and allowing you access to the medical records.
- If a patient will not allow phone follow-up – clarify if they will allow medical record review.
- If a patient will not allow medical record review, no longer wants to participate in the study and withdraws consent then do not contact them further.

After internal consultation with Site PI/Investigator, the site is required to contact the HFN help line anytime that a patient request to discontinue any or all study participation, as described above, for additional guidance/instruction. In addition, sites must document these discussions and decisions in the source records.

10.2 Lost to Follow-Up Procedures

It is essential to have biomarker samples, safety and mortality status on all patients within the HFN studies. Below are the procedures for locating a lost to follow-up patient:

Five Telephone Contact Attempts

There should be at least 5 attempts to contact the patient at home. 2 of these contacts should be in the evening hours and 1 attempt should be on the weekend. In addition, these calls should be spread over a 2-week period.

Call Primary Care Physician

If the above attempts fail, a call to the primary care physician should be made. Often times the primary physician may have additional information that may not have been relayed to the Study Coordinator.

Send Certified Letter

If these attempts fail, then a certified letter should be sent to the patient with return receipt requested. Any information completed on the return receipt will at least give you a date the patient was last known to be alive.

Other Methods for tracking patients:

- Hospital medical records – further assistance in obtaining patient information admission/discharge dates with treating physician names
- Hospital demographic database – encounter dates (office visits, ER visits, admissions)
- Vital records/register of deeds – verify and obtain actual date of death (verify copy of death certificate), location of death
- Public libraries – assistance in determining/locating death information via obituaries.
- National Death Index – may be used to determine if a patient is alive
- Internet – may be used to find patients who may have moved.

11 ELECTRONIC CASE REPORT FORMS (eCRF)

This study will use InForm, a web-based electronic CRFs developed through a validated, electronic records and electronic signatures (ERES)-compliant platform (21 CFR Part 11). Site staff who will be entering data will receive training on the system, after which each person will be issued a unique user identification and password.

Qualified study staff at each site will perform primary data collection from source-document reviews.

Refer to the LIFE-HF eCRF instructions for detailed instructions on entering data into InForm.

The investigator is responsible for the integrity and accuracy of the data. The investigator must ensure completeness, legibility, and timeliness of the data reported. In addition, the PI must review and sign electronically to verify data accuracy. Data will be entered from the subject medical records into the eCRF. Subject medical records will be maintained at the site and considered the source documents for this clinical trial. Study records and regulatory documents will be retained at the study site, along with adequate source documentation, according to NIH requirements. All study records, including source documents, must be available for inspection by the DCRI CC and the NIH.

Data management expectations include:

- Maintain a minimum of 90% on-time data entry and cleaning
- Enter all visit data into InForm within 5 business days of visit completion
- Comply with protocol windows and schedule of assessments
- No visit has missing items for more than 30 business days
- No queries are open for more than 30 business days
- Requests for source documentation are submitted via secure fax or FTP site within 5 business days
- Requests for PI signature on safety events occur within 5 business days
- PI signature is obtained on all subject data in InForm at trial completion

12 METHODS TO PROMOTE ADHERENCE

Protocol training and adherence will be a major focus of the Investigator training. Based on our experience in prior studies, identifying and correcting non-adherence is best accomplished in a stepped approach. The site will be responsible for protocol compliance, maintaining high data quality, and managing participant compliance with study drug administration and visit adherence. The CC will provide data quality reports for review and will follow-up to re-emphasize the importance of adherence as needed. Data Quality reports will be provided to the sites to assist with identifying process issues, and significant non-adherence concerns will be escalated to the Executive Committee.

13 SAFETY MONITORING AND REPORTING

The reporting of information from an adverse experience (AE) can lead to important changes in the way a new treatment is developed, provide integral safety data, and foster awareness of new and important information concerning serious adverse events (SAE) among regulators, investigators and other appropriate people. The Site Investigator is responsible for monitoring the safety of patients enrolled in this study at each study site.

Consented subjects will be followed for serious adverse events through week 26 for randomized subjects and 2 weeks post last study drug dose for run-in failures.

13.1 Safety Definitions

AE, SAE, and endpoints: Refer to HFN LIFE protocol adverse events section for study specific definitions.

Business Day: Any day which is not a Saturday, Sunday or public holiday. Business hours are 08:00 to 17:00 Eastern Standard Time.

Calendar Day: Any 24-hour day of the seven-day week.

Receipt Date: The date when DCRI Safety Surveillance becomes aware of safety related information. The date of receipt of each initial and follow-up report will be clearly marked on all documents. If information is received on a non-business day or after normal working hours on a business day, the receipt date will be the next business date. Additional information received during processing of the initial version of a case (prior to reporting to the LIFE-HF DCRI trial team/designee) does not reset the regulatory reporting clock, based on receipt of follow up information at this point; however, new information will be incorporated within the initial case.

Day 0: The calendar day that DCRI Safety Surveillance is notified of an SAE or, if different from day received by DCRI Safety Surveillance, the date the medical monitor has determined the event qualifies for voluntary reporting to the regularity authorities.

Safety Medical Monitor: A physician assigned to the study to perform a review of serious adverse events, review the investigator's brochure or product labeling for listedness, and to confirm the MedDRA coding for the event.

Study Medical Monitor: A physician assigned to answer clinical questions regarding the protocol.

Valid Case: A case that includes each of the following minimum criteria for the purposes of reporting:

- an identifiable patient
- the name of the suspect medicinal product(s) or clinical study if considered related to a clinical study or procedure/design
- an identifiable reporting source
- a serious adverse event

13.2 Anticipated Disease Related Events

The following are anticipated, disease-related events in patients with HF or anticipated events of interest in patients with heart failure taking valsartan or valsartan/sacubitril:

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias.
- **Sudden Cardiac Death:** This refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy.
- **Acute coronary syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI).
- **Unplanned hospitalization, ER visit or clinic visit for worsening HF:** This refers to treatment for acute heart failure such as receiving intravenous diuretics.
- **Cerebrovascular event:** This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA).
- **Venous thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus.
- **Lightheadedness, Presyncope, or Syncope:** This includes dizziness, lightheadedness, or fainting from any cause.
- **Worsening renal function:** This refers to acute kidney injury, typically defined as a decrease in eGFR ≥ 20% over 48 hours, or progressive loss of renal function over time.
- **LVAD implantation:** This refers to implantation of a temporary or durable LVAD.
- **Cardiac Transplantation**
- **Hyperkalemia ≥ 5.5 mEq/L**
- **Acute renal failure with serum creatinine > 2.5 mg/dL**
- **Angioedema**
- **Symptomatic hypotension**

Anticipated events will not be captured as AEs/SAEs during the study, but will be entered on the appropriate electronic case report form (eCRF) module ("Events of Interest" page).

13.3 Recording and Reporting of Adverse Events

Non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs, except the above listed anticipated events, occurring from signed informed consent through study visit 11 will be captured on the SAE eCRF. Subjects that have screen failed will be followed for SAEs until two weeks post last study drug dose. Unless exempted (anticipated, disease-related events, as described in section 12.2), all SAEs whether or not deemed drug-related or expected must be reported by the investigator or qualified designee within 24 hours of first becoming aware of the event. For this study, the cause of death will be reported on either the SAE or Events of interest (EOI) eCRF, as well as the Death eCRF page. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will result in

distribution of the information to DCRI Safety Surveillance. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to DCRI Safety Surveillance at 1-866-668-7138. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

Any misuse or abuse of the study drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective of whether a clinical event has occurred) must also be reported to DCRI. DCRI Safety Surveillance will share all SAE reports with Novartis Pharmaceuticals.

13.4 Follow-up

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. It is understood that complete information about the event may not be known at the time the report is submitted. The Investigator must assign causality to the study drug and should make every attempt to obtain enough information about the event to do so. As additional information pertaining to an SAE becomes available, the eCRF should be updated. It is the responsibility of the Investigator to follow all reportable SAEs until there is a return to the patient's baseline condition, or until a clinically satisfactory resolution is achieved, and to respond to queries for missing data or data clarifications.

DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, until otherwise explained, or until the last subject completes the final follow-up, whichever occurs first. DCRI Safety Surveillance will forward all SAEs to the DCRI LIFE Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs within 1-2 business day(s) of receipt. Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements. The DSMB will be provided detailed safety data approximately every 6 months throughout the study.

13.5 Suspected Unexpected Serious Adverse Reaction

Adverse events which meet the criteria of serious, related to study drug, and unexpected for that drug, per product labeling, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events confirmed by DCRI Safety Medical Monitor, as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

A copy of this report should be kept at the site and also forwarded to the assigned DCRI study monitor.

13.6 Pregnancy

Pregnancy will be ruled out prior to randomization. Thus pregnancy occurrence during the study period is not expected and only those patients who are either post-menopausal or surgically sterile or have a negative pregnancy test will be included in this study. Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated SAEs that occur to the mother or fetus/child will be recorded in the SAE eCRF, within InForm. The pregnancy outcome of a female partner to a male study participant will not be followed. DCRI will share all pregnancy reports with Novartis Pharmaceuticals.

13.7 Study Site Responsibility

1. The site will identify an SAE.
2. Site will determine whether the event is an anticipated disease related event.
3. Enter anticipated disease related events on the **EVNTINT** eCRF page, as these events will not be captured as AEs/SAEs, regardless of relationship to study drug.
4. Enter all serious adverse events on the SAE page, including the SAE narrative, relevant laboratory/diagnostic tests and relevant concomitant medications.
5. Once information is entered on the SAE page in InForm, this will generate an SAE email notification to DCRI or site will complete a paper SAE form and fax/email to DCRI if InForm is down.
6. Sites will complete the online voluntary MedWatch for events confirmed by the safety medical monitor to be **RELATED** to study drug and **UNEXPECTED.**
7. Sites will submit a copy of the voluntary MedWatch to the regulatory authorities, DCRI Safety Surveillance and LIFE trial Team.
8. Sites will enter all patient deaths on the **Death eCRF page**, regardless of expectedness or relatedness.
9. Sites will report SAEs resulting in death: record on the SAE eCRF + Death eCRF.
10. Sites will report Anticipated disease related events resulting in death: record these events on the EVNINT eCRF + Death eCRF.

13.8 DCRI Safety Surveillance

1. Will be notified of SAEs via InForm generated emails.
2. Will generate the SAE report from InForm as a PDF document.
3. Will perform a clinical review of all SAE forms to verify that all sections are complete and consistent.
4. Will write a clinical narrative of the event in sufficient detail to enable event. processing for all serious, related and unexpected adverse events.
5. Will enter the data into the DCRI safety database.
6. Will code the event using the current MedDRA dictionary
7. Will independently issue queries on the SAE eCRF in InForm or will fax/email queries for incomplete or inaccurate information for the following fields:
    - Serious adverse event term
    - Event onset date and time
    - Event stop date and time
    - Severity
    - Relationship to study drug including rationale (if positive assessment provided)
    - Serious criteria
    - Outcome
    - SAE narrative
    - Relevant concomitant medications
    - Relevant labs/diagnostic test data
    - Study Drug start date and dose
    - Action taken with Study Drug
    - PI verification

8. Will email the SAE reports to the DCRI LIFE Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs, including any queries generated for the site within 1-2 business days of initial receipt.
9. Will assist with SAE data reconciliation of the LIFE safety database with the InForm database on the following data variables: Subject ID, Verbatim Term, MedDRA Preferred Term, Onset date, Outcome and Causality.
10. DCRI Safety surveillance will inform site Investigators to submit a voluntary MedWatch if the DCRI safety medical monitor confirmed an event as serious, related to study drug and unexpected per product labeling.
11. DCRI Clinical Operation will be responsible for filing copies of the voluntary MedWatch/CIOMS-I reports (generated by the sites), in the master project file at DCRI.

13.9 DCRI Safety Surveillance Medical Monitor

1. Will review all study drug related SAEs
2. Will review the MedDRA coding for the event
3. Will review the site reported causality assessment
4. Will assess and verify the event for causality assessment and listedness per the product labeling.
5. Request additional follow-up, as needed

13.10 Coordinating Center PI

1. Will be responsible for reviewing all SAEs/SUSARS for MedDRA coding, and evaluating the event for voluntary reporting to the regulatory authorities.
2. Will send any additional queries to DCRI, as needed, to be entered into InForm.
3. Will assess and confirm the event for listed per the current documents or product labeling.

13.11 Data and Safety Monitoring Board (DSMB)

The DSMB will be provided detailed safety data approximately every 6 months throughout the study including all SAE data in accordance with the HFN DSMB charter.

13.12 SAE Reconciliation

The clinical data, including all SAEs will be housed in the InForm database. A separate safety database will be maintained in Argus. DCRI Safety Surveillance will assist with reconciling the data within InForm, with the information within the Argus safety database to ensure that the data matches and/or is clinically consistent. Additionally, the clinical and Safety data received by DCRI Safety for the HFN_LIFE trial will be reconciled annually with the list of SAEs received by Novartis Safety from DCRI Safety Surveillance for the HFN_LIFE study, per contractual agreement.

13.13 Disposition of Safety Records

DCRI Safety Surveillance will forward a copy of the SAE reports to the LIFE trial team and to Novartis Pharmaceuticals during the study. The electronic safety files will be archived in DCRI Safety Surveillance at the end of the study.

14 RECORD RETENTION

Records relating to the study, including receipt and disposition of the study materials will be retained for at least 3 years after completion of the research or earlier termination of the study. Source documents, such as patient charts, will be retained for not less than five years.

15 ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CC	Coordinating Center
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DAL	Drug Accountability Log
DCRI	Duke Clinical Research Institute
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAR	Suspected Adverse Reactions
SUSAR	Suspected Unexpected Serious Adverse Reaction

16 REFERENCES

(Refer to HFN Website: LIFE Protocol Manuals, Protocol, Regulatory Documents, Study Coordinator Materials, and Subject Materials).

17 Revision History

V1	30Jun2016	Initial version
V2	15May2019	Updated to reflect protocol amendment changes (v6/15/2017 & v2/20/2019) and expanded on study expectations throughout the document to promote study compliance and quality.