Manual of Operations

Addendum for IRONOUT

Oral **I**ron **R**epletion effects **ON** **O**xygen **U**p**T**ake in **H**eart **F**ailure: **IRONOUT-HF**

July 14, 2014

Table of Contents

1 IRONOUT Contacts

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Please refer to the Core Lab Manual of Operations (MOP) for additional details regarding the procedures for the collection, storage and shipment of biomarker samples and transfer of CPET data for the IRONOUT study.

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 entering subject data, queries, traffic lights, etc., contact the DCRI Site Management team

1.4 Clinical Helpline and aXcess

Almac Clinical Technologies	Telephone Number
Clinical Helpline	919-970-4433
Axcess Helpline (US	1-800-923-3209

2 TABLE 1 - Process for Activation as a HF Network Clinical Center

TABLE 1: Documents for Completion by each Clinical Center *(refer to 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. Original stays at site.
(2)	Investigator CV/Biosketch	RCC PIs and site PI must provide current CV. Sites send to the DCRI project team prior to activation.
(3)	Medical License	RCC PIs and site PI must send to the DCRI project team prior to activation. Medical licenses must be updated annually and sent to the DCRI project team.
(4)	Protocol and Amendment Signature Pages	The study PI from each site signs/dates and sends to the DCRI project team prior to activation. Once a site is activated if there is a change in PI or an amendment, the signature page should be sent to the CC project team. Original maintained at site.
(5)	COI Form	PI and Sub-Investigators listed on the 1572 must sign a COI at the start of the study and update it annually or upon change in COI status.
(6)	1572	Upon completion, the site PI must sign and date and send to the DCRI Project team prior to site activation. (Once a site is activated if there is a change in PI or information included on the 1572, an updated form must be sent to the DCRI Project team.)

(7)	Federal Wide Assurance Number	Number is updated per expiration date. Sites to send to the DCRI project team prior to activation and send to CC project team upon expiration.
(9)	Copy of IRB approval for Protocol & Approved Informed Consents	IRB approval must be updated yearly. Sites to send to the DCRI project team prior to activation and send to CC project team upon expiration.
(9)	Document Human Subject Protection Training	Required for all key personnel. Form is located at http://cme.nci.nih.gov. Sites to send to the DCRI project team prior to activation.
(10)	Signed Contract with CC	Each RCC and Enrolling Center in the USA needs an executed Rapid Start Network-Federally Funded Grants Participation (RSNG) and Contract Addenda prior to activation.
(11)	Protocol Training	Training Certifications for each individual protocol will be provided by the DCRI Project team. The PI and SC (at minimum) must receive protocol training prior to activation.
(12)	Axcess Training	Quick User Reference Guides will be provided by Almac to all site users for training. Upon request, ALMAC will generate a User ID and password (User ID is lower case letters from your first and last name followed by numbers, initial password is temporary. You will be asked for a new password (8 characters) when you login.
(13)	InForm Training	Each site user must complete InForm training.
(14)	CPET Core Laboratory Training/Certification	Training/Certifications will be provided by the CC/ Core laboratory. Sites not previously certified in HFN 1.0 must be CPET certified prior to activation.

3 Screening and Randomization

Screening will be conducted in outpatients with chronic symptomatic HFrEF. Willing participants who are found to have Fe deficiency and meet other entry criteria will be consented for the trial. All individuals followed at participating Heart Failure Network (HFN) centers with chronic,symptomatic HFrEF who are thought to be able to perform maximum incremental exercise testing may be considered for recruitment. 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 participation of the study and to undergo further screening evaluations. Suitable candidates will be approached by investigators regarding the study and be provided with detailed study information and a copy of the informed consent form. Informed consent will be obtained from eligible candidate to undergo further evaluations and potential enrollment as required by the local institutional review boards. There can be no changes in the protocol without the prior agreement of the Heart Failure Network (HFN) Steering Committee.

3.1 Baseline/Randomization

After providing written informed consent and completing screening procedures research participants will complete all baseline procedures, including: clinical evaluation, blood samples, and CPET. Participants who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized. Eligible participants will be randomized with a 1:1 allocation ratio to either oral Fe polysaccharide 150mg twice daily or matching placebo. Randomization will be stratified by site and anemia status.

During randomization visit, participants will be counseled on optimal study drug administration (after 2 hours of fasting when possible while avoiding concomitant ingestion of proton pump inhibitors, H_2 blockers, dairy products or calcium supplements). Arrangements will be made for an initial phone call follow-up 7 days after randomization. Participants will receive a written description of the study with contact numbers of study staff to present to their usual care provider(s) (refer to the patient wallet card).

At the baseline visit, all study participants will undergo:

- Clinical evaluation:
  - Interim history
  - NYHA class assessment
  - Medication review
  - Physical examination
- Phlebotomy for core laboratory blood samples:
  - Fe studies
  - Fe bioavailability markers
  - Biomarkers
  - HFN Bio-repository ± HFN Genetic samples (if consented)
- Cardiopulmonary Exercise Test (CPET)
- 6MWT
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

3.2 aXcess (IVRS)

Subjects will be randomized by using Almac's aXcess randomization system. All study personnel who wish to access the aXcess system must attend Axcess training or read the aXcess training quick reference guide. The project team will then request access.

A Randomization Worksheet with evidence that the patient meets inclusion/exclusion criteria and a signed Informed Consent Form should be completed prior to accessing aXcess. To randomize a patient all randomization questions must be answered including the following:

- Date of birth (mm/dd/yyyy)
- Gender (Male or Female)
- Anemia status (is the subjects HB less than 12grams/dL? Yes/No)
  The system will provide the following:
- Subject ID
- Bottle Number (note: 2 bottles will be dispensed at baseline)
- Transaction Confirmation via fax and/or email

- For aXcess technical support, 24 hours a day, 7 days a week, please call 1-877-738-8831. When you access technical support, please provide them with the following information:
- Study Code: 404250
- Site Number
- Protocol Number: HFN IRONOUT
- Your Phone Number

For email support contact IVRSSupport@almacgroup.com

4 Patient Follow Up

Day 7 Clinic Visit

Participants will receive a phone call from study staff at Day 7 to monitor compliance and tolerance to study medication. Specific queries regarding gastrointestinal symptoms will be included. Study staff will be discouraged from specifically asking questions regarding stool discoloration. Phone scripts will be provided by the Coordinating Center.

Week 8 Clinic Visit

Participants will be seen in clinic at week 8 and will undergo the following study procedures:

- Clinical evaluation:
  - Interim history
  - NYHA class assessment
  - Medication review and study medication adherence assessment
  - Physical examination
  - 6MWT
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Dispense study medication kits

Week 16 Clinic Visit

Participants will be seen in clinic and will undergo the following study procedures:

- Clinical evaluation:
  - Interim history
  - NYHA class assessment
  - Medication review and study medication adherence assessment
  - Physical examination
- Phlebotomy for core laboratory blood samples (after overnight fasting):
  - Fe studies and hemoglobin
  - Fe bioavailability markers
  - Biomarkers
  - HFN Bio-repository ± HFN Genetic samples (if consented)
- Phlebotomy for local laboratory blood samples:
  - Complete blood count
  - Renal function and liver function (BUN, creatinine, ALT, AST, alkaline phosphatase and total bilirubin)
- Cardiopulmonary Exercise Test (CPET)
- 6 minute walk test

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Discontinue study medication

Refer to the protocol for additional details.

4.1 Study Treatment

On July 15, 2014 an IND number was granted by the FDA. See protocol for additional details.

4.2 Study Drug Supplies

Drug dispensation will be managed by the CC in collaboration with Almac Clinical Services. At the baseline study visit, participants will receive two bottles of Polysaccharide Iron Complex (PIC) or placebo to permit eight weeks of dosing until the next study visit. At the eight week visit, one bottle of additional drug will be dispensed to permit dosing through the 16 week visit.

Patients will be instructed to take the medication as required by the protocol, and compliance will be assessed at each visit or by phone contact (as described in the protocol).

Permitted dose adjustment: For all participants, Fe polysaccharide should be initiated with a dose of 150mg twice daily. At each of the follow-up visits, the dose can be reduced to once daily if required for participant tolerability. If a dose is missed, the twice daily regimen should be resumed with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose. The study treatment regimen will be administered for a total duration of 112 days unless clinical reasons require discontinuation earlier**.** The site should contact the helpline anytime a patient discontinues. It is very important that the site try to obtain as much data as possible for the duration of the trial for all patients. Since this is an —intent to treat study, the CC is requesting that every attempt be made to have the patients complete all study assessments, evaluations and lab work even if he/she is no longer participating in the study treatment. If a patient states that he/ she no longer wants anything to do with the study and withdraws consent then do not contact him/ her further.

If the patient does not want to take the study drug and will not agree to complete the study assessments per protocol then the site should request that he/she allow follow up via phone, contact with the physician, and access to medical records.

If the patient does not want you to contact him/her any further, ask for access to the medical records for the duration of the study.

4.3 Storage, Accountability and Destruction

4.3.1 Storage

The study drug should be stored at controlled room temperature 15°-30°C (59°-86°F). Temperature excursions are to be reported immediately to the CC. Study drug will be dispensed in a light-resistant container. Excessive moisture should be avoided. Investigators should ensure proper storage conditions and record and evaluate the

temperature. Trial product should be stored in a locked and secure environment only available to study personnel.

4.3.2 Drug Accountability

Subjects should be instructed to return all used, partly used and unused trial product (study drug bottling/packaging) at each study visit and at the final study visit. The patient should be instructed to return all bottles even if they are empty. Returned trial product should be stored separately from the non-allocated trial product(s) until drug accountability has been reconciled.

The investigators will keep track of all received, partly used and unused trial products. Shipments from Almac will be confirmed in the system prior to the bottles being available for dispensation. Subject specific bottle information will be maintained in the accountability log.

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

- All study drug shipment invoices should be retained.
- All aXcess confirmations should be printed documenting allocation numbers for each subject.
- Drug Accountability Logs:

Site Drug Accountability Logs- This log will enable you to keep track of how much drug you have onsite. The accountability log should be used to document when a shipment of drug has been received lot # of study drug, when study drug is dispensed to whom, amount of drug lost/ damaged, and the balance. The site should initial by each entry.

After a patient is dispensed study drug the **Subject Drug Accountability Log** should be completed. The subject number, bottle #, amount and date dispensed, and amount and date returned must be documented on the subject drug accountability log (DAL).

Subjects should be reminded to return all study drug at each study visit. Pill counts should be done to assess subject compliance at the week 8 and week 16 visits. All efforts should be made to have all study drug returned.

4.3.3 Destruction

Excess or unused study drug is to be destroyed per institution policy upon occurrence of either of the following:

- Conclusion of the study
- If the study is stopped prematurely

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 Subject Specific Drug Accountability Log.

4.4 Randomization, Stratification and Blinding

Randomization to active drug/placebo (1:1 allocation ratio) is stratified by site. Blinding is ensured by preparation of identically appearing placebo and active drug. Subjects will be randomized using procedures determined by the CC to one of 2 treatment groups. A permuted block randomization method stratified by site will be used to ensure relatively equal distribution of subjects to each arm within each clinical site.

Blinding of the study, with respect to treatment groups will be preserved by the use of matching placebo capsules. The investigator may be asked at the end of the trial if they had obtained any information which may have led to the unblinding of treatment.

4.5 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.

4.6 Patient Materials

All randomized participants will receive a written description of the study with contact numbers of study staff to present to their provider(s).

5 eCRF Instructions

See appendix for detailed instructions for entering data into the IRONOUT eCRF. Data should be entered within 7 days of the completed study visit and queries should be resolved within 5 days of issue.

6 Safety Monitoring

The reporting of information from an adverse experience 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 purpose of this document is to outline the trial specific processes for reporting adverse events and serious adverse events for the HFN IRONOUT trial.

6.1 Safety Definitions

AE, SAE, and endpoints: Refer to HFN IRONOUT 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 becomes aware of safety related information. The date of receipt of each initial report 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 HFN 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 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
- an adverse event

6.2 Scope

This Safety reporting procedure defines the safety reporting responsibilities for the following country: ***United States***

6.3 Process

6.3.1 Study Site

The site investigator is responsible for monitoring the safety of participants enrolled into the study at the study sites. For this study, AEs/SAEs will be collect on the AE/SAE eCRF within InForm. All AEs/SAEs (except for those events reported as anticipated disease related events) occurring from signing of the informed consent through the Week 16 visit, will be captured on the AE/SAE eCRF. All AEs/SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee, within 1 working day of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the AE/SAE into the appropriate module of the eCRF. If InForm 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.

6.3.2 Study Site Responsibility

1) The site will identify an AE/SAE.
2) Site will determine whether the event is an anticipated disease related event (See IRON-HF protocol, section 14.3).

3) Enter disease anticipated events on the **EVNTINT** eCRF page, as these events will not be captured as AEs/SAEs, regardless of relationship to study drug.
4) Enter AEs/SAEs on the AE/SAE eCRF page.
5) All SAEs will require the SAE narrative, relevant laboratory/diagnostic tests and relevant concomitant medications.
6) Once information is entered on the SAE eCRF 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.
7) Sites will enter all patient deaths on the **Death and SAE eCRF page,** except, anticipated disease related deaths will not be reported on the SAE eCRF page.

6.3.3 Screen Failures

A screen failure subject is defined as a one who signs an informed consent document and does not go on to be randomized. Screen failure subjects who experience SAEs from signing of the informed consent until the point of screen failure must have the event reported via a paper SAE form. Screen failures should be recorded in the IRONOUT screen failure log.

6.3.4 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. The investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

It is understood that complete information about the event may not be known at the time the initial report is submitted. The Investigator must assign an initial level of 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.

6.4 Anticipated Adverse Events and Procedure Effects

The following AEs are anticipated, disease-related events in patients with HF with preserved EF (HFpEF):

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias
- **Sudden cardiac death**: 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 rise in creatinine $\geq$ 0.3 mg/dL over 48 hours, or progressive loss of renal function over time
- **Cardiogenic shock** due to progressive heart failure is an anticipated event

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the appropriate **EVNTINT** eCRF module (Events of Interest page).

6.5 DCRI Safety Surveillance

1) Will be notified of SAEs via InForm generated emails.
2) Will save 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 within 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 IRONOUT-HF trial team a copy of the SAE report, and any queries generated for the site within 1-2 business days of initial receipt.
9) Will conduct SAE data reconciliation of the IRONOUT safety database in Argus, with the InForm EDC system on the following data variables: Subject ID, Verbatim Term, MedDRA Preferred Term, Onset date, Outcome and Causality.
10) DCRI Safety surveillance will generate a MedWatch for all events, the DCRI safety medical monitor deemed as serious, related to study drug and unexpected per investigator brochure or product labeling.

11) DCRI Safety surveillance will forward the MedWatch to DCRI Regulatory Services for submission to the FDA, within 7 calendar days for death or life-threatening events, and 15 calendar days for all other events, assessed as serious, related to study drug and unexpected.
12) DCRI Clinical Operation will be responsible for filing copies of the MedWatch reports, in the master project file at DCRI.

6.6 DCRI Safety Medical Monitor

1) Will review all site reported SAEs
2) Will review the MedDRA coding for the event
3) Will review the site reported causality assessment
4) Will assess and confirm the event for listedness per the investigator's brochure or product labeling.
5) Request additional site queries or follow-up, as needed

6.7 IRONOUT-HF Trial Team

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

6.8 Data and Safety Monitoring Board

a) Will be provided with all SAEs by DCRI Data Management
b) Will review all SAE data in accordance with the IRONOUT protocol and-HF DSMB charter.

6.9 Unblinding Process

Will be performed per protocol.

7 Pregnancy

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 (within one business day of becoming aware of the pregnancy). The pregnancy will be recorded on the appropriate paper Pregnancy Tracking Form. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus/child, will be recorded by the site staff on the AE/SAE eCRF, as applicable.

7.1 Study Site Responsibilities

The site will follow the pregnancy and report the status to DCRI Safety Surveillance, once a trimester, via the paper Pregnancy Tracking Form, or until final outcome has been determined. If there is an unknown pregnancy outcome by the end of the study, the site will provide follow up via the Pregnancy Tracking form, directly to the IRONOUT-HF trial Team.

7.2 DCRI Safety Surveillance Responsibilities

1) Will receive paper Pregnancy Tracking Form via fax or email from the site.

2) Will forward the pregnancy form to the IRONOUT-HF trial team within 2 business days of receipt.
3) Will follow the reported pregnancy until final outcome has been reported.
4) If there is an associated SAE with the reported pregnancy, DCRI Safety will forward the SAE report according to Section 7.7 (above).
5) If there is an SAE for the infant, DCRI will follow infant SAE until outcome is known and forward the SAE report according to Section 7.7 above.

8 SAE Reconciliation

The clinical data, including all serious adverse events 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.

9 Disposition of Safety Records

DCRI Safety Surveillance will forward the safety files to the IRONOUT-HF trial team Project Leader or designee at the end of the study. The electronic safety files will be saved as portable document formats (PDFs) and provided to the HFN Team or designee via compact disc (CD).

10 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.

11 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
IA	Investigator Alert
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
PK	Pharmacokinetic
ROW	Rest of World (non-North America)
SAE	Serious Adverse Event
SAR	Suspected Adverse Reactions
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
US	United States