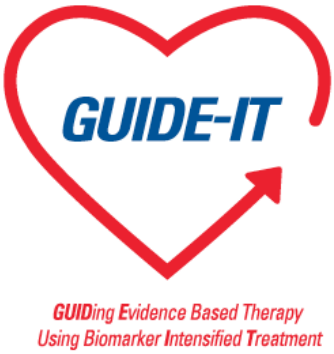


Study Protocol Amendment 2

GUIDing **E**vidence Based Therapy Using Biomarker **I**ntensified **T**reatment in Heart Failure (**GUIDE-IT**)

Version Date: December 3, 2013

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
BNP	B-type Natriuretic Peptide
CCC	Clinical Coordinating Center
CEC	Clinical Endpoints Committee
CES-D	Center for Epidemiologic Studies Depression Scale
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
DASI	Duke Activity Status Index
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQOL	Economics and Quality Of Life
EQOL CC	Economics and Quality Of Life Coordinating Center
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
mL	Milliliter
NHLBI	National Heart, Lung, and Blood Institute
NT-proBNP	Amino-Terminal pro B-type Natriuretic Peptide
SAE	Serious Adverse Event
SIRE	Simple Internal Randomization Engine
QOL	Quality of Life

PROTOCOL SYNOPSIS

Title:	GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT)
Indication:	Heart Failure
Location:	Approximately 40 clinical centers in North America
Rationale:	Current guidelines recommend that medical therapy be titrated toward the target doses used in clinical trials, but "therapeutic inertia" often represents a barrier to aggressive titration of medical therapy. There is a pressing need to develop strategies to improve utilization of proven therapies for HF in order to improve clinical outcomes and control costs. Observational studies have shown an association between decreasing natriuretic peptide levels over time and improved outcomes in patients with HF.
Objectives:	To compare a strategy of medical therapy titration aimed at achieving and maintaining an NT-proBNP target of < 1000 pg/mL (biomarker-guided therapy) to usual care in high risk patients with systolic heart failure.
Study Design:	Prospective, randomized, parallel controlled groups, unblinded, 2-arm, multicenter clinical trial of approximately 1100 patients.
Primary Endpoint:	Time to cardiovascular death or first HF hospitalization
Secondary Endpoints:	• Time to all-cause mortality • Recurrent hospitalizations • Days alive and not hospitalized for CV reasons • Time to cardiovascular death • Time to first HF hospitalization • Health-related quality of life (HRQOL) • Resource utilization, cost and cost effectiveness • Safety

STUDY FLOW CHART

SCREENING

High risk systolic heart failure patients, with EF ≤ 40%, a heart failure event within prior 12 months, and NT-proBNP > 2000 pg/mL or BNP > 400 pg/mL during the 30 days prior to randomization

RANDOMIZATION

Randomized to either Usual Care (N=550) or Biomarker Guided NT-proBNP < 1000 pg/mL (N=550)

Baseline visit (day 0)
History and physical exam, CV medication history, serum creatinine, BUN and electrolytes and NT-proBNP (local lab), QOL questionnaire, medical resource use and cost assessment, 6MWT, biomarker and DNA sample collection

FOLLOW-UP

2-week follow-up (± 1 week)
History and physical exam, CV medication history, change in HF therapy rationale, serum creatinine, BUN and electrolytes (local lab), NT-proBNP (local lab biomarker guided arm only), medical resource, cost assessment and biomarker samples

6-week follow-up (± 1 week)
History and physical exam, CV medication history, change in HF therapy rationale, serum creatinine, BUN and electrolytes (local lab), NT-proBNP (local lab biomarker guided arm only), medical resource, cost assessment and biomarker samples

3-month follow-up (months 3, 6, 9, 12, 15, 18, 21, and 24) (± 1 week)
History and physical exam, CV medication history, change in HF therapy rationale, serum creatinine, BUN and electrolytes (local lab), NT-proBNP (local lab biomarker guided arm only), medical resource, cost assessment and biomarker samples

Notes:

- Minimum 12 months of follow-up.
- Study visits occur every 3 months until a maximum of 24 months.
- 2-week (+/- 1 week) follow-up after adjustment of therapy or hospitalization.
- Follow-up visits include brief clinical assessment, serum creatinine, BUN and electrolytes (local lab), and NT-proBNP (local lab biomarker guided arm only).
- Follow-up visits continue every 2 weeks until therapeutic targets are reached, or until further titration of therapy is not possible.
- QOL questionnaires to be administered by EQOL CC at 3 months, 6 months, 12 months and yearly until the end of the study
- EQOL CC will collect medical resource and cost assessments throughout the length of the study

1. HYPOTHESES AND OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to determine the efficacy of a strategy of biomarker-guided therapy compared with usual care on the composite endpoint of time to cardiovascular death or first heart failure (HF) hospitalization in high risk patients with left ventricular systolic dysfunction.

1.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effects of biomarker-guided therapy on:

- Time to All-cause mortality
- Recurrent hospitalizations
- Total days alive and not hospitalized for cardiovascular reasons
- Time to cardiovascular death
- Time to first HF hospitalization
- HRQOL
- Resource use, cost and cost effectiveness
- Safety

2. BACKGROUND AND RATIONALE

2.1 Scope of the Heart Failure Problem

Heart failure (HF) is a major and growing public health problem in the United States (U.S.), affecting over 5 million Americans, causing over 1 million hospitalizations, and accounting for over 30 billion dollars in total costs annum[1]. Among U.S. adults age 40, 1 in 5 will develop HF in their lifetime.[2] Current practice guidelines for pharmacologic management dictate that neuro-hormonal antagonists such as beta-blockers and ACE-inhibitors be titrated toward the target doses studied in large clinical trials.[3,4] Despite these recommendations, available data suggest that most patients in clinical practice are either not treated with these agents or are treated with substantially lower than recommended doses.[5-8] "Therapeutic inertia" often represents a barrier to aggressive titration of medical therapy for both providers and patients. A variety of disease management strategies have been evaluated to improve the chronic management of HF patients, ranging from nursing-based interventions to technologically complex interventions using implantable hemodynamic monitors and telemedicine. The majority of these interventions have focused on the monitoring of symptoms and body weight and/or on patient education. Overall, the results from disease management strategies have been mixed,[9] and many are personnel intensive, complex[10] or costly to implement.[11] Thus, there is an unmet need for a simple, effective and easy-to-implement strategy to improve the management of patients with chronic HF such that patient outcomes are demonstrably improved.

2.2 Biology and Clinical Uses of Natriuretic Peptides

The natriuretic peptides are a family of important counter-regulatory hormones with vasodilatory, lusitropic, anti-fibrotic, and natriuretic effects.[12] The natriuretic peptides b-type natriuretic peptide (BNP) and amino-terminal pro-b-type natriuretic peptide (NT-proBNP) are released from the myocardium in response to hemodynamic stress and provide important diagnostic and prognostic information in HF patients. Multiple studies have linked higher levels of natriuretic peptides to worse clinical outcomes in patients with HF as well as other cardiovascular disorders and in healthy persons.[13-16] Both BNP and NT-

proBNP have been shown to be very powerful predictors of future risk in both acute[17,18] and chronic HF.[19,20]

2.3 Guiding Therapy Based on Natriuretic Peptides: Observational Data

A large number of studies have also investigated the impact of HF therapies on natriuretic peptide levels. HF therapies proven to have beneficial long-term effects on morbidity and mortality, such as ACE inhibitors,[21] angiotensin receptor blockers (ARB),[22] beta-blockers,[23] aldosterone antagonists,[24] and cardiac resynchronization therapy,[25] all generally decrease natriuretic peptide levels. Observational studies have shown an association between decreasing natriuretic peptide levels over time and improved outcomes in both inpatients and outpatients with HF.[20,26-29]. In a representative study, Masson *et al* examined the prognostic value of baseline and 4 month NT-proBNP values in a prospective substudy of patients enrolled in the placebo arm of the Valsartan Heart Failure (Val-HeFT) study (Figure 1). [29]

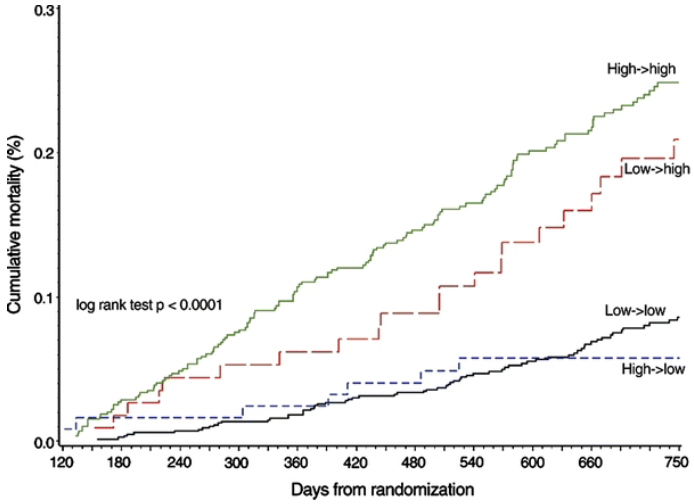


Figure 1. Changes in NTproBNP and outcome in Val-HeFT study.

This study demonstrated the powerful association of change in NT-proBNP levels over time with subsequent clinical outcomes. Using a cut-point NT-proBNP level (derived from receiver operator curve analysis) of 1078 pg/mL, this study showed the prognostic significance of change in NT-proBNP values across this threshold over time. A similar analysis focused on BNP by Latini *et al* demonstrated substantially similar results.[30] These findings appear to be consistent across multiple studies and provide a strong observational foundation for the concept of natriuretic peptide guided therapy in HF.

2.4 Prior Studies of Biomarker-Guided Therapy in Heart Failure

These observational data have led to the hypothesis that serial measurements of natriuretic peptides may serve as a guide to the titration of chronic medical therapy— "biomarker-guided therapy". This concept has been tested over the last decade in multiple small randomized controlled studies ranging from 69 to 499 patients.[31-38] As shown below, the design of each study has differed with regard to patient population, the biomarker used, the natriuretic peptide target, the nature of the control group, and the study endpoint (Table 1).

Table 1. Design of selected RCTs of Biomarker-guided Therapy in Heart Failure

	Troughton	STARBRITE	STARS-BNP	TIME-CHF	BATTLE-SCARRED	PRIMA	PROTECT
N	69	137	220	499	364	345	151
Marker	NT-proBNP	BNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP
Target	1692 pg/mL	2 x discharge level	100 pg/mL	400 pg/ml if age<75, 800 pg/ml if age>75	1270 pg/mL	Discharge level	1000 pg/mL
Length of f/u	9.6 mos	3 mos	15 mos	18 mos	12 mos	12 mos	10 mos
Endpoint	Death + CV hospital or worsening HF	Days alive and out of hospital	HF death + HF hospital	All-cause death or hospital	All-cause mortality	Days alive and out of hospital	Total CV events

The initial experience with biomarker-guided therapy in HF was a small (N=69) pilot study by Troughton, et al. that randomized patients to a strategy of titrating medical therapy to achieve an NT-proBNP level < 1692 pg/mL or a control group in which medical therapy was titrated based on a clinical HF score.[34] This study showed a significant decrease in cardiovascular events with biomarker-guided therapy vs. control. These findings were confirmed in the STARS-BNP study, which randomized 220 well-treated ambulatory HF patients to BNP-guided therapy (BNP target < 100 ng/mL) or usual care. This study showed a significant reduction in cardiac events in the BNP guided arm (p<0.01).[36] Notably, although no specific instructions were provided for responding to BNP levels above the target threshold, up-titration of therapy in the BNP guided arm was significantly greater for not just diuretics but also ACE-inhibitors, beta-blockers, and spironolactone (Figure 2).

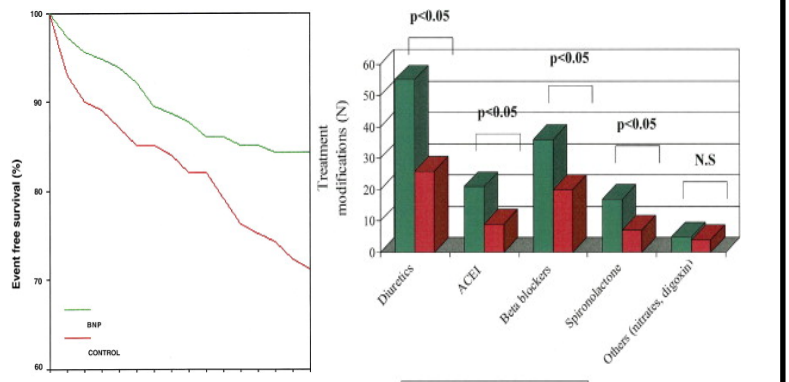


Figure 2. Event free survival curves for BNP guided therapy vs. control in the STARS BNP trial and number of treatment modifications in each group.

The largest published study of biomarker-guided therapy to date is TIME-CHF, which randomized 499 patients with chronic HF to either usual care or an NT-proBNP target based on the subject's age (< 400 pg/mL if age < 75 or < 800 pg/mL if age > 75). A notable difference in TIME-CHF compared to previous studies was a specific focus on elderly patients (mean age of 77). This study did not meet its primary endpoint of the composite of all-cause mortality and all-cause hospitalization (HR = 0.91, p=0.39), but did demonstrate a trend towards improvement in all-cause mortality (HR = 0.68, p=0.06) and showed significant benefit on survival free of HF hospitalization (HR=0.68, p=0.01).[36,39]

In a recent prospective 3-arm study performed at 8 hospitals in Vienna, Austria, 278 patients were randomized at the time of discharge from a HF hospitalization to 1 of 3 arms; usual care, a multidisciplinary disease management program, or disease management plus individualized HF therapy based on NT-proBNP levels.[38] In the biomarker-guided arm, both the frequency of visits and the titration of HF treatment were based on serial measurement of NT-proBNP levels with a goal of decreasing NT-proBNP

levels to below 2200 pg/mL. The primary endpoint of the study was the composite of time to death or rehospitalization for HF over 18 months. In this study, biomarker-guided therapy was associated with a greater proportion of patients receiving intensified medical therapy (defined as being treated with spironolactone as well as ACE-inhibitors and beta blockers at ≥ 50% of target doses) compared to usual care or disease management, and this greater intensification of proven therapies resulted in a significantly greater reduction of NT-proBNP levels in the biomarker-guided therapy arm than in the disease management arm. Most importantly, randomization to biomarker-guided therapy was associated with a significant improvement in the survival free of HF hospitalization (37%) compared to disease management alone (50%) or usual care (65%). These data suggest that biomarker-guided therapy may have additional biologic effects and provides additive and clinically important benefits above and beyond that provided by intensified disease management alone.

The recently published PROTECT study demonstrated a highly significant clinical benefit on total cardiovascular events (logistic odds for event = 0.44, p = 0.02) in a 151 patient single center trial, using an NT-proBNP target of 1000 pg/mL (the same target proposed for the current study). Importantly, the PROTECT data suggested that there were important clinical benefit in both younger and older patients alike[37].

Two systematic reviews and meta-analyses of the available literature on natriuretic peptide guided therapy in HF, have been published.[40,41] Both analyses demonstrated a significant impact on all-cause mortality with biomarker-guided therapy compared to control (Figure 3). Notably, the point estimate for the benefit of biomarker-guided therapy in these meta-analyses was approximately a 30% improvement in survival, a treatment effect comparable to that observed with individual components of HF therapy such as beta-blockers,[42,43] ACE-inhibitors[44], aldosterone antagonists[45], and implantable cardioverter defibrillators (ICDs).[46]

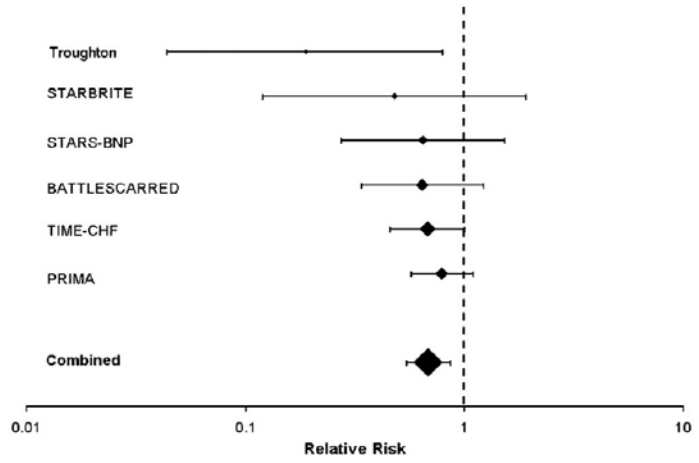


Figure 3. Meta-analysis of all-cause mortality in previous studies of biomarker-guided therapy in HF. **The overall hazard ratio for mortality was 0.69 (95% confidence intervals 0.55-0.86).**

2.5 Design of GUIDE-IT: Rationale for an Unblinded Study

GUIDE-IT will be an unblinded trial because blinding would eliminate one potentially important mechanism of treatment effect: the impact of patient knowledge of their own natriuretic peptide levels on adherence and health-related behaviors. Blinding GUIDE-IT would remove the patient from the critical role of active partnership in the management of his or her disease and would not reflect how biomarker-guided therapy will ultimately be used in practice, thus raising important issues about generalizability. We have taken multiple steps to minimize potential biases related to lack of blinding, including the use of an objective primary endpoint (cardiovascular death or HF hospitalization) and centralized adjudication of events by a Clinical Event Committee blinded to treatment assignment.

2.6 Design of GUIDE-IT: Rationale for Using NT-proBNP and Specific Target

Both BNP and NT-proBNP are widely clinically available and both markers have been used in previous trials of biomarker-guided therapy. We have selected NT-proBNP as the biomarker to be used for guiding therapy in the intervention arm of the GUIDE-IT study. The half-life of NT-proBNP is substantially longer than that of BNP (6 hours vs. 20 minutes), suggesting it is preferable for long-term therapeutic monitoring over time. For this reason, more prior studies have used NT-proBNP rather than BNP. NT-proBNP performed better in predicting long-term morbidity and mortality in a head-to-head comparison in Val-HeFT. Finally, the data supporting the validity of a specific natriuretic peptide target are stronger for NT-proBNP than for BNP.

Several lines of evidence have led us to select an absolute NT-proBNP target rather than a percentage change. First, the use of specific targets for physiologic parameters is standard in the management of other cardiovascular diseases such a hypertension, hyperlipidemia, and diabetes. A strategy of targeting a specific percentage reduction may leave patients with elevated baseline values with a target that is still associated with substantial risk. The rationale for specific cut points is strongest if there is evidence for specific inflection points in the association of continuous physiologic parameters with risk. Data from the PRIDE study strongly suggests the presence of such a cut-off at approximately 972 pg/mL of NT-proBNP (Figure 4)[17]. Similarly, in an analysis of VAL-HeFT, the optimal cut point of NT-proBNP to define increased risk was 1078 pg/mL. Finally, as described above the interim results from the PROTECT pilot study demonstrated a strong signal for efficacy using an NT-proBNP target of 1000 pg/mL.[32] The consistency of these findings around an NT-proBNP threshold of ~1000 pg/mL has led us to target that level of NT-proBNP suppression for GUIDE-IT.

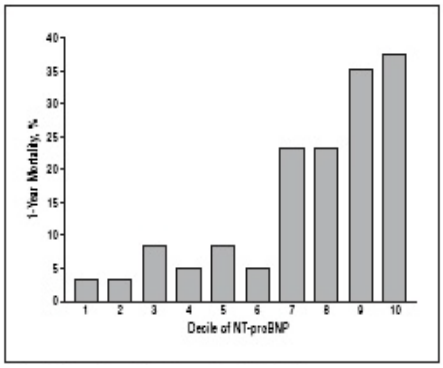


Figure 4. 1-year mortality by deciles of initial NT-proBNP value in PRIDE study; Increased risk at 7th decile corresponds to NT-proBNP level of 972 pg/mL.

2.7 Natriuretic Peptide Variability over Time

Understanding of intra-patient variability over time is of significant importance in using a biomarker-guided approach in order to distinguish between actionable change and normal biologic variation (i.e., to separate "signal" from "noise"). Araujo *et al* examined change in NT-proBNP levels over a period of 3 weeks in clinically stable, ambulatory HF patients without changes in therapy, and observed a high degree of intra-patient variability in subjects with low levels (<1000 pg/mL), but a more modest amount of variability in patients with levels in the HF range (~1000-10,000 pg/mL).[47] These data suggest that intra-patient variability is sufficiently limited to distinguish a clinical meaningful change from biological variability in chronic HF.

3. STUDY DESIGN

3.1 Overview

This study will be a multicenter, prospective, randomized, parallel control group, unblinded, 2-arm multicenter clinical trial comparing biomarker-guided therapy to usual care in patients with systolic HF at high risk for hospitalization or death.

3.2 Planned Number of Subjects and Centers

The planned enrollment for the GUIDE-IT study is approximately 1,100 subjects at approximately 40 centers in North America. To maximize generalizability, centers outside of North America may be considered for participation if HF management is sufficiently similar to U.S. practice and appropriate use of guideline-based therapy can be verified.

3.3 Study Duration

We anticipate the study duration will be 5 years: 6 months of start-up activities (i.e., finalize protocol, prepare study sites and contracts, receive site Institutional Review Board [IRB] approval), 36 months of active enrollment, 12 months of patient follow-up after the final patient is enrolled, and 6 months of study close-out, data analysis, and reporting of results.

4. STUDY POPULATION

4.1 Overview of Study population

The enrolled population will be high-risk patients with systolic HF (left ventricular ejection fraction [LVEF] ≤ 40%). High-risk patients are defined below.

4.2 Inclusion Criteria

- Age ≥ 18 years
- Most recent LVEF ≤ 40% by any method within 12 months of randomization
- High risk heart failure as defined by the following criteria
    - A Heart Failure Event in the prior 12 months, defined as any one of the following:
        - HF Hospitalization
        - Treatment in the Emergency Department (or equivalent) for Heart Failure
        - Outpatient treatment for heart failure with intravenous diuretics

      AND

    - NT-proBNP > 2000 pg/mL or BNP > 400 pg/mL at any time during the 30 days prior to randomization
- Willing to provide informed consent

4.3 Exclusion Criteria

- Acute coronary syndrome or cardiac revascularization procedure within 30 days (NOTE: Given that cardiac biomarkers such as troponin are frequently elevated in HF patients, the diagnosis of acute coronary syndrome should be based on clinical diagnosis, not biomarkers alone)
- Cardiac resynchronization therapy (CRT) within prior 3 months or current plan to implant CRT device
- Active myocarditis, Hypertrophic obstructive cardiomyopathy, pericarditis, or restrictive cardiomyopathy
- Severe stenotic valvular disease
- Anticipated heart transplantation or ventricular assist device within 12 months
- Chronic inotropic therapy
- Complex congenital heart disease
- End stage renal disease with renal replacement therapy
- Non cardiac terminal illness with expected survival less than 12 months
- Women who are pregnant or planning to become pregnant

- Inability to comply with planned study procedures
- Enrollment or planned enrollment in another clinical trial

5. STUDY INTERVENTIONS

GUIDE-IT will randomize patients in a 1:1 allocation to either:

- Biomarker-guided arm (approximately 550 subjects): Titration of HF therapy with a goal of achieving and maintaining a target NT-proBNP < 1000 pg/mL
  OR
- Usual care (approximately 550 subjects): Titration of HF therapy based on target doses from current evidence based guidelines

5.1 Biomarker-guided Arm

In the Biomarker-guided arm, NT-proBNP values from the local clinical laboratory will be utilized by treating physicians for the purpose of achieving at NT-proBNP target of < 1000 pg/mL. The GUIDE-IT protocol will specify interventions to be considered to achieve the NT-proBNP target in the biomarker-guided arm, but specific treatment decisions will be at the discretion of the treating physician. The order of implementation will be based on clinical judgment, and more than one intervention can occur in a single encounter. Titration of neurohormonal antagonists will be emphasized over titration of diuretics except in the case of clinically apparent congestion or in the case of very high NT-proBNP levels, which usually indicate subclinical volume overload. Specific changes in therapy and the rationale for them (e.g., in response to clinical change or NT-proBNP levels) will be captured on the eCRF. Potential interventions to decrease NT-proBNP levels will include:

- Up-titrate or add Angiotensin Converting Enzyme (ACE)-inhibitor or ARB
- Up-titrate or add beta-blocker (if not clinically congested)
- Up-titrate or add hydralazine-nitrates in African-American patients
- Increase loop diuretic dosage (if clinically congested or NT-proBNP > 5000 pg/mL)
- Up-titrate or add spironolactone if tolerated by renal function and potassium
- Add oral thiazide diuretic
- Add digoxin
- Consider adding ARB to ACE-I (if not on spironolactone)
- Consider hydralazine-nitrates in non-African-American patients
- Intensified or repeated heart failure education regarding diet, sodium restriction, etc.
- Consider optimization of cardiac resynchronization therapy (if CRT device implanted)
- Reconsider potential indications for CRT (if not previously implanted)
- If in atrial fibrillation, maximize rate control or consider more aggressive attempts at normal sinus rhythm
- Consider exercise training or cardiac rehabilitation

5.2 Usual Care Arm

Patients randomized to the usual care group will receive care based on the most recent AHA/ACC guidelines.[4] Investigators will be provided with specific information on evidence-based target doses of neuro-hormonal antagonists (beta-blockers, ACE-inhibitors). Diuretics will be titrated based on clinical judgment of the treating physician. Routine assessment of natriuretic peptides **will not be performed** in the usual care group except for compelling medical reasons, consistent with current guidelines.[4]

6. STUDY PROCEDURES

A complete schedule of assessments throughout the study is given in Appendix A.

6.1 Screening

Clinical site staff will screen patients in both the inpatient and outpatient setting to identify high risk patients with systolic heart failure. If identified during a heart failure hospitalization, patients will not be randomized until the time of hospital discharge. A screening log will be maintained at each site. Eligible patients will provide written informed consent prior to randomization.

6.2 Randomization

Subjects who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 fashion using the Simple Internal Randomization Engine (SIRE) system to either biomarker-guided therapy or usual care. The unit of randomization will be at the patient level rather than the site level. Treatment allocation will be conducted using a complete randomization scheme. At randomization, subjects will undergo a brief interval history and physical exam, cardiovascular (CV) medication history, local laboratory testing for renal function and electrolytes, assessment for adverse events, 6 minute walk test, QOL questionnaires, medical resource use and cost assessment, and core laboratory samples.

6.3 Study Visits

6.3.1 Baseline

Baseline assessments will occur at the time of randomization and will include:

- Focused physical examination
- CV medication history
- Serum creatinine, blood urea nitrogen (BUN), and electrolytes (local laboratory)
- NT-proBNP (local laboratory)
- Health Related QOL questionnaire (as described in 6.7)
- 6 minute walk test
- Biomarker and DNA collection for biorepository (as described in 6.4)

6.3.2 Follow-Up Visits

Follow-up visits will occur at 2 weeks, 6 weeks, 3 months, and then every 3 months for the remainder of the study duration period (minimum of 12 months and a maximum of 24 months). All study visits will be completed within a ± 1-week window. The following assessments will occur at each follow-up study visit.

- Focused interval history and physical examination
- CV medication history
- Document rationale for changes in HF therapy
- Serum creatinine, BUN, and electrolytes (local laboratory)
- NT-proBNP (local laboratory, Biomarker-guided Arm only)
- QOL questionnaire (as described in 6.7)
- Medical resource use and cost assessment
- Ascertainment of interval safety events and endpoints
- Biomarker collection for biorepository (as described in 6.4)

Subjects in the biomarker-guided arm will have NT-proBNP testing performed in the local laboratory by appropriately trained personnel, and these values will be used for the purposes of titrating therapy to the

protocol-specified target. If therapy is adjusted, the changes in therapy and the rationale for the adjustment (e.g. clinical reason, not at biomarker target) will be recorded on the eCRF. Subjects in the usual care arm will not have routine assessment of natriuretic peptides except for compelling medical reasons.

6.3.3 Follow-up Assessments after Adjustment of Therapy or Hospitalization

There will be a 2-week (± 1 week) reassessment for patients who have a change in therapy, resulting from clinical findings or natriuretic peptide levels. **This follow up can be in person or a remote laboratory evaluation at the discretion of the treating physician**. This follow-up assessment will include a brief clinical assessment (if in person visit), measurement of renal function and electrolytes, and local laboratory NT-proBNP measurement (biomarker-guided arm only. Follow-up assessments will continue every 2 weeks until therapeutic targets are reached, or the investigator determines that further titration of therapy is not possible. Patients hospitalized for HF during the study will have a 2-week follow-up study visit post discharge to reassess and adjust medical therapy, which will include all standard follow-up assessments as defined above (Section 6.3.2).

6.4 Biorepository and Core Lab Biomarker Assessment

Local laboratory NT-proBNP values will be used to adjust therapy in patients randomized to the biomarker-guided arm. Additionally, at each regular study visit, all subjects (regardless of treatment arm) will have blood samples sent to the Biomarker Core Laboratory for the central blinded assessment of NT-proBNP levels. Data from this core lab assessment will not be provided to the sites but will be used to standardize assessments for all study patients (including those in the usual care arm) during data analysis at the completion of the study. As a quality control measure, the correlation between local site laboratory NT-proBNP values and central core lab NT-proBNP values will be assessed after enrollment of the first 100 patients, and as needed thereafter.

Additional plasma, serum, and DNA samples (once only) will be collected and stored in the GUIDE-IT biorepository at each regular study visit (see Schedule of Assessments). Individual study subjects will be permitted to opt out of the biorepository while still participating in the main trial, but participation in the biorepository for all subjects will be strongly encouraged. Samples will be collected, processed, and labeled at the study site and shipped to the biorepository as described in the Manual of Operations. These biorepository samples will be used by GUIDE-IT investigators to evaluate the role of specific "biomarkers" (including genetic biomarkers) in the biology and pathophysiology of HF and the biology of the response to biomarker-guided therapy. A Biomarkers and Genetics Committee will establish and manage the process for scientific review of proposals to use these biologic samples.

6.5 Minimizing Potential Bias

To address potential effects of an unblinded trial design on outcome determination, we have chosen an objective primary endpoint (HF hospitalization or CV death) and will use a blinded Clinical Endpoints Committee (CEC) to classify potential endpoints. Source data (i.e., history, laboratory procedures and discharge summaries) on all deaths and hospitalizations will be reviewed by the CEC in a consistent, standardized and unbiased manner. Final cause for each event will be adjudicated using definitions that will be established in the CEC Charter.

Another potential source of bias relates to the possibility that the greater frequency of medical visits due to natriuretic peptide guidance will lead to improved patient outcomes through a mechanism other than

biomarker-guided titration of HF therapy. While GUIDE-IT will mandate frequent visits in the usual-care group (as consistent with standard practice), any observed differential in the number of medical interventions (driven by out-of-range natriuretic peptide levels in apparently stable patients) may be the mechanism by which any treatment effects are realized. The alternative of mandating extra clinical visits for the usual-care arm to mirror the visit pattern of the biomarker-guided arm carries risk of biasing the trial results. Those extra visits, which would not occur in regular clinical practice, could lead to extra testing and treatment modifications that result in the outcomes of the two arms converging, thus masking a real treatment benefit. While there is no perfect solution to this problem, we will have detailed data on the content of each clinic visit in both treatment arms; thus, we will determine how often these visits included significant modifications of medical therapy.

6.6 Maximizing Protocol Adherence

In order to persuasively test the primary hypothesis of GUIDE-IT, we will maximize adherence to the assigned strategies. In the case of the biomarker-guided arm, the investigators will act on above-target NT-proBNP levels even in the absence of worsening symptoms or signs of HF. Similar to studies of intensive glycemic control or blood pressure control, adherence monitoring and feedback to providers will be critical to the success of GUIDE-IT. To ensure that investigators adhere to the protocol, GUIDE-IT will convene an Adherence Committee to focus on investigator education and training.

Based on our experience in prior studies to identify and correct non-adherence, adherence monitoring and intervention will take a stepped approach. For example, the clinical coordinating center (CCC) will collect patient feedback on adherence. Investigators at sites with two episodes of non-adherence will be contacted to review episodes and the importance of adherence will be reemphasized. Reports on adherence will be provided to the Executive Committee. The Executive Committee will consider suspending enrollment at sites not performing at appropriate levels. Adherence performance will be used in determining authorship of trial manuscripts. Although we recognize that such substantial efforts at ensuring investigator adherence are not practical in all real-world settings, we believe they are critical for a proof-of-concept efficacy trial such as GUIDE-IT.

6.7 Quality of Life Assessments

GUIDE-IT will use a battery of validated instruments that build on a disease-specific core, supplemented by generic measures to provide a comprehensive assessment of health related QOL. These assessments of quality of life (QOL) will be performed at baseline by site coordinators and then 3 months, 6 months and annually to a maximum of 24 months by structured telephone interview conducted by the EQOL CC staff. A detailed description of each of these instruments with instructions will be included in the Manual of Operations. Assessments at each visit will include the following:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Duke Activity Status Index (DASI)
- enter for Epidemiological Studies Depression Scale (CES-D)
- Medical Outcomes Study Short Form (SF-12)
- Medical Outcomes Study Short Form (SF-36) subscales: General Health, psychological well-being, vitality, social functioning)
- EQ-5D

6.8 Economic Data Collection Procedures

Total medical costs can be divided into five major components: inpatient hospital care, inpatient physician care, outpatient (ED visits, observational stays, rehabilitation stays, nursing home stays) physician care,

outpatient testing, and outpatient medications. Hospital costs will be calculated using hospital billing data, with charges converted to costs using the departmental charge-to-cost conversion factors available from each hospital's annual Medicare Cost Report. Physician costs (both inpatient and outpatient) will be estimated by mapping major procedures and physician services recorded on the case report form and hospital bills to appropriate current procedural terminology (CPT) codes in the Medicare Fee Schedule. Outpatient medication costs will be based on the *Drug Topics Red Book* average wholesale price, discounted as appropriate to reflect market acquisition costs. Outpatient testing costs will be assigned using the Medicare Fee Schedule for the physician component and the Medicare ambulatory payment classification (as per rates for the institutional and laboratory component).

Hospital bills for patients in the U.S. (detailed, summary ledger, and UB-04) will be collected by the GUIDE-IT EQOL CC staff after discharge from the hospital This process typically starts with a call to the head or the representative of the given hospital's patient accounting department to request the bill, and is followed by a written letter including a copy of the signed consent form if requested. Once received, in order to maintain confidentiality, the patient's name will be removed and replaced with the GUIDE-IT patient study number and patient initials before further processing.

In addition, cost-to-charge ratios (Medicare Cost Report Worksheets C and D-1, Part 2) will be obtained for each hospital where a GUIDE-IT hospitalization is reported. These reports can be obtained from the hospital in question, the Medicare Intermediary for that region, or the Centers for Medicare and Medicaid Services. Reports will be obtained for each year of study enrollment and follow-up up to the most recent report available at the start of the data analysis phase.

6.9 Removal or Replacement of Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. In the case of subject withdrawal, the investigator will discuss with the subject the most appropriate way to terminate study participation to ensure the subject's health. All efforts will be made to complete and report the observations as thoroughly as possible up to the date of study termination. Randomized subjects who withdraw from the study will not be replaced.

7. OUTCOME DETERMINATIONS

7.1 Primary Endpoints

The primary endpoint is the time to CV death or first HF hospitalization.

7.2 Secondary Endpoints

- Time to All-cause mortality
- Recurrent hospitalizations
- Days alive and not-hospitalized for CV reasons
- Time to CV death
- Time to first HF hospitalization
- Health Related QOL
- Resource utilization, cost and cost effectiveness
- Safety

7.3 Exploratory Endpoints

- Global Rank Endpoint, incorporating death, hospitalization, and change in quality of Life

- Win-ratio, incorporating death, hospitalization, and change in quality of life

7.4 Safety

The main safety objectives in GUIDE-IT are to characterize the risk profiles of the two management strategies and to monitor for unanticipated risks to study participants. In this study, all medications and procedures commonly used or performed as a part of standard of care for the management of HF have well defined safety profiles. For this trial, reporting is primarily governed by the Common Rule (45 CFR Part 46, Subpart A), Investigational Device Exemptions (Part 812), as well as ICH Guidelines, IRBs and local regulations.

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding events into the appropriate module of the eCRF within InForm. Investigators are to report serious adverse events in accordance with their local IRB requirements. Investigators should follow usual clinical practices at their institution for reporting to regulatory authorities serious, unexpected events related to standard of care medications and devices.

7.4.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered an investigational intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the investigational intervention, whether or not considered related to the investigational intervention (ICH1996).

A serious adverse event (SAE) is any adverse event that may result in any of the following outcomes:

- Death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above

AEs of Interest for the GUIDE IT trial, which may or may not meet serious criteria, include any of the following:

- Symptomatic hypotension
- Symptomatic bradycardia
- Hyperkalemia (Potassium > 6.0 meq/dl or requiring change in therapy)
- Worsening renal function (increase in creatinine by 0.5 mg/dl from last visit or requiring change in therapy)

7.4.2 Reporting Adverse Events

Adverse Events that do not meet SAE criteria and that are not an AE of Interest will not be reported in the InForm database.

SAEs and AEs of Interest that occur from randomization through completion of the final study visit will be reported in the InForm database in the following manner:

- AEs of Interest that do not meet SAE criteria will be recorded on the AE eCRF.
- SAEs that require hospitalization will be reported on the HOSP eCRF noting the reason for the hospitalization. AEs of Interest that require hospitalization will be reported on the HOSP eCRF rather than the AE eCRF.
- Secondary SAEs that may occur while a subject is hospitalized due to a different reason will be reported on the AE eCRF.
- Deaths will be reported on the DEATH eCRF.
- If the subject was hospitalized for the event that led to death, the event will need to be reported both on the HOSP eCRF and the DEATH eCRF.

The Investigator will follow all SAEs and AEs of Interest until resolution, stabilization or the event is otherwise explained.

8. STATISTICAL CONSIDERATIONS

8.1 Determination and Justification of Sample Size

Several design factors and research objectives have been considered in developing an appropriate sample size for the study. First, patient enrollment has been determined so there would be a sufficient number of endpoints to provide a high degree of confidence for testing the primary hypothesis. Second, the statistical power for secondary endpoints has been considered, including the EQOL endpoints. Finally, the sample size has been determined to provide a reasonable level of confidence for detecting clinically important differences in outcome between the two strategies—even if current projections of enrollment rates and hypothesized differences in clinical outcomes between the two arms prove to be optimistic.

Based on the anticipated patient population, we have projected a 1-year CV death and HF hospitalization rate of 40% for subjects randomized to the usual care arm. We estimate our patient population will be similar to that on the EVEREST study, a contemporary multicenter trial of patients with systolic HF randomized at the time of HF hospitalization and followed for a median of 10 months.[48] In EVEREST, the event rate for CV death or HF hospitalization at 10 months was 41%. Given that the meta-analysis of Felker et al. found an aggregate reduction of about 30% in all-cause mortality with biomarker-guided therapy, the impact of biomarker-guided therapy can conservatively be expected to reduce the primary composite endpoint (which we expect to be more sensitive to the effects of the biomarker-guided strategy than all-cause mortality) by 20% (from 40% to 32% at 1 year).

Based on the event rates for each arm discussed above, we have determined the sample size required to provide high power for detecting the postulated 20% relative risk reduction. As we recognize that the actual event rates and the outcome differences between the two testing strategies in GUIDE-IT may vary somewhat from these estimates, and we have determined the power of the study under several different combinations of enrollment rates, event rates and effect sizes. We have conducted the power analyses using simulation studies to mimic the key features of GUIDE-IT. As the primary treatment comparisons will be based on a time-to-event endpoint using the Cox proportional hazards model, we created 1,000 data

sets under each condition, and analyzed them using the Cox regression model to estimate the power under a variety of assumptions about the enrollment rates, event rates and effect sizes (Table 2).

Table 2. Summary of the Power Simulations for the Primary Endpoint

Control Event Rate*	Biomarker-guided Event Rate*	Relative Event Rate Reduction	Enrollment Rate (per month)	Estimated Power (%)	Number of Primary Endpoint Events	Minimum follow-up (months)	Total Study Duration (month)**
40%	**32%**	**20%**	**35**	**89.4**	**566**	**12**	**52**
40%	34%	15%	35	67.1	579	12	52
35%	28%	20%	35	84.6	506	12	52
35%	29.75%	15%	35	57.7	518	12	52
45%	36%	20%	35	93.8	623	12	52
45%	38.25%	15%	35	76.3	637	12	52
40%	**32%**	**20%**	**35**	**91.2**	**605**	**24**	**64**
40%	34%	15%	35	69.6	618	24	64
35%	28%	20%	35	86.8	542	24	64
35%	29.75%	15%	35	58.9	555	24	64
45%	36%	20%	35	95.8	662	24	64
45%	38.25%	15%	35	77.2	677	24	64
40%	32%	20%	26.25	89.7	573	12	62
40%	34%	15%	26.25	67.3	586	12	62
35%	28%	20%	26.25	85.1	513	12	62
35%	29.75%	15%	26.25	57.8	525	12	62
45%	36%	20%	26.25	94.0	630	12	62
45%	38.25%	15%	26.25	76.2	644	12	62

*1-year event rate.

**Duration from study award date to last patient in the last study visit—the assumed yearly rate of loss to follow-up was 4% and the yearly non-CV death rate was 4%.

8.2 Projected Enrollment rate

We anticipate starting enrollment within 6 months from the study award date to finalize the protocol, complete DSMB review and approvals, and activate the sites. Given the complexities of site contracts, IRB approvals and regulatory requirements, we conservatively expect to activate 5 sites each month for enrollment. The recent NHLBI-funded HF-ACTION study enrolled a similar patient population, but required those patients to complete exercise training, which limited recruitment. The average enrollment for HF-ACTION in the U.S. was 0.84 patients per site per month. The 2-site STARBRITE study of biomarker-guided therapy enrolled 137 patients over a 28-month period for an average rate of 2.4 patients per site per month[32]. In the single-center PROTECT study of biomarker-guided therapy, a total of 151 patients were enrolled over a 2-year period for an average rate of 6.3 patients per site per month.[49] For ASCEND HF, the U.S. enrollment rate varied between 1.5-2 patients per site per month. GUIDE-IT's enrollment will resemble a combination of these trials—patients will be identified at the time of acute HF, and, much like an outpatient HF study, they will be randomized soon after discharge. We believe that once a site is activated, an enrollment rate of 1 patient per site per month is achievable. Once all sites are activated, the target enrollment for GUIDE-IT will be 35 patients per month.

8.3 Projected Event Rates

In EVEREST, the event rate for CV death or HF hospitalization at 10 months was 41%. Based on a similar patient population, we have assumed a 1-year event rate with a 40% control arm, which we believe is a conservative estimate. Unlike EVEREST, GUIDE-IT will require elevated natriuretic peptide levels during the

index hospitalization, a powerful marker of increased risk, suggesting GUIDE-IT will have a higher event rate than EVEREST. Power simulations were conducted varying this rate from 35% to 45%. Event times were created using randomly generated exponential variables. The non-CV death and the loss-to-follow-up rates were generated as independent exponential random variables with 1-year event rates of 4% for each variable. In the simulations, the primary outcome variable was censored if the non-CV death or loss-to-follow-up occurred first. The non-CV death rate was based on unpublished data from EVEREST. Drop-in and drop-out rates were assumed to be distributed uniformly in 5% of subjects over the 2-year follow-up. At the time of drop-in or drop-out, the hazard rate was switched to the rate for the other treatment group.

8.4 Anticipated Effect Size

We planned the sample size to detect a relative reduction in the 1-year event rate of 0.20. The power simulations shown below also examine the power with 15% relative reductions. Simulations with relative event rate reductions greater than 25% typically resulted in power greater than 99%.
Results are based on 1,000 simulated data sets in each scenario with a 2-sided Type I error rate of 0.05 (Table 2). The estimated power is based on the proportion of simulations using the Cox regression model Wald chi-square p-value < 0.05. It is expected that the final subject enrollment will be followed for 12 months resulting in follow-up times varying from 12 to 24 months. However, to illustrate the power increase of additional follow-up, we have examined scenarios with 24 months follow-up on all patients.

Based on our best estimates for event rates and enrollment with a 20% reduction in events from a 1-year rate of 40% in the control group to 32% in the biomarker-guided group, we anticipate having 89.4% power with the proposed sample size of 1,100 subjects. With the same event and enrollment rates, we would have a slight increase in power to 91.2% if every subject was followed for 24 months. If per site enrollment is lower than we project at 1 patient per site per month and is closer to 0.75 patients per site per month, Table 1 shows that we can still achieve our target number of primary outcome events by extending the study duration by 10 months. Alternatively, we will have the option of adding more sites in order to maintain total study enrollment at 35 patients per month.

Although GUIDE-IT has been powered for the primary endpoint of time-to-CV death or HF hospitalization, a key secondary endpoint is the time to all-cause mortality. The power for this endpoint was evaluated with simulations as described above. With an assumed 1-year all-cause mortality rate of 25% in the control group, we estimated the power at 86.0% and 96.3% to detect relative event rate reductions of 25% and 30%, respectively, which are consistent with the treatment effect seen in a recent meta-analysis of biomarker-guided therapy.

8.5 Power Calculations for Age Group by Treatment Interaction

Two prior studies (TIME-CHF and BATTLESCARRED) stratified randomization by age (> or < 75) and pre-specified sub-group analysis based on age.[31,33] Although these subgroups were small, the beneficial effects of biomarker guidance in both studies appeared to be primarily in patients < 75. Given that HF is primarily a disease of the elderly, whether there is a differential treatment effect based on age is of substantial clinical relevance and will be examined in GUIDE-IT. To determine the power to detect possible interactions by age, we have simulated data as described above. Additional parameters were added to define the proportion of the population above 75 years of age, and to define event rates that differ by age group. A binary variable was created to identify those patients in the biomarker-guided group and those 75 or more years of age. The results of the simulations are shown in Table 3. With a sample size of 1,100 patients, we have more than 99% power to detect large, qualitative interactions by age group. As expected, the power to detect quantitative interactions is not as great. If we assume 25% of patients are in the older age group, 40% vs. 30% 1-year event rates in the younger group, and 40% vs. 40% 1-year event

rates in the older group, we will have 71.6% power to detect a statistically significant interaction at the 2-sided 0.05 level.

In summary, our calculations suggest that a cohort of 1,100 patients will provide robust statistical power for detecting clinically relevant and realistic benefits of NT-proBNP-guided therapy for the primary and key secondary endpoints. Furthermore, this sample size estimate accounts for a combined 8% loss to follow-up or death due to non-CV causes and an allowance for 5% drop-in and drop-out.

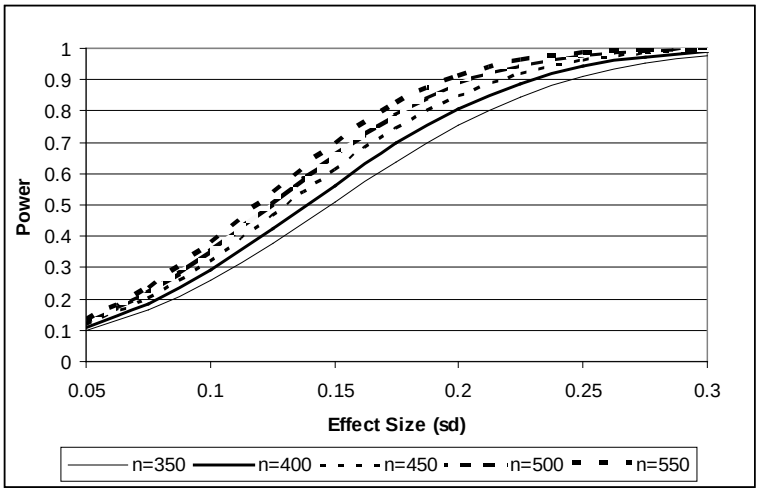
Table 3. Power Simulations for the Interaction between Treatment and Age Groups

Proportion of the population greater than 75 years old	Treatment difference in the younger cohort (control vs. biomarker-guided – 1 year rates)	Treatment difference in the older cohort (control vs. biomarker-guided – 1 year rates)	Estimated power to detect the interaction effect (%)
20%	**40% vs. 30%**	**40% vs. 50%**	**99.8**
25%	**40% vs. 30%**	**40% vs. 50%**	**99.9**
33.3%	**40% vs. 30%**	**40% vs. 50%**	**99.9**
20%	40% vs. 30%	40% vs. 42%	80.7
25%	40% vs. 30%	40% vs. 42%	88.9
33.3%	40% vs. 30%	40% vs. 42%	92.6
20%	40% vs. 30%	40% vs. 40%	66.2
25%	**40% vs. 30%**	**40% vs. 40%**	**71.6**
33.3%	40% vs. 30%	40% vs. 40%	80.7
20%	40% vs. 30%	40% vs. 38%	49.1
25%	40% vs. 30%	40% vs. 38%	54.4
33.3%	40% vs. 30%	40% vs. 38%	61.6

8.6 Sample Size Justification for Secondary Endpoints

In Figure 5, a set of power curves is presented to describe the power to detect treatment effects for secondary endpoints. These power calculations are based on the following assumptions: 2-sided Type I error rate of 0.05, a test statistic based on a 2-sample t-test, and sample sizes ranging from 350 to 550 subjects per treatment group. Mixed models will be used in the analysis of the longitudinal QOL data. However, calculations based on the 2-sample t-test provide a conservative approximation for the power to detect treatment differences. Assuming at least 350 subjects per treatment group, GUIDE-IT will have >90% power for detecting a treatment difference of ¼ standard deviation. For many of the QOL instruments being proposed for this study, a treatment effect size equal to ¼ of a standard deviation is a reasonable benchmark for a clinically meaningful change.

Figure 5. Power curves for secondary endpoints



8.7 Statistical Analysis: General Approach

Statistical analysis will be performed by the GUIDE-IT data coordinating center (DCC) at Duke Clinical Research Institute (DCRI). All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention-to-treat;" that is, subjects will be analyzed (and endpoints attributed) according to the treatment strategy to which patients are randomized, regardless of subsequent additional post-randomization treatment and medical care. Statistical comparisons will be performed using 2-sided significance tests. Additional perspective regarding the interpretation of the data will be provided through extensive use of confidence intervals and graphical displays.

Baseline demographic and clinical variables will be summarized for each randomized arm of the study, for example: relevant descriptors from the history, physical and laboratory examination; CV risk factors; co-morbidity descriptors; and course of the patient's symptoms. Descriptive summaries of the distribution of continuous baseline variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages. Because randomization is expected to produce excellent balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics will be more informal. For comparisons of continuous baseline variables, emphasis will be given to nonparametric procedures such as the Wilcoxon rank sum test. Group comparisons with respect to discrete baseline variables will use the conventional chi-square test or Fisher's Exact Test as appropriate.

8.8 Analysis for the Primary Hypothesis

The statistical comparison of the two randomized arms with respect to the primary endpoint will be a time-to-event analysis, and therefore will be based on the time from randomization to the first occurrence of CV death or HF hospitalization. The Cox proportional hazards regression model will be the primary tool to analyze and assess outcome differences between the two treatment arms. A hazard ratio and 95% confidence interval for summarizing the difference in outcomes between the two treatment arms will be computed using the Cox model. This comparison will constitute the primary statistical assessment of the effect of biomarker guidance versus usual care on overall clinical outcomes. The Cox model will include an indicator variable for treatment group and baseline adjustment variables for age, sex, NT-proBNP, diabetes mellitus and ejection fraction.

In order to select the best set of adjustment covariates, we reviewed prognostic models from other large datasets in chronic HF. We selected covariates based upon the importance of choosing variables with

minimal missing data and adjusted the primary analysis for the following baseline variables: age, sex, NT-proBNP, ejection fraction, and diabetes mellitus.

8.9 Supportive Analyses of the Primary Endpoint

If the data provide evidence of an overall difference in outcome between randomized arms, we will examine whether the effect is similar for all patients, or whether it varies according to specific patient characteristics. In particular, we will focus on whether the relative benefit differs according to patient age, sex, race, co-morbidity, and selected risk factors. These analyses will use the Cox model by testing for interactions between the randomized groups and specific baseline variables. In addition to the statistical hypothesis testing, Kaplan-Meier survival estimates will be constructed based on the time from randomization to the first occurrence of CV death or HF hospitalization.

8.10 Analysis of Secondary Endpoints

The analyses for the time-to-event secondary endpoints will be similar to those outlined for the primary endpoint using the time from randomization through the first occurrence of any component of a specific secondary endpoint (or censoring) as the response variable, and assessing group differences using the Cox proportional hazards model. The effect of the NT-proBNP-guided treatment strategy on these time-to-event secondary endpoints will be summarized using hazard ratios (with associated confidence intervals) computed from the Cox model. Kaplan-Meier curves will be constructed to display the cumulative event rates of the two treatment groups. For analysis of the total days alive and out of the hospital endpoint, we will apply the inverse probability weighted estimators of Bang and Tsiatis to account for the potential bias due to censored and incomplete data.[50]

8.11 Multiple Comparisons and Composite Endpoints

With the primary hypothesis and the various secondary endpoints, there is a multiplicity of analyses to be performed and an increased probability that at least one of the comparisons could be "significant" by chance. There are adjustments (e.g., based on the Bonferroni inequality) that can be used to preserve the overall type I error level by adjusting for the multiplicity of secondary endpoints by requiring small significance levels for every comparison. We will be conservative in the interpretation of these analyses, taking into account the degree of significance, and looking for consistency across endpoints. Also, we have pre-specified the primary and secondary outcome variables to help avoid over-interpretation and to reduce the problems inherent with multiple testing. A related issue is the interpretation of composite endpoints in clinical trials. To understand the importance of the components of the primary endpoint, we will estimate the treatment effect and frequency of each component (CV mortality and HF hospitalization) separately. Based on the prior biomarker-guided studies in HF, we have pre-specified age (≥75 or < 75 years of age) as a key subgroup of interest. The examination of this subgroup will include a formal test of interaction with the Cox regression model. Hazard ratio plots with point estimates and 95% confidence intervals will be used to examine the consistency of the treatment effect across subgroups.

8.12 Exploratory Endpoints

In order to explore the contribution of recurrent hospitalization and quality of life to the overall efficacy and safety of biomarker guided therapy, alternative methodologies for assessing multiple endpoints will be analyzed. These will include the global rank approach as previous described[51]. Generally, a pre-specified hierarchy of endpoints will be created that will include death, hospitalization, and quality of life. All patients will be ranked according to this hierarchy, and the primary statistical comparison will be the

comparison of ranks between the treatment and control group. An alternative approach to be explored will be the "win ratio" as described by Pocock et al[52]. In this approach, patients randomized to biomarker guided therapy and control will be matched based on baseline characteristics, and the overall post randomization experience between each pair will be compared using a pre-specified hierarchy of endpoints in order to determine a "winner". The primary metric will be the proportion of pairs with the biomarker guided arm wins relative to control.

8.13 Analysis of Economic and Quality of Life Data

For each of the QOL measures examined in this study, data analysis will proceed in several stages. Initially, we will provide simple descriptive and comparative analyses by intention-to-treat. A nonparametric bootstrap will be used to estimate treatment differences with 95% confidence intervals (CI) and p-values. Since there is currently no consensus in the statistical literature about the best way to deal with the multiple comparisons problem arising from testing each individual scale at each time point separately, we propose two complementary approaches. First, we will pre-specify the overall summary score from the KCCQ and functional status using the Duke Activity Status Index as the primary QOL comparisons of interest and assign all other comparisons to a secondary (descriptive) status. Second, we will fit mixed models, which make use of all available QOL data at each study assessment point. Statistical power estimates for the KCCQ, based on data collected in the HF-ACTION trial demonstrate that we should have > 90% power to detect a ¼ standard deviation difference (about 5 points on a 0-100 scale) in the KCCQ overall score and in the DASI (about 4 points on a 0-58 scale). We expect refusal rates to be quite low overall. In a 2966-patient QOL substudy in GUSTO, we had a 1% refusal rate at each of three interviews. The rate of patient incapacity expected for GUIDE-IT is uncertain, but should be similarly low.

Several important methodologic challenges must be considered in the analysis of QOL data: the effect of differential mortality in the treatment arms and the effect of missing data (from death, incapacity or loss to follow-up). Our approach to missing data is to minimize it as much as possible. If the primary study hypotheses are confirmed, analysis of QOL data may be complicated by the fact that the biomarker-guided strategy was more successful at keeping patients alive. Even a relatively small difference in mortality due to treatment may create a paradox in the QOL data such that the more effective therapy is associated with worse QOL (for example, if the patients with the worst QOL died in the usual care arm but were saved in the biomarker-guided arm.) We will address this problem by estimating the Survivor Average Causal Effects, which involves a counterfactual analysis to predict the QOL scores of interest assuming that the patient had not died or been otherwise unable to provide their own data.

For the economic analyses, the primary statistical comparisons between the two treatment arms will be performed by intention-to-treat. A nonparametric bootstrap will be used to estimate treatment differences with 95% CI and p-values. Estimates and confidence limits around the observed cost differences can be created using several different approaches. In recent work, we have used bootstrap methods for this.

Although our data analysis will not make parametric assumptions about the distributions of costs, we can approximate the precision of our estimates by assuming that costs follow a log-normal distribution. Previous studies suggest that this is a reasonable assumption. For data that are log normally distributed, the coefficient of variation (i.e., the standard deviation divided by the mean) remains constant, an observation that we have seen empirically across different studies and treatment arms. In fact, our experience has shown that the coefficient of variation is very close to 1 (i.e., the standard deviation is equal to the mean). Under the assumption of log normal distributions and CV=1, with > 500 patients (> 90%) with cost data per treatment arm, we will be able to estimate the difference in mean costs between

treatments to within approximately 0.12 standard deviations based on the half-width (1.96 times the standard error) of the 95% confidence interval. This means, for example, if the mean cost per treatment arm was $10,000, then the 95% confidence interval for the treatment difference in cost would be the point estimate for the difference +/- $1,208.

In order to provide a second (descriptive) perspective on cost differences for each strategy in GUIDE-IT, we will also directly measure major health care resource items used including hospital days (e.g., intensive care, step-down units, wards) and cardiac procedures (e.g., ICD, VAD placement, catheterization, coronary revascularization, atrial fibrillation ablation) as well as selected smaller ticket items such as outpatient physician and emergency department visits. A basic set of resource data will be collected on the eCRF, and will be supplemented by the additional resource data that can be collected from the detailed hospital billing forms.

To estimate the incremental cost effectiveness of the biomarker-guided approach relative to usual care, we will calculate a base case cost-effectiveness ratio that defines the incremental cost required to add an extra life year with the biomarker-guided strategy relative to usual care. A second series of analyses will calculate the corresponding cost-utility ratio, using utility data from the EQ-5D collected in the GUIDE-IT trial. These analyses will use the societal perspective and a lifetime time horizon so that the estimated incremental cost-effectiveness and cost-utility ratios can be compared with societal benchmarks. Where extrapolations from empirical data and other assumptions are required, they will be based, to the extent possible, on the empirical data from the GUIDE-IT trial and will be accompanied by appropriate examination of the effects of uncertainty using both stochastic methods and sensitivity analyses. For descriptive purposes, we will also calculate within-trial cost-effectiveness and cost-utility ratios, since they do not require any extrapolations. However, these within-trial ratios are limited due to their failure to account fully for long-term benefits and costs, and the absence of comparative benchmarks. At the time of analysis, costs will be adjusted to the most recent year for which the Producer Price Index has been published. Both costs and life expectancy will be discounted to present value at a 3% annual discount rate (with rates from 0 to 7% examined in sensitivity analyses).

Since many of the patients will remain alive at the conclusion of the trial, a method is required for converting observed trial experience into the corresponding lifetime survival and cost figures needed for use in the incremental cost-effectiveness calculations. There are three general methods that we have previously used to make the necessary lifetime extrapolations called for in cost-effectiveness analysis: use of the trial data for extrapolation, use of secondary data sources to base the extrapolations upon, and use of Markov models. GUIDE-IT will provide a rich empirical data set involving up to 2 years of clinical outcome, cost, and utility data, with over 2,000 patient-years of follow-up information. We will use these data in age-based survival models to create estimates for each GUIDE-IT patient of life expectancy, quality-adjusted life expectancy and lifetime medical costs.

The method, in brief, involves 5 basic steps. 1) Using Cox Proportional Hazards regression methodology for left-truncated and right-censored data, we model the hazard of death as a function of age, adjusting for additional prognostic factors through covariates. This model "adjusts for" age as the metric over which the hazard is computed, treats additional prognostic factors as covariates, and stratifies on treatment group (if necessary to satisfy the proportional hazards assumption). By estimating the hazard over the age metric (rather than over the time metric, as is traditionally done), we can produce data-based survival predictions through a much longer time period due to the broad representation of ages in our database. 2) This hazard relationship, which under proportional hazards is well estimated through the age range represented in our data, is used for prediction on a patient-by-patient basis. The predicted survival estimates for each patient

are then combined with the empirical GUIDE-IT survival data and averaged over all the patients for both treatment groups. 3) Again using a Cox Proportional Hazards regression model, together with the post-HF hospitalization survival experience available in the GUIDE-IT data (and if necessary, secondary data sources available at the DCRI including HF-ACTION), we will estimate the long-term survival impact of a HF hospitalization, the non-fatal component of the study primary endpoint. This model will provide a quantitative measure of the increased relative risk attributable to these non-fatal events for later incorporation in the individual patient predictions. 4) For the oldest age range, where the amount of empirical data may not be sufficient, we will use a Gompertz-based function for extrapolation. The estimated mean survival curves are integrated over a lifetime to obtain life expectancy for each treatment group. 5) The difference between the areas under each survival curve is computed to obtain the biomarker-guided arm incremental life expectancy.

Uncertainty in cost-effectiveness estimates related to sampling variation will be quantified using non-parametric bootstrap techniques (1,000 samples with replacement with a cost-effectiveness ratio calculated for each sample) and expressed in three complementary formats. First, cost-effectiveness ratios arising from the bootstrap will be displayed on the cost-effectiveness plane to characterize the precision and magnitude of the estimates. Second, we will examine the net monetary benefit of the intervention, defined as the difference between the increase in effectiveness (valued using the willingness- to-pay threshold per unit of effectiveness), and the increase in cost. Net monetary benefit and associated confidence intervals will be displayed for a range of willingness-to-pay thresholds. Finally, we will plot the cost-effectiveness acceptability curve, which indicates the probability that that the intervention is cost effective (i.e., incremental net benefit > 0) for a range of willingness-to-pay thresholds. We will also perform sensitivity analyses to address uncertainty related to methodological assumptions regarding key parameters. If appropriate, bootstrap analyses will be repeated for alternative parameter values. It must be emphasized that although the general plan of our cost-effectiveness analyses can be specified prospectively, there is clearly an iterative quality to building successful cost-effectiveness models.

8.14 Data Safety Monitoring Board and Interim Analyses

For ethical reasons, an interim examination of key safety and endpoint data will be performed at regular intervals during the course of the trial. The primary objectives of these analyses will be to evaluate the accumulated data for high frequency of negative clinical outcomes in either of the two randomized arms. In addition, the interim monitoring will also involve a review of the control arm event rates, patient recruitment, compliance with the study protocol, status of data collection, and other factors that reflect the overall progress and integrity of the study. The results of the interim analyses and status reports will be carefully and confidentially reviewed by an NHLBI-appointed DSMB.

It is anticipated that the DSMB will meet every 6-months to review the accumulating data. Prior to each meeting, the DCC will conduct any requested statistical analyses and prepare a summary report along with the following information: patient enrollment reports, rates of compliance with the assigned testing strategy, frequency of protocol violations, and description of SAEs (statistical comparisons of the randomized arms with respect to these SAEs will use chi-square or other appropriate 2-sample methods). The extracted data files and analysis programs for each DSMB report will be archived and maintained at the DCC for the life of the study.

For futility monitoring, we will apply the inefficacy monitoring rule of Freidlin, Korn, and Gray[53] to stop the trial if the biomarker-guided strategy is not beneficial. We propose to use the conservative boundary LIB0 along with a harm look at 25% of expected information. This approach will include 7 interim looks scheduled at roughly 25%, 40%, 50%, 60%, 70%, 80%, and 90%. With the proposed design, a total of 566

events are expected and the first interim review for futility and efficacy would be scheduled to occur after approximately 140 primary endpoint events have been observed. If the data suggested a benefit for the usual care arm with a p-value of <0.05, the Freidlin, Korn, and Gray approach would suggest stopping the trial at the 25% look. The second interim review would be scheduled after approximately 226 primary endpoint events have been observed. For the interim reviews at 40%, 50%, 60%, 70%, 80%, and 90%, the LIB0 conservative boundary would suggest stopping the trial for inefficacy if the biomarker-guided arm had a hazard ratio > 1.0 compared to usual-care arm. The Freidlin, Korn, and Gray approach will result in a trivial loss of power and requires no sample size adjustment. The DSMB will weigh any trade-offs between short-term versus long-term results. We propose to use the method of Haybittle and Peto as a guide in interpreting interim efficacy analyses.[54,55] This procedure requires large critical values (Z=3, p≤0.001) for every assessment until the planned final analysis. Because of the conservatism throughout the trial, the critical value at the final analysis is conducted at the "nominal" critical value.

The DSMB will weigh any trade-offs between short-term versus long-term results. The DSMB will play a valuable role in advising the study leadership on the relevance of advances in the diagnosis and treatment of patients with systolic HF. The DSMB would be asked to offer proper perspective on any therapeutic or diagnostic testing advances that may occur during the course of the trial. If protocol modifications are warranted, close consultation among the DSMB, the NHLBI staff and the study leadership will be required. A separate DSMB charter will outline the operating guidelines for the committee, and the protocol for evaluation of data—the charter will be created prior to patient randomization and agreed upon during the initial meeting of the DSMB. Minutes of all DSMB meetings will be prepared and distributed to committee members.

9. DATA MANAGEMENT PROCEDURES

9.1 Electronic Data Capture (EDC) System

To ensure an efficient and timely data capture system, a rapid transmission and integration of this information into the trial processes and study database, and the elimination of paper documents, the web-based electronic data capture system, known as InForm will be used.

9.2 Electronic Case Report Form (eCRF)

The eCRF for GUIDE-IT will have several forms including enrollment and demographics, relevant history, HF symptoms, physical exam results, laboratory results, baseline biomarker levels, and other baseline presenting characteristics; follow-up worksheets for use during regular follow-up visits and to track the patient's clinical course over time; and event worksheets for recording the circumstances and details surrounding the occurrence of a death or hospitalization. Economics and Quality of Life (EQOL) data will be collected as summarized above and detailed in the Manual of Operations. A dictionary, glossary of terms and instructions for completing the forms will be provided to the sites.

9.3 Data Management Process

We will use InForm software (described above) for data entry, screen handling and simple reports. We will use an Oracle database server on an existing UNIX-based network server for this operational database management. Data will be entered into the InForm eCRF by clinical site personnel. Any out-of-range values and missing key variables will be flagged and addressed, or answered at the site during the data entry process, allowing many queries to be resolved in real-time. Queries can also be generated from manual review of the data forms. These will be entered into the database and tracked in the same manner as the computer-generated queries.

We will compare distributions of selected variables across sites to ensure that consistent definitions are used. Examples of these variables include the following: frequency of missing critical variables, biological or medical history parameters, fields that define study procedure compliance and safety irregularities. In our surveillance, we will use statistical process control to ensure that issues not likely to be the result of normal random variation are investigated. The DCRI will create reports to identify trends in the data that may require additional clarification and training. These reports will be available to the sites and to the study leadership, as we work with the sites to correct negative trends and eliminate future data errors.

The DCRI will perform internal database quality-control checks and data audits during the trial and at the conclusion to track the frequency of random errors and to identify any systematic deviation requiring correction. Patients whose data are audited will be randomly selected from the total enrollment. Data management operations are also reviewed internally for their compliance with standard procedures, rules and guidelines for processing, quality control and productivity.

9.4 Data Quality Control

Data quality control goes beyond the data management process. All groups at the DCRI will work in tandem to ensure that the data collected in this study are as complete and correct as possible. A 4-step, multi-functional approach to data quality control will be implemented and is summarized below:

1. Training: Prior to the start of enrollment, the physician investigators and study coordinators at each site will be trained with the clinical protocol and data collection procedures, including how to use the InForm system and complete the eCRF data. Initial investigator and coordinator training will occur with an InForm trainer and hands-on database interaction. This trainer will present slides, demonstrate key InForm functionality and guide attendees through practice exercises. Follow-up training and training for new study personnel will be conducted by DCRI personnel who will present slides, demonstrate the system and guide attendees through practice exercises using on-line web-based teleconferences.
2. Monitoring: The clinical and data coordinating center will ensure that data collection is being handled properly, will provide in-service training, and address questions from site investigators and coordinators. Data quality and completeness will be reviewed by the DCRI team on a regular and ongoing basis, and any issues noted will be addressed with the site. Monitoring visits will be completed as described in the Clinical Monitoring Plan.
3. Managing data: After the data have been transferred to SAS for statistical summarization, data description, and data analysis, further cross-checking of the data will be performed with discrepant observations being flagged and appropriately resolved through a data query system.
4. Reviewing data: Deaths and hospitalization events will be reviewed by the CEC to ensure an appropriate standardized classification of the component events comprising the primary composite endpoint. The DCC will provide the CEC with detailed information for classification and adjudication of these events. The CEC will be blinded to the randomized treatment strategy assignment to ensure unbiased evaluation of outcome events.

10. STUDY GOVERNANCE AND COMMITTEES

The governance and management of the GUIDE-IT study will be organized as follows.

10.1 Clinical Coordinating Center (CCC)

The CCC will be at the DCRI. The CCC functions as a clinical trial center and is responsible for all aspects of conducting this trial, including: clinical operations; oversight of all committees and working groups; development of the protocol and all amendments; site identification, recruitment, education, and

retention; oversight of core laboratories; quality control; site reimbursement; monitoring of study progress; maintenance of a 24-hour helpline for questions from clinical sites; and leadership in data analysis, presentations, and publications. Clinical Operations is the critical functional component of the CCC, and will provide project management; development and preparation of study materials; site management; education of all site-based personnel on the rationale, design, and execution of GUIDE-IT; oversight of the study helpline; and assistance with preparation of manuscripts and publications.

The CCC will be the primary day-to-day contact for sites. CCC staff will develop and implement educational and training plans, communication initiatives including phone and email contact, conference calls, newsletters, website, and will use social networking technology. The CCC staff will collaborate with the sites to ensure their understanding of the protocol, the operationalization of the protocol, and the successful identification of eligible patients for screening and enrollment. From working on many other multicenter randomized controlled studies, these project team members bring substantial operational experience. The CCC expects that our efforts to significantly vet sites for interest and capabilities, to extensively educate sites, and to carefully and clearly state the expectations for sites will minimize problems with sites performance. An important asset to the site management component of the CCC will be the use of the DCRI's Clinical Trials Management System, a web-based application that provides the DCRI project teams with direct access to trial data, and can be used to manage various aspects of the study, including: protocols, accounts, contracts, sites, site monitoring, and subject management. Using this centralized system will ensure an integrated approach to handling trial information, and will help the CCC and the DCC work together seamlessly.

10.2 Data Coordinating Center (DCC)

The DCC will be at the DCRI. The DCC will support the GUIDE-IT trial in study design, study start-up, and project implementation. This includes developing the eCRF and instructions; establishing data management methods; creating and maintaining a patient database; resolving queries; collecting and reporting SAEs; analyzing the data; and assisting with trial design, protocol development, presentations and manuscripts.

10.3 Economics and Quality of Life Core

The EQOL core will be at the DCRI. Integration of the EQOL core into overall trial operations will be facilitated by the fact that the CCC, DCC, and EQOL are all located at DCRI. The CCC, DCC, and EQOL core will coordinate site management and data management activities as they relate to the collection of EQOL data.

10.4 Biomarkers Core Lab and Biorepository

The core lab and biorepository will be located at the NC Research Campus at Kannapolis, a joint enterprise between the research universities of NC to provide core lab services. Instructions for collection, processing, labeling, and shipping of biological specimens will be provided in a manual of operations.

10.5 Executive Committee

The Executive Committee is the primary decision making body of the study and is responsible for its successful completion. The Executive Committee will meet weekly by teleconference. They will review and have input on the trial protocol, manual of operations, monitoring plan, electronic case report form (eCRF), site materials, data management plan and statistical plan. On issues requiring a vote, 1 vote per member will be allowed. This Committee will meet in person at least twice a year, typically at the annual scientific sessions of the American Heart Association and American College of Cardiology. All members of the

Executive Committee will be expected to make ongoing substantive intellectual and operational contributions to the study.

10.6 Steering Committee

The Steering Committee will address enrollment issues, education and training to promote compliance with the study protocol. Membership will include the EC, committee chairs, core lab directors, and other selected site PIs, selected study coordinators, and other members as required. The Steering Committee will meet in person and/or via teleconference throughout the conduct of the trial.

10.7 Clinical Event Classification Committee

The Clinical Events Classification Committee (CEC) is an independent committee providing independent and blinded adjudication of determined primary outcome events. Members of the CEC will not be participating in the GUIDE-IT study in any way, and will be blinded as to treatment assignment. Endpoint definitions will be formulated prior to the initiation of the study, and will be approved by the EC. A charter will be developed to guide CEC activities.

10.8 Adherence Committee

This committee will serve to promote and monitor investigator adherence to the study protocol, particularly with regard to responsiveness to natriuretic peptide levels in the biomarker-guided arm. They will review data on adherence to the protocol and results of interventions by the CCC on a monthly basis. When necessary, the committee will intervene with individual investigators or the investigators as a whole. Given the importance of adherence to testing the hypothesis of GUIDE-IT (as outlined in the Research Plan), the Adherence Committee will play an active and engaged role in the ongoing operations of the study.

10.9 Biomarkers and Genetics Committee

The Biomarkers and Genetics Committee will establish and operationalize policies and procedures for analysis of biorepository samples by GUIDE-IT investigators.

10.10 Publications and Presentations Committee

The Publications and Presentations Committee will review publication proposals and manuscripts, and will assist in dissemination of trial results.

10.11 Data and Safety Monitoring Board (DSMB)

The DSMB is an independent committee that oversees the safety of research subjects. It is anticipated that the DSMB will meet every 6-months to review the accumulating data. Prior to each meeting, the DCC will conduct any requested statistical analyses and prepare a summary report along with the following information: patient enrollment reports, rates of compliance with the assigned testing strategy, frequency of protocol violations, and description of SAEs (statistical comparisons of the randomized arms with respect to these SAEs will use chi-square or other appropriate 2-sample methods). The extracted data files and analysis programs for each DSMB report will be archived and maintained at the DCC for the life of the study.

11. REGULATORY ISSUES

11.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with DCRI standard operating procedures. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

11.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Coordinating Center before study initiation. The name and occupation of the chairman and the members of the IRB/IEC must be supplied to the Coordinating Center if this information is released by IRB/IEC. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

11.3 Informed Consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained. The informed consent forms are part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval. The Coordinating Center will supply proposed informed consent forms, which comply with regulatory requirements, and are considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the approved version must be provided to the Coordinating Center after IRB/IEC approval.

12. Remote Monitoring

The study will be monitored remotely by representatives of the DCRI or its designee according to the prospective clinical monitoring plan (CMP) for the following purposes:

- Real-time monitoring of compliance with study protocol inclusion/exclusion criteria is enabled via triggers and range checks programmed in the InForm database.
- Assist site personnel who will verify data identified within query reports against source documents through frequent telephone and email contact.
- Verify that written informed consent was obtained before initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the patient's randomization to a procedure.

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14. APPENDICES

14.1 Appendix A. Schedule of Study Assessments

	Screening	Day 0 (Randomization)	2 wks (± 1 week)	6 wks (± 1 week)	3 mos (± 1 week)	6 mos (± 1 week)	9 mos (± 1 week)	12 mos* (± 1 week)
Informed Consent	X							
History and physical	X	X	X	X	X	X	X	X
CV Medication History	X	X	X	X	X	X	X	X
Document rationale for changes in therapy			X	X	X	X	X	X
6 minute walk		X						
QOL**		X			X	X		X
Medical resource use and cost assessment		X	X	X	X	X	X	X
Local lab NT-proBNP (standard of care group)	X	X						
Local lab NT-proBNP (guided only)	X	X	X	X	X	X	X	X
Cr, BUN, electrolytes (local lab)	X	X	X	X	X	X	X	X
Core lab plasma sample		X	X	X	X	X	X	X
Core lab serum sample		X	X	X	X	X	X	X
Core lab DNA sample (once only)		X						
Safety assessments			X	X	X	X	X	X

*Patients will be followed for a minimum of 12 months up to a maximum of 24 months
** QOL will be administered yearly after the 12 month visit. QOL interviewing windows per QOL MOO.