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Rationale and Design of the GUIDE-IT Study

Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure

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ABSTRACT

OBJECTIVES The GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study is designed to determine the safety, efficacy, and cost-effectiveness of a strategy of adjusting therapy with the goal of achieving and maintaining a target N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of <1,000 pg/ml compared with usual care in high-risk patients with systolic heart failure (HF).

BACKGROUND Elevations in natriuretic peptide (NP) levels provide key prognostic information in patients with HF. Therapies proven to improve outcomes in patients with HF are generally associated with decreasing levels of NPs, and observational data show that decreases in NP levels over time are associated with favorable outcomes. Results from smaller prospective, randomized studies of this strategy thus far have been mixed, and current guidelines do not recommend serial measurement of NP levels to guide therapy in patients with HF.

METHODS GUIDE-IT is a prospective, randomized, controlled, unblinded, multicenter clinical trial designed to randomize approximately 1,100 high-risk subjects with systolic HF (left ventricular ejection fraction ≤40%) to either usual care (optimized guideline-recommended therapy) or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP level of <1,000 pg/ml. Patients in either arm of the study are followed up at regular intervals and after treatment adjustments for a minimum of 12 months. The primary endpoint of the study is time to cardiovascular death or first hospitalization for HF. Secondary endpoints include time to cardiovascular death and all-cause mortality, cumulative mortality, health-related quality of life, resource use, cost-effectiveness, and safety.

CONCLUSIONS The GUIDE-IT study is designed to definitively assess the effects of an NP-guided strategy in high-risk patients with systolic HF on clinically relevant endpoints of mortality, hospitalization, quality of life, and medical resource use. (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure [GUIDE-IT]; NCT01685840) (J Am Coll Cardiol HF 2014;2:457-65) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CV = cardiovascular

HF = heart failure

LVEF = left ventricular ejection fraction

NP = natriuretic peptide

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Heart failure (HF) is a public health problem of massive proportions in both developed and developing countries (1). In the United States alone, more than 5 million patients are estimated to have HF, more than 1 million hospitalizations and 270,000 deaths result annually from HF, and disease management accounts for more than $30 billion in total costs per annum (2). Evidence-based therapies such as beta-blockers and renin-angiotensin-aldosterone system inhibitors can significantly improve outcomes in patients with HF, but available data suggest that many patients in clinical practice are either not treated with these agents or are treated with doses that are substantially lower than recommended (2–7).

What accounts for this underuse of cardiac medications of proven benefit? Signs and symptoms suggestive of disease progression in HF may be subjective and subtle and therefore underrecognized by providers and patients (8). Additionally, "therapeutic inertia"—the reluctance on the part of both patients and providers to increase or modify therapy given apparent clinical stability and the additional follow-up required—may also play a role (9).

A variety of disease management strategies have been evaluated to improve the management of patients with chronic HF, ranging from nursing-based interventions to technologically complex interventions using implantable hemodynamic monitors and telemedicine. The success of these approaches has been highly variable, and many are personnel-intensive, complex, or costly to implement (10–12). Therefore, there is a need for a cost-effective and objective measure of disease stability that can be used to favorably affect care of patients with chronic HF and demonstrate improvements in outcomes (13).

The natriuretic peptides (NPs), specifically B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), provide a readily evaluable objective biochemical marker that reflects many aspects of the physiology of HF and disease progression. It is well established that the NPs are among the most powerful predictors of adverse outcomes in patients with HF (14–17). Concentrations decline in response to use of guideline-recommended therapies for HF (**Table 1**), and rising levels portend poor patient outcomes (18–22). These observational data have led to the hypothesis that serial measurements of NPs may be used to guide titration of chronic medical therapy in patients with HF.

TABLE 1 Therapies for HF That May Lower Natriuretic Peptide Levels

Diuretics (loop or thiazide)	↓
ACEIs	↓
ARBs	↓
Beta-blockers	transient ↑, mostly ↓
Mineralocorticoid receptor antagonists	↓
CRT	↓
Exercise	↓
Rate control of atrial arrhythmia	↓

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CRT = chronic resynchronization therapy; HF = heart failure.

Previous clinical trials of varying size and design have tested this hypothesis over the past 2 decades with mixed results (**Table 2**) (23–31). Although pooled analyses of these studies indicate a 20% to 25% reduction in mortality with biomarker-guided therapy, generalizability has been limited by the small size of studies as well as significant heterogeneity in the inclusion criteria, treatment strategies, and NP cut points (32,33). In light of this uncertainty, current guidelines do not recommend the use of serial measurement of NP levels to guide titration of therapy in patients with HF (2). Thus, the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study is designed to prospectively evaluate the efficacy of a biomarker-guided HF treatment strategy compared with optimized medical therapy alone in a large cohort of high-risk patients with systolic HF. The GUIDE-IT study is funded by the National Heart, Lung, and

Critical Diagnostics and has served as a consultant for Roche Diagnostics. Dr. Ezekowitz has received research funding from the National Institutes of Health and Alere Inc. Dr. Fiuzat has served as a consultant for Roche Diagnostics and has received research funding from Roche Diagnostics, BG Medicine, and Critical Diagnostics. Dr. Januzzi has served as a consultant for Critical Diagnostics and Novartis and has received research funding from Critical Diagnostics, Roche Diagnostics, Siemens, Singulex, Thermo Fisher Scientific, Sphingotec, Amgen, and Zensun. Dr. Mark has received grant funding from AstraZeneca, Gilead, Eli Lilly, Bristol-Myers Squibb, and AGA Medical; and has served as a consultant for Janssen, Medtronic, and Somahlution. Dr. O'Connor has served as a consultant for Roche Diagnostics and has received research funding from Roche Diagnostics, BG Medicine, and Critical Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, served as Guest Editor for this paper.

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Blood Institute (NCT01685840) and will be the largest study of biomarker-guided therapy in patients with HF performed to date.

METHODS

STUDY OBJECTIVES. The primary objective of the GUIDE-IT study is to determine the efficacy and safety of a strategy of biomarker-guided therapy compared with optimized care in high-risk patients with HF who have left ventricular systolic dysfunction. The primary endpoint is time to cardiovascular (CV) death or first hospitalization for HF. The secondary objectives are to evaluate the effect of biomarker-guided therapy on hospitalization, all-cause mortality, CV death, resource use, quality of life, cost, and cost-effectiveness.

STUDY POPULATION. The GUIDE-IT study is designed to enroll approximately 1,100 patients with known systolic HF (left ventricular ejection fraction [LVEF] ≤40%) and at high risk for HF events at sites in the United States and Canada. Inclusion and exclusion criteria are summarized in Table 3. Patients are considered high risk if they have been hospitalized because of HF, visited the emergency department because of HF, or have been treated with intravenous diuretics as an outpatient within the prior 12 months and had an NT-proBNP level >2,000 pg/ml or BNP level >400 pg/ml at any time during the 30 days before randomization. Patients must also have an LVEF of ≤40% determined by an accepted imaging method within 12 months before randomization.

STUDY DESIGN. The overall scheme of the GUIDE-IT study is shown in Figure 1. The trial is a multicenter, prospective, randomized, parallel control group, unblinded, 2-arm clinical trial comparing biomarker-guided therapy with usual care in high-risk patients with systolic HF. Patients enrolled in the GUIDE-IT study are randomized in a 1:1 allocation to either usual care (titration of HF therapy on the basis of target doses from current evidence-based guidelines for the management of HF) (2) or biomarker-guided care (titration of HF therapy using guideline-recommended therapies [Table 4] with a goal of achieving and maintaining a target NT-proBNP level <1,000 pg/ml).

USUAL CARE. Patients receive care on the basis of the 2013 American Heart Association/American College of Cardiology guideline recommendations (2). Investigators are provided with specific information on evidence-based target doses of neurohormonal antagonists. Diuretics are titrated on the basis of the

TABLE 2 Design of Selected Randomized Controlled Trials of Biomarker-Guided Therapy in HF

Study (Ref.#)	GUIDE-IT (ongoing)	Troughton et al. (25)	STARS-BNP (30)	Berger et al. (29)	PROTECT (28)	STARBRITE (24)	TIME-CHF (27)	BATTLESCARRED (26)	PRIMA (23)	SIGNAL-HF (31)
Sample size	1,100	69	220	278	151	137	499	364	345	252
Marker	NT-proBNP	NT-proBNP	BNP	NT-proBNP	NT-proBNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP
Target	1,000 pg/ml	1,692 pg/ml	100 pg/ml	2,200 pg/ml	1,000 pg/ml	½ × discharge level	400 pg/ml if <75 yrs of age, 800 pg/ml if >75 yrs of age	1,270 pg/ml	Discharge level	50% decrease from entry
Length of follow-up (months)	12–24	9.6	15	12	10	3	18	12	12	9
HF-preserved EF included	No	No	No	No	No	No	No	Yes	Yes	No
Primary endpoint	CV death or hospitalization for HF	Death + CV hospitalization or worsening HF	Death + hospitalization for HF + time to endpoint	Days alive and out of hospital	Total CV events	Days alive and out of hospital	All-cause death or hospital	All-cause mortality	Days alive and out of hospital	Days alive and out of hospital
Favors biomarker-guided therapy	Unknown	Yes	Yes	Yes	Yes	No	No	No	No	No

BATTLESCARRED = NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death; BNP = B-type natriuretic peptide; CV = cardiovascular; EF = ejection fraction; GUIDE-IT = Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PRIMA = Can pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; PROTECT = ProBNP Outpatient Tailored Chronic Heart Failure Therapy; SIGNAL-HF = Swedish Intervention Study-Guidelines and NT-proBNP Analysis in Heart Failure; STARBRITE = Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting; BRain Natriuretic Peptide Versus the Clinical CongesTion Score; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure; other abbreviations as in Table 1.

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TABLE 3 Primary Inclusion and Exclusion Criteria for the GUIDE-IT Study

Inclusion criteria
Age ≥18 yrs
HF event in prior 12 months*
Recent documented LVEF ≤40% by any method within 12 months before randomization
BNP level >400 pg/ml or NT-proBNP level >2,000 pg/ml within 30 days before randomization
Exclusion criteria
Clinical diagnosis of ACS† or cardiac revascularization within 30 days
CRT within prior 3 months or current plans to implant CRT device
Severe stenotic valvular disease
Anticipated orthotropic heart transplant or ventricular assist device within 12 months
Chronic inotropic therapy
Complex congenital heart disease
End-stage renal disease with renal replacement therapy
Noncardiac terminal illness with expected survival <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

*An HF event in the prior 12 months is defined as any 1 of the following: hospitalization for HF, treatment in the emergency department (or equivalent) for HF, and outpatient treatment for HF with intravenous diuretics. †Diagnosis of ACS should not depend entirely on positive cardiac markers because this can be noted in patients with acute HF.

ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

clinical judgment of the treating physician. Importantly, routine assessment of NP levels will not be performed in the usual care group except for compelling medical reasons, which is consistent with current guidelines (2). Follow-up visits are identical to the schedule of visits for the biomarker-guided arm, including interim visits when changes in medication relevant to the treatment of HF occur.

BIOMARKER-GUIDED ARM. Although both BNP and NT-proBNP are widely clinically available and have been used in previous trials of biomarker-guided therapy, NT-proBNP was selected as the marker to guide therapy in the GUIDE-IT study. The rationale for this was that NT-proBNP has a longer half-life (6 h vs. 20 min), was better able to predict long-term morbidity and mortality in a head-to-head comparison in the Val-HeFT (Valsartan Heart Failure Trial), and has stronger data supporting the validity of a specific NP target (34). The target of 1,000 pg/ml was selected on the basis of prior data suggesting an inflection point in the risk curve at this concentration, as well as the favorable results of the PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure Therapy) study using the same cut point (16,28,35).

In the biomarker-guided arm, NT-proBNP levels are ascertained at a local laboratory and used by treating physicians for the purpose of achieving values of <1,000 pg/ml. The GUIDE-IT protocol specifies interventions to be considered to lower NT-proBNP levels in the biomarker-guided arm, but specific treatment decisions are at the discretion of the treating physician (Table 4). The order of implementation is on the basis of clinical judgment, with more than 1 intervention allowed during a single encounter. Titration of neurohormonal antagonists is emphasized over titration of diuretics because of a mortality benefit of such agents, except in the case of clinically apparent congestion or in the case of very high NT-proBNP levels (>5,000 pg/ml).

FOLLOW-UP VISITS. For patients in either arm of the study, follow-up visits occur 2 weeks after randomization and subsequently every 3 months for the duration of the study once optimal doses of therapies have been achieved. For patients in either arm of the study, there is a 2-week follow-up visit after a change in therapy for HF. These follow-up visits after a change in therapy usually occur as a face-to-face encounter but can also be conducted via a "laboratory only" visit to reduce patient hardship at the discretion of the treating physician. Follow-up visits 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 have a 2- to 4-week follow-up study visit post-discharge to reassess and adjust medical therapy, which includes all standard follow-up assessments as defined in the preceding text.

STUDY DURATION AND ENDPOINTS. The anticipated study duration is approximately 5 years: 6 months of start-up activities (i.e., finalizing of protocol, preparing study sites and contracts, and receiving site institutional review board approval), 36 months of active enrollment, 12 months of patient follow-up after the final patient is enrolled, and 6 months of study closeout, data analysis, and reporting of results.

The primary endpoint of the GUIDE-IT study is time to CV death or first hospitalization for HF (Table 5). To minimize potential bias in an unblinded study, a clinical event committee blinded to treatment assignment adjudicates all deaths and hospitalizations. The components of the primary endpoint will also be considered separately in secondary analyses. Important secondary endpoints include cumulative morbidity, assessed by recurrent hospitalization and total days alive and out of the hospital during follow-up. Other secondary endpoints include measures of quality of life, resource use, cost, and cost-effectiveness. An economics and quality-of-life core will perform all quality-of-life and economic analyses.

Quality-of-life assessments are performed at baseline, 3 months, 6 months, and then annually to a maximum of 24 months. Assessments at each visit include the Kansas City Cardiomyopathy Questionnaire, the Duke Activity Status Index, the Center for Epidemiological Studies Depression Scale, the Medical Outcomes Study Short Form Health Survey, the Medical Outcomes Study Short Form Healthy Survey subscales, and the EQ-5D.

In addition to routine safety reporting of adverse events, events that could be related to the risks of aggressive titration of medications for HF (hypotension, bradycardia, renal dysfunction, and hyperkalemia) are specifically monitored and reported.

QUALITY-OF-LIFE ASSESSMENTS. Statistical analysis. All major treatment comparisons between the randomized groups will be performed on an intention-to-treat basis. Statistical comparisons of the 2 randomized arms with respect to the primary endpoint will be performed with a time-to-event analysis (time from randomization to the first occurrence of CV death or hospitalization for HF). The Cox proportional hazards regression model will be the primary tool to assess the effect of biomarker guidance versus usual care on both the composite outcome and each component. An adjusted model will be used for the primary efficacy analysis to maximize the precision of the estimate of treatment effect (36). The model will include an indicator variable for treatment group and the following baseline variables: age, sex, NT-proBNP level, diabetes mellitus, and LVEF. These variables were selected on the basis of their known association with outcomes in HF as well as the expectation of few missing data for these variables. To avoid any potential for bias, the functional form of each adjustment variable will be pre-specified in the statistical analysis plan. In subgroup analyses, we will examine the effect according to specific patient characteristics. The effect of the NT-proBNP-guided treatment strategy on all endpoints will be summarized using hazard ratios with associated confidence intervals. For analysis of the endpoint of the total number of days alive and out of the hospital, we will apply the inverse probability weighted estimators to account for potential bias due to censored and incomplete data (37).

STATISTICAL POWER AND SAMPLE SIZE. The sample size of this study (N = 1,100) was selected on the basis of the primary endpoint: time to CV death or first hospitalization for HF. Given the anticipated patient population and recently published clinical trial data, we have projected a 1-year CV death and hospitalization rate of 40% for subjects randomized to the usual care arm (27,38). A meta-analysis by Felker et al. (32) found an aggregate reduction of approximately 30% in all-cause mortality with biomarker-guided therapy, so the impact of biomarker-guided therapy can be conservatively expected to reduce the primary composite endpoint by 20% (32). If we account for reasonable estimates of drop-in and drop-out (5% for each over 2 years), loss to follow-up (4% per year), and non-CV death (4% per year), 1,100 subjects will provide approximately 90% power to detect a 20% relative reduction (from 40% to 32%) in the primary endpoint with biomarker-guided therapy. Also, the GUIDE-IT study has a fixed sample size design with the flexibility of an event-driven study design. For secondary endpoints, assuming at least 350 subjects per treatment group, the study will have >90% power to detect a treatment difference of 0.25 SD in secondary endpoints.

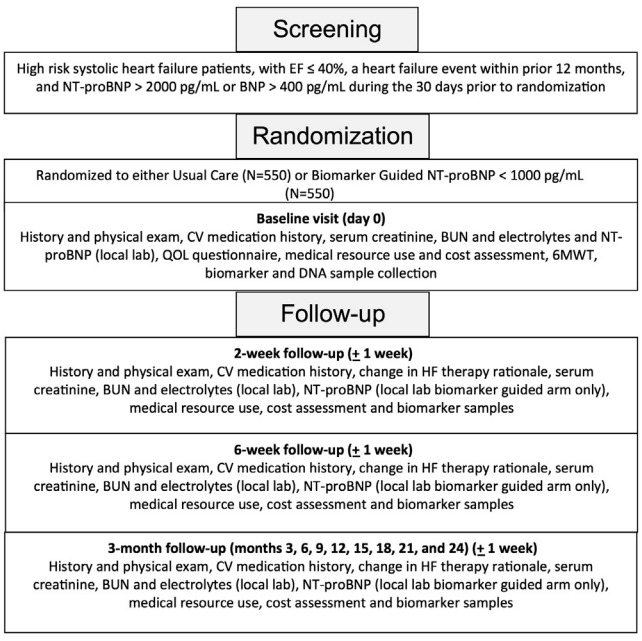

FIGURE 1 Schematic Diagram of the GUIDE-IT Study

The aim of the GUIDE-IT study is to randomize approximately 1,100 high-risk patients with chronic HF who have a left ventricular EF ≤40% to either optimized guideline-recommended therapy or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP level of <1,000 pg/ml. Patients in either arm of the study are followed up at regular intervals and after treatment adjustments for a minimum of 12 months. Assessments during these visits are delineated in the figure. BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CV = cardiovascular; EF = ejection fraction; GUIDE-IT = Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; QOL = quality of life; 6MWT = 6-min walk test.

TABLE 4 Potential Interventions to Decrease NT-proBNP Levels

Up-titrate or add an ACE-I or ARB
Up-titrate or add a beta-blocker (if not clinically congested)
Up-titrate or add hydralazine nitrates in African-American patients
Increase the dosage of the loop diuretic (if clinically congested or NT-proBNP level >5,000 pg/ml)
Add an oral thiazide diuretic
Add digoxin
Consider adding an ARB to an ACE-I (if not on spironolactone)
Consider optimization of CRT (if CRT device implanted)
Up-titrate or add spironolactone if tolerated by renal function and potassium
Consider hydralazine nitrates in non–African-American patients
Intensified or repeated HF education regarding diet, restriction of sodium, and so on
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

Abbreviations as in Tables 1 and 2.

NP-GUIDED TREATMENT IN ELDERLY PATIENTS. Two prior studies (TIME-CHF [Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure] and BATTLESCARRED [NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death]) (Table 2) suggested a differential benefit of NP-guided treatment according to age, with elderly patients (≥75 years) deriving less benefit; however, other studies such as PROTECT have not reproduced these findings (26–28). As a result of the lack of clarity surrounding this question, and given that HF is primarily a disease of elderly patients, the differential effect of NP-guided treatment on the basis of age will be examined in the GUIDE-IT study. We have pre-specified an interaction analysis, with the population stratified at 75 years of age, and determined that we will have adequate power to detect statistically significant interactions.

DATA AND SAFETY MONITORING BOARD REVIEWS. The National Heart, Lung, and Blood Institute-appointed data and safety monitoring board will meet every 6 months to review the accumulating data. Before each meeting, the coordinating center 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 serious adverse events. For futility monitoring, the study will apply the inefficacy monitoring rule of Freidlin, Korn, and Gray to stop the trial if the biomarker-guided strategy is not beneficial (39). We plan to use the conservative boundary LIB0 along with a harm look at 25% of expected information, including 7 interim looks scheduled at roughly 25%, 40%, 50%, 60%, 70%, 80%, and 90% trial completion. With the proposed design, roughly 566 events are expected, and the first interim review for futility and efficacy is scheduled to occur after approximately 140 primary endpoint events have been observed. If the data suggest a benefit for the usual care arm with a p value <0.05, this approach would suggest stopping the trial at the 25% look. 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 has a hazard ratio >1.0 compared with the usual care arm. Lastly, an interim efficacy analyses will also be performed (40,41).

TRIAL ORGANIZATION. An overview of the trial organization is shown in Figure 2. The study is being conducted under the leadership of an executive committee composed of cardiologists with extensive experience caring for patients with HF that has overall responsibility for study conduct. The clinical coordinating center, data coordinating center, and economics and quality-of-life cores are at the Duke Clinical Research Institute. Given the importance of investigator adherence to the study protocol to successfully test the primary hypothesis, a protocol adherence committee oversees investigator adherence to the study protocol. Specifically, investigators record their rationale for specific adjustments of medications for HF at each encounter in the case report form. If investigators choose not to intensify therapy at a given patient visit in the biomarker-guided arm despite an NT-proBNP level >1,000 ng/ml, they record their clinical rationale for not making adjustments (e.g., hypotension limits further up-titration). The adherence committee reviews data on the extent to which investigators are responding to NT-proBNP levels >1,000 ng/ml in the biomarker-guided arm and perform educational interventions with investigators in need of additional training.

TABLE 5 Trial Endpoints

Primary endpoint
Time to CV death or first hospitalization for HF
Secondary endpoints
Time to all-cause mortality
Days alive and not hospitalized for CV reasons
Recurrent hospitalization
Time to CV death
Time to first hospitalization for HF
Health-related quality of life
Resource use, cost, and cost-effectiveness
Safety

Abbreviations as in Tables 1 and 2.

If investigator adherence is persistently poor at a given site, the adherence committee may recommend halting enrollment at that site.

CORE LABORATORIES AND SUBSTUDIES. To understand the mechanisms underlying the treatment effect of biomarker-guided therapy (if any), core laboratories for biomarkers, genetics, and echocardiography have been established. At each clinical encounter, local laboratories are used for assessment of NT-proBNP levels (biomarker-guided arm only), but an additional plasma sample for centralized NT-proBNP testing is submitted to the biomarker core laboratory. These values are not transmitted back to investigators but are used to validate the results of local laboratory testing and to provide NT-proBNP data on patients in the usual care arm at the conclusion of the study. In addition, DNA samples as well as serial plasma and serum samples are collected and stored at a central biomarker genetics core laboratory for future use. An echocardiographic substudy includes echocardiography at baseline and 12 months for a subset of patients; these images are interpreted centrally by a core laboratory blinded to treatment allocation or other clinical data.

DISCUSSION

Existing clinical guidelines for the treatment of patients with chronic systolic HF recommend that therapies be titrated to target doses from clinical trials or maximally tolerated doses (2). This is unlike management of most chronic diseases that use a paradigm of therapeutic titration on the basis of "biomarker" targets known to be associated with patient outcomes (e.g., hemoglobin A_{1c} for diabetes and viral load for human immunodeficiency virus). In HF, NPs have emerged as important biochemical gauges of disease state, with both baseline and serial levels having important prognostic value (22,33,42,43). However, since a landmark study (25) in 2000 showed dramatic benefits with NP-guided treatment of HF, several randomized trials that differed considerably in design and execution have yielded varied results. Meta-analyses of these studies have determined that using NP levels to guide therapy in patients with chronic systolic HF may lead to significant improvements in clinical outcomes, but these conclusions are susceptible to known limitations of meta-analyses in the face of small heterogeneous trials (32,33,43,44).

The GUIDE-IT study has attempted to incorporate lessons learned from prior studies about how best to apply NP-guided therapy to high-risk patients with HF (42). First, because the advantages of NP guidance are limited by the benefits of specific HF therapies, it stands to reason that biomarker-guided therapy is most likely to be efficacious in patients in whom medical therapy is known to be effective. Therefore, we have focused on patients with systolic HF and not included patients with HF and preserved ejection fraction, given the lack of effective therapeutics for this group of patients. Second, many prior studies with neutral results may have set NP goals that were too high (i.e., not aggressive enough), potentially leaving patients "at target" but still with a persistent amount of residual risk (28,30). For the GUIDE-IT study, we adopted the target of 1,000 pg/ml, which was successfully used in the PROTECT study; although a significant percentage of patients may not achieve this value, data have indicated that even modest lowering of the NT-proBNP level and even intermittent periods with the level ≤1,000 pg/ml are associated with superior outcomes compared with less reduction of the biomarker level (28,45). Thus, although it would be desirable to reach the goal in every study participant, a concerted effort to produce a reduction in NT-proBNP levels is hypothetically likely to produce favorable results. Third, although treating physicians in the biomarker-guided arm retain responsibility for specific treatment decisions, we emphasize up-titration of therapies that have been shown to have mortality benefits, such as beta-blockers and renin-angiotensin-aldosterone system antagonists over diuretics; trials emphasizing use of neurohormonal

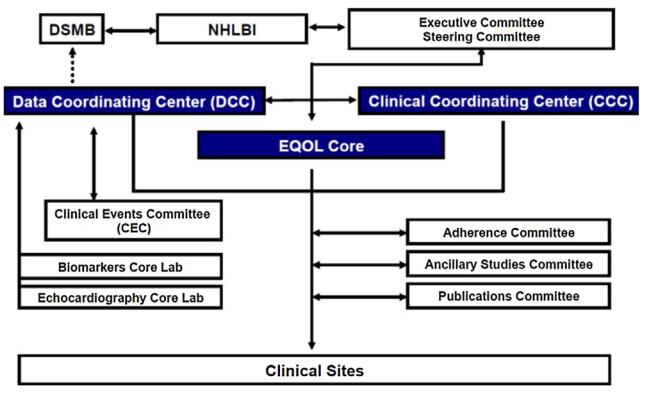

FIGURE 2 Trial Organization

The study is being conducted under the leadership of an executive committee composed of cardiologists with extensive experience caring for patients with heart failure that has overall responsibility for study conduct. The Duke Clinical Research Institute will house the clinical coordinating center, data coordinating center, and economics and quality of life (EQOL) cores at the Duke Clinical Research Institute. DSMB = Data and Safety Monitoring Board; NHLBI = National Heart, Lung, and Blood Institute.

antagonists were more likely to show efficacy. Fourth, some prior studies have suggested differential treatment effects of a biomarker-guided strategy by age, with greater efficacy in younger patients (33). For this reason, we pre-specified age (≥75 or <75 years of age) as a key subgroup of interest, and the GUIDE-IT study is adequately powered to examine this interaction appropriately.

The GUIDE-IT study is an unblinded trial because blinding would eliminate one potentially important mechanism of treatment effect: the impact of patients' knowledge of their own NP levels on adherence and health-related behaviors. Blinding the GUIDE-IT study 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 (CV death or hospitalization for HF), and centralized adjudication of events by a clinical event committee blinded to treatment assignment.

The GUIDE-IT study is primarily designed to determine the efficacy of a strategy of biomarker-guided therapy compared with optimized medical care on clinical outcomes in high-risk patients with systolic HF. However, data from the trial may also clarify several other important unanswered questions. For example, it is unknown whether the hypothesized mortality benefits derived from aggressive attempts at lowering biomarker levels could occur at the expense of increased morbidity related to side effects of therapy, especially among elderly patients. The economics and quality of life core laboratory will use a battery of validated instruments, such as the Kansas City Cardiomyopathy Questionnaire, that provide a comprehensive assessment of health-related quality of life and allow for assessment of differences in these measures between treatment arms. The economics and quality-of-life laboratory will also collect wide-ranging economic data, thereby allowing for an evaluation of resource use and cost-effectiveness of a biomarker-guided strategy. The inclusion of a detailed quality-of-life analysis and robust health economic measures will serve to enhance the overall value of the findings from the GUIDE-IT study. Furthermore, the inclusion of a robust biorepository and echocardiography substudy will provide insight into the mechanistic underpinnings of any observed impact of biomarker-guided therapy on clinical outcomes.

CONCLUSIONS

Numerous studies have found that elevations in NP levels are among the best predictors of adverse outcomes in patients with chronic systolic HF and that use of guideline-based therapies is associated with a decrease in serial plasma levels of these markers. The results of several observational studies and small randomized controlled trials have suggested that a biomarker-guided strategy aimed at decreasing NP levels, compared with standard care, may lead to improvements in outcomes among patients with chronic systolic HF. The GUIDE-IT study is designed to provide the definitive answer about the safety, efficacy, and cost-effectiveness of NP-guided therapy for chronic systolic HF.

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