

HF-ACTION

PROTOCOL

for Heart Failure and A Controled Trial Investigating Outcomes of Exercise TraiNing

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Signature Page for NHLBI

HF-ACTION: Heart Failure and A Control Trial Investigating Outcomes of Exercise Training

Protocol Version : 08

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

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List of Abbreviations

| | |
|------------------|---|
| AACVPR | American Association of Cardiovascular and Pulmonary Rehabilitation |
| ACC | American College of Cardiology |
| ACE | Angiotensin converting enzyme |
| ACEI | Angiotensin-converting enzyme inhibitor |
| ACS | Acute Coronary Syndrome |
| <u>AE</u> | <u>Adverse Event</u> |
| AHA | American Heart Association |
| AICD | Automatic Implantable Cardioverter-Defibrillator |
| ARB | Angiotensin Receptor Blocker |
| ATP | Adenosine Triphosphate |
| BP | Blood pressure |
| CABG | Coronary Artery Bypass Graft |
| CAD | Coronary Artery Disease |
| CPX | Cardio Pulmonary eXercise |
| CCS | Canadian Cardiovascular Society |
| DBP | Diastolic blood pressure |
| DCRI | Duke Clinical Research Institute |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| EDRF | Endothelium-derived relaxing factor |
| EF | Ejection Fraction |
| EQOL | Economics and Quality of Life |
| HF | Heart failure |
| HF-ACTION | Heart Failure and A Control Trial Investigating Outcomes of Exercise TraiNing |
| HFSA | Heart Failure Society of America |
| mm Hg | Millimeters of mercury |
| HRV | Heart rate variability |
| ICD | Implantable Cardioverter-Defibrillators |
| IPAQ | International Physical Activity Questionnaire |
| IV | Intravenous |
| IVRS | Interactive voice response system |

| | |
|-------------------|---|
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| LBBB | Left bundle branch block |
| LV | Left ventricle |
| METs | Metabolic Equivalents of Task |
| MI | Myocardial infarction |
| MOO | Manual of Operations |
| MQ | Motivation Questionnaire |
| NHLBI | National Heart, Lung, and Blood Institute |
| NO | Nitric oxide |
| NYHA | New York Heart Association |
| <u>PAQ</u> | <u>Physical Activity Questionnaire</u> |
| PI | Principal Investigator |
| QOL | Quality of life |
| RER | Respiratory exchange ratio |
| RPE | Ratings of Perceived Exertion |
| RRAP | Recruitment and Retention Assistance Program |
| SAE | Serious Adverse Event |
| SBP | Systolic blood pressure |
| UCLA | University of California at Los Angeles |
| V-HeFT | Veterans Administration Heart Failure Trail |
| VO ₂ | Volume Oxygen consumption |
| VT | Ventilatory threshold |

1 Overview of the HF-ACTION Trial

Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) is a multicenter, international, randomized trial that addresses the primary hypothesis that patients with left ventricular (LV) systolic dysfunction and New York Heart Association (NYHA) class II-IV symptoms who are given exercise training in addition to standard care will have a $\geq 20\%$ lower rate of death and hospitalization over two years than patients who receive usual care alone. Important secondary endpoints include exercise testing parameters, economics, quality of life, and depression.

Over three years, regional centers in the United States and Canada and their satellite centers will recruit 3,000 consenting patients with heart failure (HF), LV ejection fraction (EF) $\leq 35\%$, and NYHA class II-IV. Once identified and screened, these patients will be randomized in a 1:1 fashion to receive usual care or usual care plus exercise training. Patients in the intervention arm will undergo 36 supervised exercise training sessions before initiating a home exercise training regimen that will be supplemented with occasional supervised review training sessions. All patients will perform gas exchange exercise tests at baseline, 3 months, 12 months, and 24 months of follow-up. All randomized patients will receive follow-up clinic and telephone calls at pre-specified times. Registries of clinical information will be maintained on eligible patients who decline trial entry.

The results of the HF-ACTION trial will have a significant impact on the health and quality of life of millions of patients who now suffer from HF.

2 Study Objectives

2.1 Primary Objective

To test the primary hypothesis that patients with LV systolic dysfunction and NYHA class II-IV symptoms who are given exercise training in addition to usual care will have a 20% lower rate of death and hospitalization over two years than patients who receive usual care alone.

2.2 Secondary Objectives

1. To test the hypothesis that the intervention to be studied will cause complications and thus will be associated with some short-term risk. However, even after considering the possible complications, (i.e., adverse events secondary to exercise training), the intervention will prove to be an important therapy for heart failure patients.
2. To test the hypothesis that patients receiving the intervention will significantly improve exercise tolerance, as measured by peak VO₂, **heart rate at end of stage 2**, and 6-minute walk distance versus patients in the usual care (control) arm.
3. To test the hypothesis that exercise training will significantly improve the health-related quality of life of patients in the intervention arm of the study versus the usual care group.
4. To test the hypothesis that exercise training will be economically attractive (cost saving or a reasonable value for the money).

3 Background

3.1 Public Health Burden of HF

An estimated 4.7 million Americans suffer from HF, with 400,000 new cases diagnosed each year. This number is expected to grow as more patients survive myocardial infarctions (MIs) but are left with cardiac dysfunction. As the number of patients with HF has grown, the number of deaths caused by HF has increased by 145% from 1979 to 1999 (American Heart Association 2001). Although a number of new therapies have been introduced, the overall five-year mortality for HF is presently estimated at 50%.

As a disease, heart failure has a tremendous impact on quality of life. Between 800,000 and 1 million patients are classified as NYHA class III or IV heart failure and suffer from dyspnea at rest or with minimal exertion. In addition, HF hospitalizations, which contribute to the poor quality of life, have increased from 377,000 in 1979 to 962,000 in 1999 (American Heart Association 2001). Heart failure patients cost Medicare over \$22 billion annually in 1995. Patients with this diagnosis consume more Medicare dollars than patients with MI and cancer combined (O'Connell 1994).

3.2 Exercise Tolerance in HF

Patients with HF have a poor quality of life compared to patients with other chronic diseases (Weinberger 1996). A major cause of decline in quality of life is reduced exercise tolerance. As the disease progresses, patients become more incapacitated and deconditioned, unable to perform simple tasks without becoming dyspneic and fatigued. The decline in exercise capacity experienced by patients is of concern, since exercise capacity, as measured by maximal oxygen uptake on an exercise test, is considered a strong predictor of survival (Szlachcic 1985, Mancini 1991a, Stelken 1996, Myers 2000).

Over the past 20 years, many studies have examined the mechanisms responsible for the exercise intolerance in patients with heart failure. Although poor LV function could be assumed to be its cause, studies have shown a poor correlation between resting LVEF and exercise capacity (Franciosa 1981, Szlachcic 1985, Higginbotham 1983, Conn 1982). Although resting EF does not predict exercise capacity, the ability to increase cardiac output does correlate with better exercise capacity (Wilson 1984, Szlachcic 1985, Sullivan 1989b). The disconnect between EF and cardiac output is most likely due to the fact that cardiac output is determined not only by LVEF, but by heart rate, end diastolic volume, severity of mitral regurgitation, and peripheral vascular resistance. Mitral regurgitation, stroke volume, diastolic filling, and heart rate response have been found to affect exercise capacity (Ross 1966, Wilson 1984, Sullivan 1989a, Colucci 1989, Lapu-Bula 1999, Dahan 1995, Pepi 1999, Tada 1997).

The lack of correlation between EF and exercise intolerance also led investigators to search for other explanations for the fatigue observed in heart failure patients. Researchers found that, as exercise intolerance increased for HF patients with different levels of maximal oxygen uptake, blood flow in the active leg decreased correspondingly at any given workload (Wilson 1984, Sullivan 1989b). The decrease in leg blood flow could be attributed to poor LV function, impaired vasodilation in the skeletal muscle, and deconditioning. The researchers found that blood flow and arterial pressure were maintained through abnormally elevated leg vascular resistance. Patients with HF have elevated sympathetic outflow, which may contribute to increased arterial resistance (Thomas 1978, Leimbach 1986, Cohn 1984), but blockade of the sympathetic nervous system does

not improve leg blood flow, leg oxygen extraction, and leg oxygen consumption (Wilson 1985). This lack of improvement with sympathetic blockade may be due to the other abnormal neurohormonal factors that cause peripheral vasoconstriction in HF patients, including the renin-angiotensin system and the pituitary-vasopressin axis (Francis 1988). In addition, vascular endothelium contributes to changes in vasoconstriction through the release of nitric oxide (NO), previously known as endothelium-derived relaxing factor (EDRF) (Palmer 1987, Ignarro 1987). NO production is abnormal in HF patients compared to normal patients (Kubo 1991, Hornig 1996, Hambrecht 1998).

The lack of improvement in oxygen uptake or lactate production at maximal exercise with vasodilation suggested that skeletal muscle abnormalities in heart failure might contribute to patients' exercise tolerance. Studies have shown that skeletal muscles of HF patients have abnormal oxygen uptake, lactate build-up, and lower pH during exercise (Wilson 1993, Wiener 1986, Massie 1988). Several metabolic abnormalities have been found in the skeletal muscle of heart failure patients, including abnormal phosphate metabolism, fatty acid metabolism, and oxidation (Wilson 1985, Massie 1988, Mancini 1989, Sullivan 1990). These changes in phosphate metabolism (and thus in ATP metabolism) were independent of blood flow or ischemia (Wiener 1986, Massie 1988). Heart failure patients' skeletal muscles are atrophied; possess a higher percentage of type IIb fibers (fast-twitch, glycolytic, and easily fatigued); have increased interstitial cellularity; show an accumulation of intracellular lipid; contain fewer total capillaries; and show increased acid phosphatase, which relates to lysosomal activity (Lipkin 1988, Mancini 1989, Sullivan 1990). Recent studies have shown that muscle metaboreceptors' renal vasoconstriction reflex is blunted in heart failure patients, suggesting alternative afferent and/or efferent pathways underlying the abnormal physiologic response (Middlekauf 2000).

Patients with LV dysfunction have an inappropriate increase in minute ventilation and a significantly steeper slope of minute ventilation by carbon dioxide output (Sullivan 1988, Sullivan 1989b, Myers 1992, Metra 1992). This inappropriate ventilation in relation to CO₂ production is also a marker of prognosis. An increase in ventilatory dead space has been attributed to ventilation-perfusion mismatch (Myers 1992). Respiratory muscle deoxygenation may also contribute to exertional fatigue (Mancini 1991b).

In summary, exercise intolerance in HF patients is a result of several factors including poor LV function, abnormal peripheral factors such as blood flow, skeletal muscle changes, and ventilatory dysfunction.

3.3 Exercise Training in HF

The initial studies of exercise training, in patients with LV dysfunction, involved patients who had suffered MI. In the 1970s, cardiac rehabilitation was accepted as beneficial for patients who had suffered MI or undergone bypass surgery (Varnauskas 1966, Sanne 1973). Patients with significant LV dysfunction usually were excluded from rehabilitation programs because of concern about excess risk (Ferguson 1975, Hellerstein 1967, McHenry 1974). In small, non-randomized studies of cardiac rehabilitation in patients with LV dysfunction following MI, rehabilitation improved work capacity and peak oxygen consumption, increased peak-exercise leg blood flow, decreased blood lactate levels at submaximal exercise, and decreased resting and submaximal heart rates (Lee 1979, Conn 1982, Sullivan 1988).

Over the last 12 years, 13 randomized, controlled studies have evaluated exercise training in heart failure patients (Coats 1990, 1992, Belardinelli 1995, 1999, Hambrecht 1995, 2000a, Keteyian 1996, 1999, Kiilavuori 1995, 1996, Koch 1992, Wielenga 1998, Willenheimer 1998) (Appendix A, Table 1). The 13 studies identified were prospective, randomized designs involving patients with ischemic and non-ischemic cardiomyopathy and NYHA class II or III heart failure. Except for one study that used resistance training, training involved bicycle ergometers or walking at 50% to 70% peak VO₂ three to seven times per week. Training occurred both in a supervised setting and/or in the home. All of the studies were single-center and were underpowered to appropriately evaluate mortality and morbidity.

These studies, along with smaller, non-randomized studies, have provided evidence for a number of mechanisms by which exercise training could impact mortality and morbidity (Table 1).

Table 1: Potential Mechanisms by Which Exercise Training Improves Outcomes Evaluated in HF-ACTION

| Organ System/Tissue | Response to Exercise Training | Effect on Mortality and Morbidity |
|---|---|--|
| Improve Central Transport and Regional Blood Flow | ↑ in cardiac output; ↑ in peak VO ₂ ; reverse chronotropic incompetence; ↑ regional blood flow | ↑ peak VO ₂ → ↑ survival ↓ hospitalization |
| Autonomic Nervous System | ↑ heart rate variability; ↓ plasma norepinephrine (rest) | ↑ HRV → ↓ arrhythmia → ↑ survival, ↓ hospitalization ↓ plasma NE → ↑ survival |
| Skeletal Muscle | ↑ aerobic enzymes; ↑ mitochondria size/density; ↑ capillary density; ↑ relative type I fibers | Muscle composition → ↑ QOL → ↓ hospitalization |
| Peripheral Vasculature | ↑ vasculature reactivity | ↑ coronary blood flow → ↓ ischemia and MI → ↑ survival, ↓ hospitalization |

Exercise training improves peak VO₂, a strong independent predictor of survival (Francis 2000, Anker 1997, Mudge 1993, Van den Broek 1992, Mancini 1991a). Although, a number of different thresholds have been suggested depending on the severity of heart failure symptoms, the prognostic value of peak VO₂ extends over a broad spectrum of thresholds from 10 to 20 ml/kg/min (Francis 2000). HF-ACTION will be using a similar range of peak VO₂ to identify patients for the trial. In addition, changes in peak VO₂ over time have been shown to predict non-transplanted survival independent of changes in LVEF (Florea 2000).

Exercise training improves autonomic dysfunction, including decreasing resting plasma norepinephrine levels, found in patients with LV function (Coats 1992, Kilavuori 1999, Hambrecht 2000a). Plasma norepinephrine level is an independent predictor of survival in heart failure patients (Cohn 1984, Francis 1993, Benedict 1996, Isnard 2000). Other therapies that reduce neurohormonal activation improve survival of heart failure patients (Francis 1993). Consistent

with the improvements in neurohormonal activation, exercise training improves heart rate variability (HRV) in heart failure patients (Adamopoulos 1992, 1995, Kiilavuori 1995, Radaelli 1996). Not only is HRV inversely related to severity of illness in HF patients, but it is also related to survival (Bonaduce 1999, Casolo 1995, Faucher 1997, Osterziel 1995, Ponikowski 1997). Derangement in HRV is a potential mechanism for sudden arrhythmic death, common in patients with HF (Barron 1996). Clinical therapies that improve heart rate variability provide significant survival benefit to heart failure patients (Binkley 1993, Dibner-Dunlap 1996, Jansson 1999, Copie 1996, Zhang 1995).

Exercise training improves exercise tolerance and functional capacity through a number of mechanisms including improved cardiac output, decreased peripheral vascular tolerance, and changes in skeletal muscle metabolism and structure (Coats 1992, Hambrecht 1995, 1998, 2000a, Belardinelli 1995, Hornig 1996, Katz 1997, Tyni-Lenne 1997). Cardiac output is an independent predictor of survival in severe heart failure (Griffin 1991, Campana 1993).

Improvements in peripheral vascular resistance are partially obtained through enhanced endothelial function and response to nitric oxide (Hornig 1996, Katz 1997, Hambrecht 1998, 2000a). In addition, exercise training improves endothelium-dependent vasodilatation and coronary blood-flow reserve in epicardial coronary vessels of patients with coronary artery disease (Hambrecht 2000b). This finding may explain how exercise training improves myocardial perfusion without regression of coronary stenosis or recruitment of collateral vessels (Ehsani 1981, Schuler 1992a, 1992b, Niebauer 1995).

Exercise training improves six-minute walk distance (Kavanagh 1996, Meyer 1997). This six-minute walk test has prognostic value for heart failure patients with mild to moderate symptoms or severe symptoms (Guyatt 1985, Bittner 1993, Cahalin 1996).

The benefits of exercise training extend to the elderly with heart failure. The majority of patients in exercise training studies involving heart failure patients have been male (94%) and relatively young (mean age 60.5 years) (European Heart Failure Training Group, 1998). No correlation between age and training response has been found, suggesting that elderly patients will benefit from training (European Heart Failure Training Group, 1998). Patients over 65 years of age have significant improvements in exercise time, six-minute walk time, and quality of life after participating in exercise training, but require special consideration to maintain training (Wielenga 1998, Owen 2000).

The response of women to exercise training is less clear. In a crossover comparison of exercise training, women with dilated or ischemic cardiomyopathy improved exercise capacity, skeletal muscle metabolism, six-minute walk time, and quality of life (Tyni-Lenne 1997). A comparison of European exercise studies found that women had a significant improvement in peak VO_2 that was similar to men (European Heart Failure Training Group 1998). However, more recent data suggests that women do not respond to exercise training similarly to men (Keteyian in press).

Although underpowered to make any conclusive findings, a recent trial provided initial evidence that exercise training can improve clinical outcomes (Belardinelli 1999). Belardinelli et al. described the impact of exercise training on 99 patients randomized to either facility-based exercise training or no exercise training. In addition to confirming that exercise training can improve physiological outcomes such as resting heart rate and peak VO_2 , the investigators demonstrated that exercise training improved quality of life, decreased hospital admissions (29% versus 10%, $p = 0.02$) and decreased cardiac death (40.8% versus 18%, $p = 0.01$). Kaplan-Meier

analysis of event-free survival revealed a significant benefit to training (log rank = 14.29, $p = 0.002$). In addition, there was an improvement in thallium uptake in patients with abnormal nuclear exercise scintigraphy, suggesting an improvement in coronary flow.

3.4 Variability of Response to and Safety of Exercise Training in HF

The complexity and variability of patients with moderate to advanced heart failure is evident in their response to exercise testing and training. Wilson et al. reported that up to 44% of a group of heart failure patients with peak VO_2 values < 14 mL/min/kg had mild or moderate hemodynamic compromise (using wedge pressure and cardiac output) and, in contrast, 25% of those with $VO_2 > 14$ mL/min/kg had severe hemodynamic abnormalities (Wilson 1995). In another study, Wilson and colleagues undertook a training program for 32 patients who had an average peak VO_2 of 12.9 ± 2.3 ml/min/kg (Wilson 1996). Of the 27 patients who completed the program, only 9 showed a $> 10\%$ improvement in functional capacity. These patients had a normal cardiac output response to exercise. Of 11 patients who had an abnormal or low cardiac output response to exercise, only one improved in functional capacity.

Etiology of cardiomyopathy may play a role in response to exercise training. Clark et al. found that for a given level of cardiac dysfunction, patients with non-ischemic heart disease had a higher peak VO_2 than patients with ischemic cardiomyopathy (Clark 1997). In a study by Keteyian et al., patients with an ischemic cardiomyopathy showed a non-significant increase in peak VO_2 (1.7 mL or 11%) compared to patients with a non-ischemic cardiomyopathy, who showed a significant increase in peak VO_2 (2.5 mL or 15%) (Keteyian 1999). In the compilation of European studies, patients with ischemic cardiomyopathy showed less improvement in peak VO_2 than patients with non-ischemic LV dysfunction, but had similar improvements in exercise duration and NYHA class (European Heart Failure Training Group 1998). It is worth noting that several of the randomized trials enrolled patients with an ischemic cardiomyopathy and showed significant increases in peak VO_2 with exercise training.

The safety of exercise training in heart failure patients has not been established in large clinical trials. When reviewing the data for patients participating in cardiac rehabilitation, the rate of cardiac complications is very low, with only 21 cardiac arrests and 8 nonfatal MIs in 51,303 patients during more than 2 million hours of exercise (Van Camp 1986). In patients with LV dysfunction undergoing only an exercise test, 2% had significant ventricular arrhythmia without any episodes of sudden death (Tristani 1987).

Although meta-analysis of cardiac rehabilitation suggests that exercise improves survival after MI, exercise training causes a short-term increased risk of MI and sudden death, possibly due to platelet activation or coronary artery shear stress (Oldridge 1988, O'Connor 1989, Siscovick 1984, Mittleman 1993, Willich 1993, Wallén 1999, Bärtzsch 1999). Compared to habitual exercisers, patients who were habitually sedentary are at a 100-fold increased risk for MI and 50-fold increased risk of sudden death. Given the high prevalence of ischemic cardiomyopathy in heart failure clinical trials and the exclusion criterion not permitting the performance of exercise training at regular intervals, we expect the majority of participants in HF-ACTION to be sedentary patients with ischemic cardiomyopathy, placing them at significant higher short-term risk for MI and sudden death (European Heart Failure Training Group, MERIT-HF-Study Group 1999, Bart 1999, Packer 1999).

In the 13 studies of stable HF patients (Coats 1990, 1992, Belardinelli 1995, 1999, Hambrecht 1995, 2000a, Keteyian 1996, 1999, Kiilavuori 1995, 1996, Koch 1992, Wielenga 1998, Willenheimer 1998), 284 patients participated in exercise training, and 257 were in the control group. Of the 284 patients participating in exercise training, 43 suffered a serious cardiac event (15.1%), 13 of which were deaths (4.6%). Of the 257 patients in the control group, 57 had a serious cardiac event (22%), 25 of which were deaths (9.7%). If the Belardinelli study published in 1999, which was an outlier in terms of events, is not included, 234 patients in exercise training experienced 26 serious cardiac events (11.1%), 4 of which were deaths, and 208 control patients experienced 20 cardiac events (9.6%), 6 of which were deaths. The complication rate for patients training was 15.1%, more than a seven-fold increase from the figures reported for exercise testing, and a very large increase from the safety data reported for all of cardiac rehabilitation. It is uncertain if the rate of complications is related to changes in compensation status which is common in HF patients or to the early recognition of symptoms and signs of decompensation related to the frequent interactions with study centers.

In addition to these studies, an ongoing study at UCLA has raised concerns regarding exercise training for heart failure patients. On preliminary analysis of this trial by the Data and Safety Monitoring Board, a significant reduction in death and hospitalization has not been demonstrated, and early in the trial, events were trending in the wrong direction. In contrast to the Belardinelli study, a recent study that randomized 181 heart failure patients to either exercise training or usual care found no significant differences between patient groups for total deaths, the composite of total deaths or heart failure hospitalization, and the composite of total deaths or worsening heart failure (McKelvie 2002). It has been recognized for some time that a larger, long-term randomized trial is necessary to confirm the promising results of smaller studies (McKelvie 1995). The current state of clinical studies of exercise training in chronic heart failure probably corresponds to a point between the clinical phases II and III of development for a pharmacologic therapy (Meyer 1999). There is the possibility that exercise training may be harmful to heart failure patients when applied in a broader fashion and should not be recommended by the medical community until a larger study is performed.

3.5 Biomarkers in Heart Failure Patients

Chronic heart failure is known to be a state of chronic neurohormonal and inflammatory activation. Multiple lines of evidence support the concept that these changes are chronically maladaptive and contribute to disease progression. Pharmacologic manipulation of these systems has met with some success (beta-blockers, ACE-inhibitors) as well as multiple failures (endothelin inhibitors, TNF antagonists) (Merit 1999; The SOLVD Investigators 1991; Louis 2001). Non pharmacologic interventions (such as exercise training) represent alternative approaches to heart failure therapy. Whether the potential benefit of exercise training would be in part mediated through changes in circulating plasma proteins is unknown. Studies investigating circulating plasma proteins in heart failure could contribute in several important ways:

1. *Mechanistic understanding*: Such studies may provide pathophysiologic rationale for observed differences in outcomes between treatment groups, suggesting mechanisms by which exercise training may alter the natural history of chronic heart failure.

2. *Risk stratification/selection of therapy*: Such studies may identify subpopulations that may have greater risk of disease progression, or that may derive greater (or lesser) benefit from exercise training. Profiles of circulating proteins (“biomarkers”) have been found to have substantial prognostic power in ischemic heart disease and heart failure, and may have implications for selection and titration of therapies (Ridker 2001; Torre-Amione 1996; Mayer 2001; Kazanegra 2001).

3. *Identification of surrogate endpoints*: Such studies may provide validation of biomarkers as surrogate endpoints in heart failure. This would be of substantial use in planning of future clinical trials, potentially allowing for smaller and more “accurate” phase I and II studies, speeding therapeutic development by focusing resources on therapies most likely to provide benefit.

4. *Identification of Therapeutic Targets*. Such studies may identify circulating proteins playing a role in heart failure pathophysiology that may be potential targets for therapeutic intervention (The VMAC Investigators 2002).

3.6 Need for Randomized Trial of Exercise Training in HF

Although improvements in exercise tolerance and physiologic markers describe potential mechanisms by which exercise training might improve survival and decrease morbidity, they are not a replacement for evaluation of clinical outcomes, specifically mortality (Lipicky 1993, Fleming 1996). The correlation of improvements in these variables with mortality reductions has been inconsistent in heart failure research. In the V-HeFT II trial, enalapril had a greater reduction in mortality as compared to the combination of hydralazine and isosorbide, but EF increased to a lesser extent and VO₂ max was lower in enalapril-treated patients than those treated with hydralazine/isosorbide (Cohn 1991). The history of heart failure research provides many examples of a pharmacologic intervention improving a number of surrogate endpoints in early studies, only to subsequently show a detrimental effect on survival in larger mortality trials. Milrinone, nifedipine, epoprostenol, flosequinan, and vesnarinone initially produced promising results based on improved physiologic endpoints, but were ultimately shown to worsen survival in controlled mortality trials (Packer 1987, 1991, 1993, Swedberg 1994, Elkayam 1990, Califf 1997, Feldman 1991, 1993, Otsuka America 1996).

The inadequacies of physiological outcomes to serve as surrogate endpoints for mortality, the limited and conflicting information about clinical endpoints from previous single-center studies, the absence of reliable safety data, and the real potential for an increased short-term risk of MI and sudden death are the fundamental reasons why exercise training has not been accepted as standard of care for heart failure patients and why the HF-ACTION Investigators maintain equipoise.

HF-ACTION will contribute to the available data in heart failure in several ways.

First, HF-ACTION proposes to study exercise training, a non-pharmacological treatment modality that has never been formally tested in a large, multicenter, randomized, controlled trial with sufficient power to detect effects on clinical outcomes. The high morbidity and mortality associated with heart failure despite optimal pharmacotherapy underscores the importance of research into novel treatment strategies such as exercise training. The primary aim of HF-ACTION is to determine the long-term safety and effectiveness of exercise training in addition to standard of care versus a strategy of standard care alone for patients with NYHA Class II-IV heart failure. Effectiveness will be defined as the primary combined endpoint of all-cause mortality and all-cause hospitalization.

Second, the EQOL study will measure the change in quality of life (QOL) for patients participating in exercise training. This becomes critical in assessing the societal value of the intervention if the intervention causes no significant change in the primary outcome.

Third, if HF-ACTION shows a significant reduction in the primary endpoint, the utilization of cardiac rehabilitation could result in a tremendous cost saving as is evident by the high resource utilization by this patient group. On the other hand, a significant reduction in mortality could result in more resources used over time by those patients living longer. Providing cardiac rehabilitation will cost a certain amount of money. The HF-ACTION Economic and Quality of Life study has been proposed to identify the cost-effectiveness of the HF-ACTION intervention.

Fourth, exercise training represents an intervention that, if proven beneficial, will be accessible to the majority of heart failure patients due to low cost, high availability, and ease of use. Physicians throughout the country will be able to recommend exercise training to patients with LV dysfunction. An important component of this study will be the ability to provide information to physicians on which characteristics identify patients more likely to benefit versus those at risk of an adverse event.

Over twenty years of heart failure exercise training research has progressed to the point where the next logical step is HF-ACTION, a study designed to measure the clinically relevant endpoints of mortality, morbidity, and quality of life.

3.7 Cost and Quality of Life Evaluation

Any new therapeutic strategy that improves the health of HF patients also is likely to reduce a portion of the overwhelming costs of this condition by reducing hospitalizations and related expensive care. However, broader use of exercise training would increase initial cost, and the resulting economic change represents a complex issue measure both in terms of cost per added quality-adjusted life year and in total medical care cost to society. This study proposes careful measure of resource use patterns and associated medical care costs to compare the two treatment strategies. Additional comparisons will examine major subgroup effects. If the primary hypothesis is established for exercise training in this trial, cost-effectiveness analyses will define whether this therapy is economically attractive relative to standard benchmarks.

HF adversely impacts patient functional status and health-related quality of life (QOL). Modern medical therapy for HF modestly improves QOL, but exercise training may produce even larger improvements. Careful serial measurements of QOL and depression using well-validated instruments are crucial in contextualizing the impact of exercise training and represent important secondary endpoints for the HF-ACTION trial.

4 Investigational Plan

4.1 Overview

HF-ACTION is a multicenter, prospective, randomized clinical trial of exercise training versus usual care for the prevention of all-cause mortality or hospitalization in 3,000 patients with class II, III, or IV HF and $EF \leq 35\%$. The primary hypothesis is that exercise training for patients with LV systolic dysfunction will reduce deaths and hospitalizations by 20% over two years versus a usual care group.

Exercise training will include 36 facility-based training sessions (including heart rate monitoring) followed by home exercise and periodic facility-based sessions. To test the impact of exercise training combined with medical management, investigators will incorporate the most updated evidence-based care for both usual care and intervention patients. This care will be provided through recommendations made to the patient's physician regarding optimization of drug therapy and education provided to the patient. The design seeks to maximize the generalizability of study results to a wide range of heart failure patients by using entry criteria and a training program that can be applied in practice.

Eligible patients who do not consent to enter the HF-ACTION trial, whose physician requests that they not be enrolled, **whose EFs increase above the 35% threshold at baseline as compared to previous prescreening EF**, or who have results on the baseline exercise test that preclude safe exercise training will be approached for consent to enter the registry. Those consenting will have baseline information captured on an initial evaluation form in a similar format used for randomized patients. No baseline or follow-up testing will be required for registry patients.

4.2 Study Population

The inclusion and exclusion criteria have been developed to achieve our stated goal of enhancing the applicability of the HF-ACTION results. The criteria are not restrictive and we expect that enrollment will not be limited by the eligibility criteria. Any qualifying patient age 18 years or older referred to the trial who meets the inclusion and exclusion criteria will be eligible. To protect high-risk patients, one exception is the requirement of completing a baseline exercise test without significant exercise-induced arrhythmia or significant new ischemia.

4.2.1 Inclusion Criteria

At the time of final screening, patients who meet the following criteria may qualify for randomization in the study:

- LVEF \leq 35%. For purposes of screening, LVEF can be \leq 35% at any time. Prior to enrollment, however, a new ejection fraction must be obtained by echocardiogram with the resulting LVEF \leq 35%. This pre-enrollment measurement must be obtained at least 6 weeks following initiation of a stable dose of any therapy or receiving any intervention (as defined in the MOO) that might improve the ejection fraction, with the stated exception below for valve replacement.

If an ejection fraction has been measured within the 30 days prior to screening and there has been no change in treatment that could change the ejection fraction or no occurrence of a clinical event that could change the ejection fraction, the echocardiogram does not need to be repeated as long as a copy of the echocardiogram being used to meet this inclusion criterion can be sent to the HF-ACTION core lab. Patient needs to meet the inclusion and exclusion criteria at the time of the baseline echocardiogram.

- NYHA class II, III, or IV heart failure for the previous three months despite a minimum of 6 weeks of treatment.
- Must be on optimal heart failure therapy according to AHA/ACC and HFSA heart failure guidelines, including treatment with ACEI and beta-blocker therapy, or have documented rationale for variation, including intolerance, contraindication, patient preference, or

personal physician's judgment. Patients will be on stable doses of medications (**beta-blocker, ACEI, and additional medications as listed in the MOO**) for 6 weeks prior to enrollment.

- Must be sufficiently stable, by investigator judgment, to begin an exercise program.

4.2.2 Exclusion Criteria

At the time of randomization, none of the following may exist:

- Age less than 18.
- Comorbid disease or behavioral or other limitations that: 1) interfere with performing exercise training, or 2) prevent completion of one year of exercise training. **Please refer to the MOO for specific conditions that will exclude a patient from participation.**
- Currently pregnant or intent to become pregnant in the next year.
- Major cardiovascular event or cardiovascular procedure within the prior 6 weeks
- Cardiovascular procedure or hospitalization for any reason planned in the future.
- Expectation of receiving a cardiac transplant in the next six months.
- HF secondary to significant uncorrected primary valvular disease (except mitral regurgitation secondary to left ventricular dysfunction). If valve replacement has been performed, patient may not be enrolled for 12 months after this procedure.
- Heart failure secondary to congenital heart disease or obstructive cardiomyopathy
- Performance of exercise training at regular intervals (> once per week) at a moderate to vigorous intensity **at any time in the previous six weeks.**
- Exercise testing results that would preclude safe exercise training as defined by the AACVPR guidelines, including abnormal blood pressure response, early ischemic changes, and unexpected life-threatening arrhythmia.
- Fixed-rate pacemakers, pacemakers with inability to attain target heart rates, or patients with AICD devices with heart rate limits set below the target heart rate for exercise training.
- **Receiving an intracardiac device such as an ICD or a cardiac resynchronization therapy within previous six weeks (must demonstrate stability for 6 weeks post-procedure). Patients in whom the primary physician considers placement of an intracardiac device such as an ICD or a cardiac resynchronization therapy probable within 6 months should be excluded from trial entry until such device has been placed and 6 weeks of stabilization have passed.**
- Participation in another clinical trial that may interfere with HF-ACTION participation, follow up, or data collection, or that may affect cardiovascular morbidity or mortality.

4.2.3 Background Therapy

Based on completed clinical trials of ACEI and beta-blockers, the study will strongly recommend (but not require) the use of ACEI and beta-blockers, and will define (but not require) the optimal doses of such agents in the manual of operations (The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991, 1992, Cohn 1991, Packer 1999, CIBIS-II Investigators and Committees 1999, MERIT HF Study Group 1999). The specific reasons for patients not being treated with ACEI or beta-blocker will be collected at the baseline visit. Stable doses of ACEI and Beta Blockers must be observed for 6 weeks duration prior to randomization.

Background diuretics will be allowed in a flexible dosing format as per the discretion of the primary physician. Digoxin use will be strongly suggested but not mandated and recommendations to limit the daily dose so as to achieve a trough level of < 1 ng/ml will be advised (Packer 1993, Uretsky 1993, Garg 1997). The use of spironolactone will be suggested only in severe heart failure, based on the entry criteria of the RALES trial (Pitt 1999).

HMG-COA reductase (Statin) therapy and antiplatelet therapy will be strongly advised in all patients with underlying coronary artery disease (Gibbons 1999, Hunt 2001). Anticoagulation will be advised based on standard guidelines that advocate use in situations such as atrial fibrillation, presence of mechanical valves and prior TIA or stroke (Hunt 2001). The routine use of amiodarone will be discouraged unless used for standard indications such as symptomatic arrhythmia control (Hunt 2001). Unique drug interactions such as between amiodarone and lipid soluble statins (simvastatin) will be highlighted, as will drugs to be avoided, in the MOO.

Based on recent trial evidence, we recognize that some patients may be candidates for ICD or cardiac resynchronization therapy (Hunt 2001, Abraham 2002, Moss 2002). Any patient receiving an intracardiac device such as an ICD or a cardiac resynchronization therapy must demonstrate stability for 6 weeks post-procedure. Patients in whom the primary physician considers placement of an intracardiac device such as an ICD or a cardiac resynchronization therapy probable within 6 months should be excluded from trial entry until such device has been placed and a 6 weeks have passed.

Recommended background medical therapy will be reviewed by the Medical Therapy Subcommittee on a regular basis in order to keep the HF-ACTION recommendations current with clinical trial evidence and heart failure guidelines. The subcommittee will inform the Executive Committee regarding the potential need to include new pharmacological and non-pharmacological therapies for the management of HF, LV systolic dysfunction, and CAD. Final approval of these changes will be made by the Steering Committee.

4.3 Study Subject Enrollment

4.3.1 Screening

4.3.1.1 Once patient referred to study, obtain consent after reviewing the trial's background and purpose, study procedures, risks for participating in the study and participant's responsibilities.

4.3.1.2 Identify specific inclusion and exclusion criteria from patient and medical record.

1. If the patient meets the enrollment criteria, a baseline clinic appointment will be made.
2. If the patient is not on optimal therapy according to AHA/ACC and HFSA heart failure guidelines, document reasons for variation, including intolerance, contraindication, patient preference, or personal physician's judgment.

4.3.1.3 Baseline clinic visit

The items required by this protocol may be completed over 4 weeks if necessary. All quality of life instruments must be completed prior to the exercise test at any study clinic visit that includes both an exercise test and QOL measurement. The 6 minute walk must be performed 2 hours or more before or after the exercise test. The order of the 6 minute walk, quality of life instruments and exercise test should be maintained for each patient throughout the study.

1. Baseline echocardiogram. Patient needs to meet the inclusion and exclusion criteria at the time of the baseline echocardiogram. If an ejection fraction has been measured within the 30 days prior to screening and there has been no change in treatment that could change the ejection fraction or no occurrence of a clinical event that could change the ejection fraction, the echocardiogram does not need to be repeated as long as a copy of the echocardiogram being used to meet this inclusion criterion can be sent to the HF-ACTION core lab.

NOTE: The site should use the biplane method to read ejection fraction.

2. Review medical history and present medications.
3. Baseline blood draw for biomarkers.
4. Obtain baseline physical exam.
5. Six-minute walk test.
6. Complete case report form including quality of life instruments.

Schedule the baseline exercise test. Prefer if patient performs the exercise test on the date of the baseline evaluation.

4.3.2 Registry

Patients meeting the following criteria will be approached for entry into the HF-ACTION Trial Registry:

- Patients who meet criteria for trial entry, but when approached for consent decline randomization. Do not require echocardiogram or exercise test.

- Patients who appear eligible to approach for consent to enter the HF-ACTION trial but whose responsible physician declines to give study investigators permission to approach the patient for further evaluation for potential randomization but agree for patient to be included in a registry. Do not require echocardiogram or exercise test.
- Patients who meet all other trial criteria but have an increase in left ventricular ejection fraction at baseline that exclude enrollment in the study.
- Patients who meet all other trial criteria but have exercise testing results that preclude safe exercise training.

Patients participating in the HF-ACTION registry must meet all the inclusion and exclusion criteria that randomized patients must meet with the exception of additional testing requirements (echocardiogram and exercise test). Patients consenting to enter the HF-ACTION trial registry will be assigned a registry number through the interactive voice response system (IVRS) and will have baseline clinical information recorded on the initial evaluation form. No follow-up testing will be required, **and patients enrolled in the registry due to an improvement in left ventricular function will not be required to undergo exercise testing.** Patients who refuse enrollment or whose physician refuses enrollment will **also** not be required to perform an exercise test. **All Registry patients will be followed for outcomes by the appropriate national or provincial database at the end of year one, and annually until the end of the main trial.**

Patients will be asked to complete a number of Quality of Life (QOL) questionnaires to assess their perception of their health status. The questionnaires will take up to 60 minutes to complete.

4.3.3 Biomarker Protocol

4.3.3.1 Specific Aims

The HF-ACTION biomarker substudy will have the following specific aims:

1. To establish a human Plasma Bank comprised of frozen plasma samples taken serially from heart failure patients in the HF-ACTION trial.
2. To evaluate circulating levels of proteins of interest in patients enrolled in the HF-ACTION trial, in order to better understand the relationships between protein expression, the response to exercise training, and clinical outcomes in heart failure. Specific protocols will be funded through a separate mechanism.
3. To allow the future evaluation of newly discovered proteins of interest as advances in genomics and proteomics provide further insight into potential mediators of outcome in heart failure.

4.3.3.2 Biomarker Methods: Blood Sampling for Plasma Storage

1. **Twenty mL** of blood will be obtained from study participants at three separate time points: baseline, 3 months, and 1 year. These time points were selected to reflect sub-acute and long-term changes in circulating proteins that may occur with exercise training. Patient study ID number, date and time will be recorded on the label of each tube of blood. Each specimen will be spun in a 4 C centrifuge for 20 minutes, and then frozen at -70°C for shipping to the Biomarker Core Lab.

2. Specimen Storage. The Center for Human Genetics at Duke University will provide specimen handling, cataloging, and storage. Specimens will be thawed and aliquoted at the Center for Human Genetics before being frozen at -70°C for long term storage. This will minimize repeated freeze-thaw cycles for individual investigations.

3. Patient Confidentiality. Patient samples in the Plasma Bank will be linked to the main HF-ACTION database through the patient study ID number. All studies using the Plasma Bank will require mechanisms in place to ensure confidentiality of patient information.

4.3.3.3 Consideration of Specific Proposals

A centralized mechanism will be established to evaluate specific proposals to utilize specimens from the HF-ACTION Plasma Bank. A steering committee will evaluate proposals from HF-ACTION investigators for use of plasma from the Plasma Bank for analyses. Proposals will be considered based on scientific merit, feasibility, and optimizing use of the material collected in the Plasma Bank. Proposals for use of material from the Plasma Bank will require an independent funding source for funding of specimen handling and planned analyses. Analyses that require data from the main trial database will require submission of ancillary study data to the Coordinating Center with appropriate budgeting for Coordinating Center resources such as statistical support and data management.

4.3.4 Run-in Period

The run-in period will be limited to the time interval required to arrange for the exercise test, which may be performed the same day as the baseline clinic exam. For those patients performing 2 baseline exercise tests (see Section 4.3.5), the run-in period will extend to the second exercise test. Patients will be randomized after the second test.

4.3.5 Exercise Testing

Using methodology consistent with the American Heart Association (Pina 1995) and HF-ACTION Exercise Testing Core Lab guidelines, all patients will undergo a baseline exercise test with gas-exchange analysis prior to randomization. The methodology for the administration of these tests (and all follow-up tests) will be standardized across all participating centers, as described in the HF-ACTION exercise testing manual. The primary modality for exercise tests will be a motor-driven treadmill, consistent with other studies that assess exercise capacity in heart failure patients (Mancini 1991a, Osada 1998, Likoff 1987, Parameshwar 1992). For patients unable to perform an exercise test on a treadmill, an exercise bike protocol will be used. Patients must use the same testing modality for all exercise tests during the trial. HF-ACTION will use an extended modified Naughton protocol (Wilson 1987, Froelicher 2000) for the treadmill test. For bike test, a ramped protocol will be used with 10 watt/minute incremental increases starting at 0 watts.

Table 2: Exercise Testing Stages

| Stage | Rest | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------|------|-----|-----|-----|-----|------|-----|------|------|------|------|
| Time (min) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 |
| Speed (mph) | 0 | 1.0 | 1.5 | 2.0 | 2.0 | 2.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.4 |
| Slope (%) | 0 | 0 | 0 | 3.5 | 7.0 | 10.5 | 7.5 | 10.0 | 12.5 | 15.0 | 14.0 |
| METs | 1.2 | 2.3 | 3.3 | 4.5 | 5.5 | 6.5 | 7.5 | 8.5 | 9.5 | 10.5 | 11.5 |

Because the mandated training modalities (treadmill walking, independent walking, or stationary cycling) all involve and stimulate the larger muscles of the upper leg (e.g., vastus lateralis), specificity of testing relative to training modality will be maintained. Additionally, using the treadmill for testing will allow for a direct comparison between the peak VO₂ values obtained in HF-ACTION and the values obtained in prior trials that stratified risk and prognosis in heart failure patients using VO₂ during treadmill testing (Mancini 1991b, Osada 1998, Likoff 1987).

The first 100 patients will perform two baseline tests. The first of the two baseline tests will be a practice test that will include appropriate monitoring. The goal will be to have the two baseline exercise tests performed within 7 days of each other. The second test will be removed from the study design if analysis of the first 100 patients enrolled in the study reveals no significant variation in the quality or results between the screening test and the baseline test. If the analysis shows a variation deemed too significant by the Steering Committee, two tests will be required prior to randomization. In addition to the first 100 patients performing two baseline tests, all centers performing exercise testing for the HF-ACTION trial will be required to perform 2 baseline tests on the first 5 patients enrolled in order to check for quality of the testing center. These 5 test-retest at baseline will be performed even if the second test is removed from the protocol after the analysis of the first 100 tests. For those patients with two baseline exercise tests, the **first** baseline test will be used in analysis of trial results.

Patients will be excluded from the study if exercise testing results preclude safe exercise training as defined by the ACC/AHA guidelines, including abnormal blood pressure response, early ischemic changes, and unexpected life-threatening arrhythmia.

If exercise-induced arrhythmia is identified as life-threatening by the HF-ACTION investigator, the patient will be asked to stop the exercise test. If the patient is performing a baseline test, he/she will not be randomized to the study. If the patient is already participating in HF-ACTION, he/she will be asked to stop any exercise whether supervised or unsupervised, and his/her physicians will be notified of the results. Patients already in HF-ACTION will be followed per the protocol for the duration of the study; and no further exercise testing will be performed. Patients who have a non-life threatening arrhythmia that stops the test can re-take the test or re-start training after it is treated.

Patients should participate in exercise testing and training between three and ten hours after taking **beta-adrenergic blocking agents**.

All tests in HF-ACTION will be symptom-limited, with strong encouragement to achieve a respiratory exchange ratio > 1.10 and a Borg rating of perceived exertion > 16. During all exercise

tests, gas exchange will be measured and data will be forwarded to the Core Exercise Lab. Sampling period will be standardized at 15 seconds or at eight breaths. A test will be identified as being maximal effort if the RER is > 1.10.

Ventilatory threshold (VT) will be determined using the V-slope method established by Beaver et al. (1986). Two independent experts, blinded to subject group assignment, will determine VT at the Core Exercise Lab. If there is a disagreement between the two reviewers, the VT will be determined by discussion and consensus between the two reviewers.

Prior to participation, all regional centers and satellite centers performing exercise tests will be required to perform **one exercise test on each of two normal subjects** and have these tests reviewed by the HF-ACTION Exercise Testing Core Lab. On a regular basis, testing centers will be required to submit normal exercise tests for review by the Testing Core Lab in order to confirm proper function of testing equipment.

4.3.6 Randomization

After a participating clinical site has identified a patient who satisfied all enrollment criteria, informed consent has been obtained, and the patient completes the baseline exercise test, the patient will be randomized to usual care, or exercise training. For patients performing two exercise tests, randomization will be performed after the second exercise test. **Randomization should generally occur the same day of the final screening test (echo or CPX).**

Randomization will be accomplished by telephone contact with IVRS using a toll-free randomization number. (This toll-free number will be prominently displayed on the randomization data forms used by the regional center and satellite site coordinators.) During this call, the regional or satellite center investigator or their designee follows the IVRS dialogue and answers the questions using the keypad on the telephone. At the end of the dialogue, the IVRS assigns the randomized treatment and the patient's study identification number.

A permuted block randomization scheme stratified by clinical center and by etiology of the heart failure (ischemic versus non-ischemic) will be used, with a selected blocking factor (block size) that will not be revealed to investigators at the participating clinical sites. **Ischemic etiology will be defined as the presence of at least one of the four following criteria: 1) angiographic evidence of $\geq 75\%$ lesion in one or more of the three major epicardial vessels; 2) history of MI; 3) history of revascularization procedure; or 4) evidence of significant perfusion defect in the setting of ischemic symptoms.**

4.3.7 Baseline Evaluation of Randomized Patients After Exercise Test

See Section 4.3.1.3 for details regarding evaluation before exercise test. The procedures described below will also be obtained for patients included in the HF-ACTION Registry. Once an exercise test is completed and the patient is randomized, patients will receive extensive patient education as part of the HF-ACTION protocol.

4.4 Initiation of Exercise Training

Personnel experienced in training patients at a regional center or satellite training center will supervise initial training. The location for starting exercise training under supervision is based on

AHA guidelines. **Training will begin as soon as possible after randomization, with a goal of initiating training no more than one week after randomization.**

4.5 Investigational Therapies

4.5.1 Usual Care Group

4.5.1.1 Usual Care

Patients in this arm will receive the following:

1. Patient education at the time of the randomization visit.
2. Telephone follow-up.
 - a. To assess symptoms, compliance with medical regimen, review education, and collect data on specific outcomes including level of activity.
 - b. Phone calls **will be made once** every 2 weeks for the first 9 months. Telephone calls will be made monthly between follow-up months 10 and 24. After 24 months of follow-up, calls will be made every 3 months.
 - c. Patients will be able to reach a healthcare provider affiliated with the trial if necessary, but all emergencies and patient care issues not pertaining to the trial will be referred to their usual healthcare providers.

The HF-ACTION Investigators recognize that participants in the usual care group will not have the potential benefit of interacting with exercise training personnel that will take place with the participants in the training arm. In order to attempt to ascertain if the differential surveillance of patients in the two arms causes a difference in patient management, **the case report form will collect information at each phone call during the study** regarding unscheduled phone calls to healthcare providers; changes in treatment due to these calls; and changes to diuretics specifically.

3. **Patients will be seen in clinic every three months during the first 24 months and yearly thereafter by study staff designated by the PI.**
4. Exercise testing with gas-exchange measurements.
 - a. Performed at three months, 12 months, and 24 months of follow-up.
 - b. The same methods and measures as those taken at the enrollment test will be used and recorded.

4.5.1.2 Patient Education

The HF-ACTION investigators and coordinators will provide a self-management educational program to all participants and their families. The foundation of the program will be an educational manual that will discuss topics such as drugs and their side effects, fluid management, symptom exacerbation, and the importance of adhering to a low-sodium diet. French and Spanish manuals will be developed.

The amount of counseling patients should receive about activity and exercise is an important issue. We recognize that some of the participants in the usual care arm will begin their own training. The HF-ACTION education manual will recommend that patients with heart failure carry out 30 minutes, or as long as tolerated, of moderate intensity activity most days of the week. Moderate intensity activity is defined as an effort level that does not cause the individual to sweat or become short of breath. Safety guidelines for initiating exercise will also be provided. No formal program (written or verbal) will be given to patients.

4.5.2 Exercise Training Group (Intervention Group)

4.5.2.1 Usual Care

Patients in this arm will receive the same care as patients in the usual care arm, including the number and time of exercise testing and the number of telephone follow-up phone calls. During telephone follow-up calls, clinic visits, and supervised training sessions, patient education about behavior modification will be provided to improve adherence with training.

4.5.2.2 Exercise Training Regimen

We will follow the principles of exercise prescription as recommended by both the American College of Sports Medicine (Franklin 2000) and the American Heart Association (Fletcher 1995).

Table 3: HF-ACTION Exercise Training Program

| Training Phase | Location | Weeks into Study* | Sessions per week | Aerobic minutes | Intensity (% hr reserve) | Training Mode |
|--------------------|---------------|-------------------|-------------------|-----------------|--------------------------|---------------|
| Initial supervised | Clinic | 1-2 | 3 | 15-30 | 60% | Walk/Cycle |
| Supervised | Clinic | 3-6 | 3 | 30-35 | 70% | Walk/Cycle |
| Supervised & Home | Clinic & Home | 7-12 | 3 & 2 | 30-35 | 70% | Walk/Cycle |
| Maintenance | Home | 13-end | 5 | 40 | 60-70% | Walk/Cycle |

*Week interval shown are goals and may vary for individual participants.

For this trial, patients randomized to the training arm will initially have 36 supervised training sessions at a qualified training facility. The goal will be to complete the initial phase of the study in 12 weeks (3 sessions per week). Not all patients will be able to meet this goal. Patients will have 6 months to complete 36 supervised training sessions. If they have completed fewer than 9 sessions at 6 months, they will be required to finish 9 sessions before moving on to the home exercise phase of the trial. **(Patients who complete more than 9 but fewer than 36 sessions in the first six months may proceed to the home exercise phase in month 7.)** Participating centers will be monitored for patient adherence to the protocol and may be prevented from enrolling patients if an excessive number of patients do not complete the 36 supervised training sessions relative to other enrolling centers.

Patients will be provided a heart rate monitor at the beginning of their supervised training. Centers that are capable of or wish to perform ECG telemetry monitoring on their patients in the program may do so at their discretion.

After the initial exercise phase, a home-based phase will continue for the duration of a patient's participation in the trial. If requested by patients, either an exercise bicycle or treadmill will be provided by HF-ACTION for home use during the duration of the study. Patients may participate in unsupervised group sessions at the cardiac rehabilitation center or other appropriate training programs as part of the HF-ACTION home-based training. Due to weight limitations on certain equipment, unsupervised group sessions or specific types of exercise equipment (i.e. recumbent bicycle) will be recommended.

The table above summarizes the exercise prescription in HF-ACTION.

The various aspects of an appropriate exercise prescription include the mode of exercise as well as its intensity, duration, and frequency. Patients will return for facility-based training sessions every three months starting at the end of 6 months of follow-up. At each session, the patient's exercise will be monitored to assess whether they are achieving target levels. Training intensities will be modified based on the most recent exercise test.

4.5.2.2.1 Modality of Exercise

The exercise training modalities used in the 36 facility-based sessions and at home will be similar to the equipment used in exercise trials involving heart failure patients to date. HF-ACTION will allow patients to use either a stationary cycle or walking (treadmill or independent). Including both modalities (bicycling and walking) will facilitate adherence, without sacrificing observed outcomes. Upper body exercises (arm ergometer, dual action cycle, rowing machine) and swimming will not be included in any of the facility-based sessions or the home-based training. Strength training will not be part of the main trial design. If patients need exercise equipment, a stationary bicycle or treadmill will be provided to them.

4.5.2.2.2 Exercise Intensity

The HF-ACTION training protocol is designed so that patients will begin therapy at a lower intensity and then increase to a moderate intensity when they are able. In HF-ACTION, the heart rate reserve method will be used to set exercise intensity. Peak heart rate will be derived from a patient's most recent exercise test and resting heart rate will be taken after five minutes of quiet **seated** rest. For the first 6 supervised training sessions of the initial conditioning phase (goal is first two weeks of the clinic-based exercise sessions), the training heart-rate range will be computed at 60% of heart rate reserve (resting heart rate + 0.6(peak heart rate - resting heart rate)). To facilitate starting patients in the training program as soon as possible, this 60% target rate will be computed by the regional center PI/exercise physiologist immediately after the patient completes the enrollment exercise test. Within 7 days, the Core Exercise Lab will confirm exercise test results and the initial goal heart rate determined by the regional center. If there is a conflict, the initial training heart-rate target will be adjusted to the Core Lab's reading.

For the last 30 supervised training sessions (the goal is for this to be during weeks 3-12 of the facility-based exercise or the improvement phase), the target heart-rate range for exercise intensity will be titrated up, such that the allowed upper value for training range will become 70% of the heart rate reserve. Again, the Core Lab will provide the upper 70% heart rate value.

After the facility-based phase of training, patients will begin the home-based maintenance program using a training intensity between 60% and 70% of heart rate reserve. Any changes in the exercise prescription will be made immediately following one of the sequential exercise tests or scheduled follow-up exercise sessions at the rehabilitation center.

To further ensure that the patient experiences an adequate and comfortable training level, rating of perceived exertion (RPE) will be maintained between 12 and 14 during training sessions.

At the beginning and throughout the facility-based training program, patients will be instructed about how to monitor their own exercise training using pulse rate palpation, heart rate monitors, and/or perceived exertion methods. All patients in the exercise training arm will learn how to use heart-rate monitors. The monitors will serve three purposes: 1) provide real-time feedback to patients while they are training at facilities and at home; 2) provide training intensity measurements for analysis; and 3) provide information on adherence. Patients will use these techniques when exercising at home to ensure that exercise intensity is within the ranges set for them following each successive exercise test and during rehabilitation follow-up visits throughout the HF-ACTION trial. A specific heart rate monitor protocol will be included in the manual of operations.

Several special issues concerning exercise intensity are addressed below. Concerning the prescription of exercise while taking a **beta-adrenergic blocking agent**, heart rate will be affected both at rest and at peak exercise. To ensure that cardiovascular responses during exercise testing reflect cardiovascular responses during exercise training, all testing and training should be done between three and ten hours after taking a **beta-adrenergic blocking agent**. The heart rate reserve method will still be used, computed using the 60% to 70% intensity levels, regardless of whether a patient is taking a beta-adrenergic blocking agent. Some patients may be unable to exercise up to the prescribed heart rate due to differences in the metabolism of the beta-adrenergic blocking agent and its effect on heart rate. **In these patients, RPE between 12 and 14 will be used to guide exercise intensity.**

Another unique issue concerning exercise intensity pertains to patients with exercise-induced angina or ischemia. Per the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines, in these patients exercise intensity will be set at a heart rate of 10 beats below the heart rate where the onset of angina or ischemia occurred. For patients with non-specific ST-T wave changes secondary to LV hypertrophy or digitalis, initial target heart rate range will be 60% of heart rate reserve.

For patients with LBBB on their resting ECG, exercise intensity will be set using the above described 60% to 70% heart rate reserve method or 10 beats below the onset of angina.

Patients with fixed-rate pacemakers, pacemakers unable to attain a target heart rate, or an ICD device with heart rate limits set below the target heart rate will be ineligible for this trial because of the inability to prescribe exercise accurately. Referring physicians will be provided with an opportunity to reprogram devices so that patients can participate.

Patients randomized to exercise training that demonstrate hemodynamic stability but have frequent ventricular beats that may cause the measurement of heart rate via palpation or commercial heart rate monitor to be invalid will use **the RPE that coincides to their heart rate range of 60-70% of heart rate reserve. For patients who have atrial fibrillation (making exercise prescription**

by heart rate invalid) we will use an RPE between 12 and 14 to guide exercise intensity.
Patients will be trained on how to recognize the appropriate RPE for the prescribed intensity.

4.5.2.2.3 Duration of Exercise

Most patients in HF-ACTION will be able to perform some degree of continuous exercise. However, during the initial training sessions, some patients may need to use intermittent exercise for the first several days to two weeks. For patients with significant symptoms who may be unable to perform continuous exercise, training will be initiated with rest periods with a goal of 50% heart rate reserve and 15-30 minutes total exercise time. A short-range goal (within 9-15 supervised training sessions) will be to ultimately have all patients training for 30-35 continuous minutes at each session rather than in an intermittent fashion.

Prior to and immediately following each aerobic phase, a 10-minute warm-up and a 10-minute cool-down period will be used. After 6 sessions in the facility-based program, it is likely that all patients will tolerate 30-35 minutes of continuous aerobic exercise. Fifty percent of the time spent during the facility-based aerobic exercise will be on the exercise modality to be used in the home program.

For the home maintenance phase, patients will perform 40 minutes of aerobic exercise (not including time for warm-up or cool-down), either in one session or two 20-minute sessions on each exercise day. Patients will be asked to perform their exercise at relatively the same time each day, to ensure better compliance and to minimize the effect of time of drug administration (beta-adrenergic blocking agents) on heart rate during exercise. These procedures are further outlined in the manual of operations.

4.5.2.2.4 Frequency of Exercise

The goal is to perform supervised training 3 times per week and complete the initial training phase in 12 weeks. During the first 18 supervised training sessions of the initial training phase, subjects will exercise only at the cardiac rehabilitation program. During the period when patients in the intervention arm are completing the last 18 supervised training sessions, they will initiate and maintain two days per week of exercise at home, in order to prepare for the home maintenance program that requires training five times per week. Home exercise equipment will be provided prior to initiation of home exercise. Training intensity at home will be maintained at 60% of heart rate reserve during this time. Training schedules will need to be monitored closely by study coordinators. The schedule will be coordinated between the study coordinator following the patient and the training center director.

After the facility-based training sessions and throughout the maintenance program, patients will exercise five days per week using stationary cycling and/or walking (treadmill or independent). Patients will be encouraged to perform an activity of their choice a sixth day per week, using a modality of their own choosing (such as swimming or road cycling). Exercise intensity for all home exercise will be set at 60% to 70% of heart rate reserve. Patients will return for facility-based training sessions once every three months starting at the end of 6 months of follow-up. Following

the exercise tests at three months, 12 months, and 24 months, the results will be used to modify training intensity at the facility-based training sessions.

All exercise will be recorded in exercise logs. **Except in the special circumstances discussed previously making use of target heart rate not applicable (frequent ventricular beats or atrial fibrillation)**, heart-rate monitors will be used and patients will record their resting and average training heart rate in an exercise training log. Patients will receive a heart-rate monitor when initiating supervised exercise training. As needed, the exercise prescription will be revised. Most changes in the exercise prescription will occur as a means to enhance subject compliance, increase the training effect if progress is not adequate, or address any concerns relative to a patient's safety or comfort.

As is common practice, patients should participate in exercise testing and training between three and ten hours after taking **a beta-adrenergic blocking agent**. The window of eight hours is compatible with most patients' schedules.

If patients experience a hospitalization for a cardiovascular event (ACS or significant arrhythmia) or have continued worsening of CHF symptoms after a heart failure exacerbation, study coordinators will be able to have patients return for 1-3 supervised training session(s). Study coordinators will discuss the need for additional supervised training session with regional center PIs. The manual of operations will have guidelines for study coordinators to use.

4.5.3 Adherence

4.5.3.1 Overview of Adherence Strategies

A major goal of the HF-ACTION trial is to maximize adherence and retention throughout the study.

Adherence refers to the degree to which study participants comply with the intervention protocol, and will be assessed using a number of measures, including attendance at facility-based exercise sessions, completion of physical activity logs for home-based exercise, use of heart rate monitors, and self-reported percentage of time at or above their prescribed training range.

Retention refers to continued involvement of study participants through the intervention and clinic follow-up phases of the protocol, and is independent of adherence to specific components of the protocol.

HF-ACTION will adopt a variety of approaches to promote adherence and retention during the study, and to aid in drop-out recovery. The first set of strategies consists of commonly used methods of assisting participants in adhering to a study protocol. The second set of strategies includes methods designed specifically to promote adherence to facility-based and home-based exercise training in Exercise Intervention participants. In addition, we will use motivational enhancement methods from the moment of recruitment in order to reinforce adherence during the study. Finally, we will implement strategies for all study participants aimed specifically at recovering drop-outs, either due to a failure to return to intervention sessions or failure to return to follow-up assessments.

Careful screening prior to randomization will be used to identify barriers to adherence. If barriers are felt to be insurmountable by study coordinators or investigators, they will have the discretion to not enroll the patient (please see exclusion criteria 4.2.2 item #2).

4.5.3.2 General Adherence Strategies

Five general strategies will be used to facilitate adherence to the intervention and to the follow-up assessments, and to retain study subjects throughout follow-up. These strategies include print reminders, interim phone calls, involvement by family and/or friends, logistical assistance, and incentives. During the initial screening we will determine patients' preferences for being contacted (e.g., mail, email, telephone) and attempt to incorporate their preferences into the follow-up process.

4.5.3.2.1 Reminders

We plan to provide all study participants with calendars indicating intervention and/or assessment sessions, and to send them reminders in advance of follow-up assessments.

In addition, to assist with patient retention and to maintain contact with and involvement of participants, **newsletters** will be written by the HF-ACTION team and provided to all regional centers for distribution to their patients. The newsletter will contain patient information, such as heart healthy recipes.

4.5.3.2.2 Close Follow-up

Because the highest rate of non-adherence to prescribed therapies often occurs within the first 6 months, the HF-ACTION trial includes many early follow-up clinic visits and telephone calls to maximize adherence. Phone calls will be used to assess symptoms, determine adherence with the medical regimen, review education, and collect data on various outcomes. These calls also will provide positive reinforcement for patients in the exercise-training arm, and will identify problems with adhering to the program. The frequency of follow-up will decrease as patients move further into the maintenance phase. However, if patients have difficulty with adherence early in the trial, coordinators will be asked to maintain a more intense telephone follow-up schedule.

Patients in the both arms of the study group will receive phone calls once every 2 weeks for the first 9 months; phone calls monthly for months 10-24; and phone calls every 3 months for months thereafter. These patients will attend clinic visits every 3 months for first 24 months and yearly thereafter. These calls and visits are designed to maintain patient involvement in the Usual Care condition and the exercise intervention.

Patients in the Exercise Intervention group will have regular contact with the exercise physiologists overseeing their exercise training during the supervised exercise portion of their treatment. Study personnel will call patients who miss **two consecutive exercise sessions** during this phase. These patients will return for facility-based training sessions during the home exercise training phase of the study. Patients' exercise will be monitored at these sessions to assess whether they are achieving target levels.

4.5.3.2.3 Family/Friend Involvement

Because spouses, partners, significant others, or friends who support participants in an exercise regimen may increase adherence, patients in the Exercise Intervention will be asked to bring to the orientation session an individual who is viewed as a primary source of social support.

4.5.3.2.4 Logistical Assistance

We will thoroughly screen patients to identify potential barriers to adherence. The study coordinator will ensure that participants have sufficient logistical assistance to attend first screening visits and then intervention and assessment sessions once they are randomized. Issues that we anticipate commonly being addressed with patients include identifying means for transportation and arranging for child care.

The coordinating center has set aside funds for regional centers to use in developing plans for logistical assistance. Funds will be distributed by the Recruitment and Retention Subcommittee based on regional and satellite center needs. If barriers are felt to be insurmountable by study coordinators or investigators, they will have the discretion to not enroll the patient.

4.5.3.2.5 Incentives

A system for providing incentives will be developed to reward adherence to home-based exercise guidelines, completing and returning activity diaries, and attending follow-up assessments. This may include study-wide and/or site-specific lotteries, as well as a system of earning points toward a reward (e.g., T-shirt, mug). The incentives will be for both the usual care group (for completing follow-up) and for the intervention group (for completing follow-up and for adhering to the exercise regimen).

4.5.3.3 Specific Adherence Strategies

4.5.3.3.1 Assessment of Motivation

Patients will be assessed for their exercise stage of readiness and related motivational factors at the baseline visit. These tools will be used to assess patients' readiness to initiate and maintain exercise. Based on the Stages of Motivational Readiness for Change model, adherence promoting strategies during exercise training will be used and tailored to individual patients.

4.5.3.3.2 Self-management Educational Program

The HF-ACTION investigators and coordinators will develop a self-management educational program to all participants and their families. The foundation of the program will be an educational manual that will discuss topics such as drugs and their side effects, fluid management, symptom exacerbation, and the importance of adhering to a low sodium diet. Tip sheets will also be developed and sent to participants (e.g., exercising in the winter season, obtaining support for exercise regimen, etc.).

4.5.3.3.3 Orientation and Motivational Materials

All patients in the Exercise Intervention group will be given written information about exercise, including a formal exercise prescription, information about how to use the heart rate monitors, and what to do in the case of increasing symptoms. In addition, motivation- and stage-matched self-help materials will be used for patients as they transition from facility-based to home-based exercise.

4.5.3.3.4 Physical Activity Diary

Patients in the exercise training arm will be asked to **keep activity logs of their exercise performance in their home-based sessions during and after the transition to home-based exercise**. These activity logs will include exercise mode, heart rate, time, rating of perceived exertion, and symptoms encountered during exercise sessions. Logs will be reviewed at follow-up clinic appointments by the study coordinators. Feedback will be provided based on the diary. Activity diaries will also be reviewed during telephone calls.

4.5.3.3.5 Heart Rate Monitors

All patients (**with exceptions noted in Section 4.5.2.2.4**) will receive a heart rate monitor at the start of the supervised training program. This will allow investigators to objectively document exercise intensity and to provide feedback to study patients regarding their adherence to the exercise prescription.

4.5.3.3.6 Cognitive Strategies

Relapse-prevention techniques and problem-solving skills will be reviewed with patients at regular intervals both face-to-face and on the phone. Discussion will focus on how negative attitudes about exercise can be modified by more realistic self-statements, identification of high-risk “adherence-compromising” situations (e.g., inclement weather, increased work responsibilities, feeling tired, etc.), and discussion of methods to cope with these situations more effectively. They will be encouraged **to contact study personnel** in the case of injury, illness, or increasing symptoms and taught what to do to get back on track when time and boredom become problematic for them. In addition they will receive formal instructions about what to do if they miss exercise training sessions for more than one week. Training materials regarding behavior change theory and techniques will be provided to study personnel.

As part of the HF-ACTION study, all participants will complete a series of instruments to assess barriers to exercise training **at baseline and at 12 months of follow-up**. The instruments will include a stages of change instrument (4 questions), exercise self-efficacy instrument (5 questions), decisional balance instrument (16 questions), and barrier scale instrument (10 questions).

4.5.3.4 Motivational Enhancement Methods

Motivational interviewing is an approach to assessment and intervention based on the stages of change model that is designed to identify and reinforce individuals’ personal self-motivating statements and reasons to change behavior. While not reasonable to teach non-clinicians these skills which are built upon basic clinical training, rudiments of motivational intervention concepts will be taught to clinic personnel in an attempt to enhance participants’ motivation to adhere with the intervention and follow-up visits. This approach to health-promotion interventions emphasizes the use of individualized risk appraisal, identification of potential risk-reduction strategies, techniques to increase self-efficacy for behavior change, and strategies to prevent relapse and promote retention. It incorporates several strategies to facilitate transition from one stage to the next, thereby preparing an individual to initiate and/or maintain a recommended behavior. Objective feedback is provided and ambivalence about behavior change explored, with specific attention to eliciting an individual’s personal goals and self-motivational statements, formulating personal goals in behavioral terms and problem-solving barriers to change. Reflective listening skills are particularly effective as a method of interaction with patients in eliciting and clarifying

their personal goals and self-motivational statements. Motivational interviewing seeks to evaluate the discrepancy between participants' stated goals and their current behaviors in a style that increases motivation for change.

Motivational enhancement methods will be incorporated in the earliest stages of recruitment. However, these methods will be extended throughout activities of HF-ACTION to encompass interactions of participants with study coordinators, interviewers and clinic follow-up staff. Our experience has been that these methods, when used consistently across contacts, are extremely effective in promoting active participation. Training in motivational interviewing methods will be incorporated into the two-day training session for all study personnel. In addition, ongoing education and support will be provided as needed by clinical psychologists at the coordinating center and/or individual study sites.

4.5.3.4.1 Drop-out Recovery

The following definitions should be used when discussing HF-ACTION participants' level of involvement in the study:

1. Integrated participants: Those who faithfully follow through and attend appointments or, if they cancel, follow through by rescheduling and attending the next appointment. Integration is defined only in terms of contact, not in terms of success with goals of treatment.
2. Reluctant participants: Those who cancel one-quarter or more of their appointments; do not show up for one-quarter or more of their appointments; repeatedly indicate that "now is not a good time"; screen calls and do not respond to messages; or fail to return one-quarter or more of their activity logs.
3. Hard refusals: Those who state, in no uncertain terms, that they do not want to participate in the study and do not want any further contacts with anyone associated with the study.

HF-ACTION will provide a systematic approach in attempting to recover reluctant participants, i.e., those who have either expressed interest in dropping out of the study or appear to be likely to drop-out due to noncompliance with any aspect of the study. Many of these individuals may be inclined to drop-out due to life changes (e.g., divorce, illness of family members, changes in jobs, etc.) and/or from misunderstandings with study staff or from concerns about study procedures.

The goal of drop-out recovery is three-fold: 1) to ensure that participants are not pushed to the point that they refuse to participate further; 2) to continue to engage participants through some form of contact (e.g., phone, e-mail) and allow an opportunity to determine participants' concerns and problem-solve for solutions to concerns and barriers to participation; and 3) to foster some form of continued participation (e.g., even an agreement to allow future contact). These goals require training by the coordinating center retention and adherence experts for all clinical staff and investigators.

Drop-out recovery methods have been demonstrated in clinical trials to re-engage participants who have become non-responsive when applied systematically. Although not originally conceptualized in this manner, this approach incorporates the use of good reflective-listening and directive skills to elicit barriers to participation from subjects. The general approach to drop-out recovery will involve contact by the study coordinator in an attempt to: 1) identify barriers to participation, 2) problem-solve for solutions to overcome identified barriers, 3) apply motivational interviewing

methods. With systematic efforts to recover these participants, many who initially express the desire to drop out can be recovered when either their life circumstances change so that it is more feasible for them to participate again or when their concerns with study staff and/or clinic procedures have been addressed. In situations where a participant's behavior suggests that he/she does not wish to participate, but does not give a hard refusal, the above strategies should be implemented. However, attempts to re-integrate a participant should be discontinued as soon as a hard refusal is communicated.

4.6 Study Subject Follow-Up

At each clinic visit at three-month intervals after study entry, a brief history and physical examination will be performed and follow-up forms will be completed. **These follow-up visits should take place in a ± 15-day window; e.g., the 3-month visit should take place between 2½ and 3½ months after randomization.** Follow-up data to be collected at each of these contacts will include an assessment of symptoms, medication changes, physical exam and interval medical events including hospitalization, major cardiac procedures, and tests. Patients completing a treadmill test at baseline will have this test repeated at 3 months, 12 months, and 24 months. Detailed quality of life assessment will be performed at the three-month visit, one year, and annually thereafter during follow-up. Table 4 and Table 5 summarize the schedule of follow-up studies in the HF-ACTION trial. Telephone contact will be maintained with patients unwilling or unable to return to the clinical site and their local care providers to assure that intensive medical therapy is continued.

4.6.1 Discontinuation from the Study

A patient will be considered lost to follow-up only after exhausting all means of contact. The status of the patient at the last visit or contact will be used for the final analysis. The vital status of patients who withdraw consent or are lost to follow-up will be followed by **the appropriate national or provincial database** until the end of the study.

Table 4: Clinical Events, Initial Three (3) Months

| Patient Care | Screening and Baseline Evaluation | 1-2 wk | 3-4 wk | 5-6 wk | 7-8 wk | 9-10 wk | 11- 12 wk | End of 12 wks |
|---|--|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------------|------------------------------|
| Clinical Visit | x | | | | | | | x |
| Telephone Follow-Up | | x | x | x | x | x | x | |
| Supervised Exercise Training † (exercise arm only) | | 6x | 6x | 6x | 6x | 6x | 6x | |
| Clinical Studies | | | | | | | | |
| Echocardiogram | x | | | | | | | |
| CPX | x | | | | | | | x |
| Outcome Measure | | | | | | | | |
| Pain Questions | x | | | | | | | x |
| KCCQ | x | | | | | | | x |
| Resource Utilization | | | | | | | | x |
| Rapid Report Form | | | | | | | | x |
| <u>EuroQoL</u> | x | | | | | | | x |
| BDI | x | | | | | | | x |
| PSSS | x | | | | | | | |
| <u>PAQ</u> | x | | | | | | | |
| 6-minute Walk | x | | | | | | | x |

† Supervised exercise training may take longer than 12 weeks. Patients will have 6 months to complete 36 supervise training sessions.

Table 5: Clinical Events, Rest of Study

| Patient Care | 4-6 months | 7-9 months | 10-12 months | 13-15 months | 16-18 months | 19-21 months | 22-24 months | 3rd year | End study |
|--|-------------------|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------------|------------------|
| Clinical Visit | x | x | x | x | x | x | x | x | x |
| Telephone Follow-Up | 6x | 6x | 3x | 3x | 3x | 3x | 3x | 4x | 4x |
| Supervised Exercise Training (exercise arm only) | x | x | x | x | x | x | x | 4x | 4x |
| Clinical Studies | | | | | | | | | |
| Echocardiogram | | | | | | | | | |
| CPX | | | x | | | | x | | |
| Outcome Measure | | | | | | | | | |
| Pain Questions | x | x | x | | | | x | x | x |
| KCCQ | x | x | x | | | | x | x | x |
| Resource Utilization | x | x | x | x | x | x | x | x | x |
| Rapid Report | x | x | x | x | x | x | x | x | x |
| <u>EuroQoL</u> | x | x | x | | | | x | x | x |
| BDI | x | x | x | | | | x | x | x |
| PSSS | | | | | | | | | x |
| <u>PAQ</u> | x | | x | | | | x | x | x |
| 6-minute Walk | | | x | | | | x | x | x |

4.7 Efficacy Parameters

The primary endpoint for HF-ACTION is combined all-cause mortality and all-cause hospitalization. Each component of the primary endpoint represents a significant outcome, and successful treatment of HF traditionally has been measured by the avoidance of both of these. The use of a combined endpoint is the standard in clinical trials of heart failure therapies. The HF-ACTION Investigators have chosen all-cause mortality and all-cause hospitalization in order to capture the full effect of exercise training.

The components of the primary endpoint also will be considered separately to ensure complete understanding of the effects of exercise training in this population. When evaluating a composite primary endpoint, it is possible that one variable may have a negative effect that is masked by a stronger, positive effect of the second composite variable.

Hospitalization is a vital component to include in the composite endpoint, as hospitalizations are frequent in this population (O'Connor 2000). Hospitalizations impose a significant burden on the healthcare system and impact on patients' quality of life (Califf 1998).

To reach a protocol-specified endpoint hospitalization, the following is required: hospitalization in a hospital-based bed (includes observation units but not emergency room beds) for at least 24 hours or involving a calendar date change if timing can not otherwise be assessed.

Physiological endpoints will be measured as they have been shown to change with exercise training. Maximal exercise tolerance (peak VO₂) is a reflection of central hemodynamic and peripheral limitations, and is, therefore, an appropriate primary measure in a study of HF.

The six-minute walk test has been shown to have prognostic value when measured at baseline in patients with mild to moderate heart failure. It has also been useful in advanced heart failure (Guyatt 1985, Bittner 1993, Califf 1997). It is a simple, inexpensive, safe method for assessing exercise capacity as a measurement of functional status, and it fulfills the criterion of reflecting normal daily activity levels of patients (Guyatt 1985).

4.7.1 Primary Efficacy Parameters

1. Composite of all-cause mortality and all-cause hospitalization

4.7.2 Secondary Endpoints

1. Composite of cardiovascular mortality and cardiovascular hospitalization
2. Composite of cardiovascular mortality and heart failure hospitalization
3. All-cause mortality.
4. Cardiovascular mortality
5. All-cause hospitalization.
6. Cardiovascular hospitalization
7. Heart failure hospitalization
8. **Myocardial infarction**
9. **Worsening heart failure event**
10. Composite of all-cause mortality and all-cause hospitalization and emergency room visit and urgent clinic visit for HF exacerbation.

11. Physiologic endpoints.
 - a. Changes in exercise test variables (baseline versus three months and one year)
 - i) Peak VO₂
 - ii) VE/VCO₂ slope
 - iii) Heart rate at a submaximal work load defined as the end of the exercise test's second stage.
 - b. Changes in six-minute walk (baseline versus three months and one year).
12. Cost
13. Quality of life

4.7.3 Safety Assessment

Safety assessments will consist of monitoring and recording the safety endpoints. Results of all safety assessments (e.g., physical examinations or laboratories) performed as part of the standard evaluation and care of the patient should be maintained in the patient's study chart (source documents).

4.7.3.1 Serious Adverse Events (SAE)

The following definitions of adverse event and serious adverse event are based on NHLBI policy.

1. Adverse event (experience):

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 adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the investigational intervention, whether or not considered related to the investigational intervention. (ICH 1996)

2. Serious adverse event (experience) (SAE):

Any untoward medical occurrences that may result in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 serious adverse event 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

Disability is defined as a substantial disruption of a person's ability to conduct normal life's functions (Federal Code of Regulations 21 CFR 312.32)

For the purpose of the HF-ACTION study, the following adverse and serious adverse events will be reported to the Data and Safety Monitoring Board (DSMB): death, hospitalization,

hospitalization/observation unit stay lasting less than 24 hours, emergency room visit, urgent clinic visits, and adverse events occurring while exercising (including angina, syncope/presyncope, palpitations, symptomatic hypoglycemia and/or falls). All cardiovascular events (including worsening heart failure, acute coronary syndrome, arrhythmia, and stroke) will be collected and reported to the DSMB. For the purpose of this protocol, hospitalizations will be identified as planned or not planned. We will not be collecting specific information on congenital anomalies. At the end of the study or at death, an attempt will be made to ascertain if any permanent disabilities occurred related to the intervention.

SAEs and AEs of interest will be collected from randomization through follow-up and recorded on the Case Report Form **(CRF). Deaths and SAEs resulting in hospitalizations that occur after informed consent is signed but before randomization will also be collected on the CRF. These events will not be included, however, in the primary intent-to-treat analysis.**

The Coordinating Center will forward this safety data to the DSMB on a routine basis. The DSMB will perform routine evaluations of this safety data in this high risk population and promptly notify the NHLBI and the HF-ACTION Executive Committee of safety concerns.

Serious adverse events resulting in a death associated with exercise training, defined as occurring while exercising or within 3 hours **after** exercising, will be reported within 5 days to the coordinating center, which will forward this information to the NHLBI and DSMB chairperson. **If it is unknown whether a SAE resulting in a death occurred while exercising or within 3 hours after exercising, this event will also be reported within 5 days to the coordinating center and forwarded to the NHLBI and DSMB chairperson.**

Investigators are also required to report serious adverse events in accordance with their local IRB requirements.

4.7.3.1.1 Laboratory Evaluations

Local, not central, laboratories will be used. Normal ranges of the local laboratory will serve as the reference for the patients of individual centers. If in the course of the study, a patient is hospitalized in a nonparticipating center, laboratory evaluations from that hospital will be considered in the same way.

4.7.3.1.2 Vital Signs

Heart rate and blood pressure will be measured **at baseline and at each supervised training session.** Blood pressure and pulse are to be measured in a similar manner at each visit preferably in the sitting position after an equilibration period of ten minutes on the right arm. New York Heart Association (NYHA) functional HF class will be recorded at each visit.

4.7.3.2 Complications Secondary to Exercise Training

A secondary analysis of adverse events related to the intervention including injuries sustained during exercise, symptomatic hypoglycemic episodes, angina symptoms, ischemia, MI, syncope, arrhythmia, hospitalizations, and death will be performed. Investigators, patient's family, and/or the patient will be asked to identify if an adverse event was related to exercise training. Adverse events will be considered related to exercise training if it took place during or within three hours **after** training (Mittleman 1993, Willich 1993). The goal of this secondary analysis will be to

identify patients at higher risk for complications, and in need of closer supervision if the intervention is proven beneficial.

4.7.4 Quality of Life and Health Status Assessment

Quality of life (QOL) questionnaire data will be collected at baseline by the site coordinators, and at set intervals during the follow-up period (see Tables 4 and 5). The QOL instruments will be completed by patients at the participating centers. In addition, patient utilities, and interval medical care consumption will be assessed every three months at each clinic visit/contact by the sites.

4.7.4.1 Content of Health-related Quality of Life Questionnaire

The QOL questionnaire consists of validated instruments to measure disease-specific health-related quality of life, pain, depression, and social support

To measure disease-specific HRQOL, the newly developed Kansas City Cardiomyopathy Questionnaire will be used (KCCQ; Green 2000). The KCCQ was designed to be a more sensitive measure of changes in health state than the frequently used alternative, the Minnesota Living with Heart Failure Questionnaire (MLWHFQ; Rector 1992). The KCCQ is a 24-item instrument that produces the following scores: Physical Limitation, Symptoms, Symptom Stability, Social Limitation, Self-efficacy, Quality of Life, and two summary measures—Functional Status and Clinical Summary. The KCCQ will be administered frequently due to this instrument's sensitivity to change (see Tables 4 and 5).

Pain will be measured by using two questions from the RAND 36-Item Health Survey 1.0. These questions will query the patient about the frequency of pain and if the pain interfered with their daily activities of living.

The HF-ACTION study design also includes measures of depression and social support. The 21-item Beck Depression Inventory II (BDI) will be used to measure depression (Beck 1996). The items are scored on a 4-point scale and are summed to generate a Total Score. A Total Score of 29 or greater is considered indicative of a clinically significant depressive disorder. The BDI will be administered at baseline, every 3 months for the first year, and annually thereafter. The HF-ACTION investigators will use two measures of patients' perceptions of social support. The 12-item Perceived Social Support Scale (PSSS) will be administered at baseline and annually thereafter (Zimet 1988). The PSSS items use a 7-point Likert response format and are combined to yield a total score and three subscale scores: Family, Friends, and Significant Others.

Activity for all patients will be measured at baseline, 6 months follow-up and yearly. **We slightly modified the International Physical Activity Questionnaire (IPAQ) (Craig 2003); the modified version will be used in the trial and is referred to as the Physical Activity Questionnaire (PAQ) in this document.** The 7 item questionnaire queries patients on the frequency and intensity of their exercise over the past 7 days. **Patients in the control arm will be asked during each scheduled telephone interview** if they have are currently participating in any regular activity or program (either on their own or in a formal class) designed to improve or

maintain their physical fitness (Schechtman 1991). This will allow us to identify control patients who cross over and begin to exercise train on their own.

4.7.4.2 Measurement of Utilities

Patient-specific utilities will be assessed using the EuroQoL. The current version of this instrument consists of a five-dimension assessment of current health-related quality of life and a self-rating (0-100) “thermometer” of “your own health state today.” This assessment will be made at baseline and at set intervals (see Tables 4 and 5). If the patient is unable to complete the form unassisted (e.g., has a broken arm and cannot complete the form), the instrument will be administered as an interview.

4.7.5 Economic Assessment

Hospital bills (detailed, summary ledger and UB 92) will be collected by the EQOL Substudy personnel at the DCRI for all hospitalizations throughout the length of the study. They will include hospitalizations at clinical sites and at institutions not participating in HF-ACTION. In addition, cost to charge ratios (CCRs) will be obtained from each hospital where HF-ACTION baseline or follow-up hospitalization is reported. We will also collect resource utilization data for outpatient visits, medication use, long-term care, rehabilitation therapy, ER visits and day hospitalizations for patients who require treatment due to heart failure decompensation. This data will be collected in the CRF at each clinic visit.

Indirect costs will be measured in the CRF and will be collected at baseline and at each annual clinic visit.

4.8 Study Organization

4.8.1 Steering Committee

The voting members of the Steering Committee will consist of the principal investigator of each clinical center, the principal investigator of the Coordinating Center, and the National Heart, Lung, and Blood Institute (NHLBI) Project Officer.

The main roles and responsibilities of the Steering Committee are:

- To oversee the overall scientific direction of the trial.
- To develop and approve the protocol.
- To review and finalize the case report forms, quality of life instruments, patient manual, and operations manual.
- To review and approve the analysis plan.
- To approve substudies and publications.
- To review study progress, including enrollment, adherence, and quality of study design.
- To review reports from each subcommittee and the Executive Committee and provide recommendations.

The committee will meet annually at the American Heart Association and the American College of Cardiology national meetings. During these meetings, the committee will act on the recommendations of the DSMB, review and vote on potential protocol amendments, and review and vote on presentations and publications of the study.

4.8.2 Executive Committee

The Executive Committee is authorized by the Steering Committee to conduct the week-to-week business of the study and to lead the implementation of policies and practices approved by the Steering Committee. Executive Committee members will include the Coordinating Center principal investigator, co-principal investigator, lead statistician, and project leader, the chair and vice chair of the Steering Committees, the NHLBI investigators, and a rotating member from the regional investigator group, and a senior clinical study coordinator.

The main roles and responsibilities of the Executive Committee are:

- To resolve issues not requiring full Steering Committee input.
- To develop and prepare the agenda and recommendations for the steering committee meetings.
- To review operational aspects of the trial on an ongoing basis.
- To oversee the conduct of the study and initiate the approval process for any protocol changes needed to improve the quality of the study.
- To implement all protocol amendments approved by the Steering Committee and the DSMB.
- To propose membership of the other committees to the Steering Committee.
- To serve as a liaison between the NHLBI and the other committees.
- To present the trial results to the Steering Committee in advance of national presentations.
- To approve all manuscripts prior to submission.

4.8.3 Coordinating Committee

The Coordinating Committee will act as a liaison between the various subcommittees and the Executive Committee. It will report monthly as necessary in writing or by conference call to the Executive Committee to apprise the latter of progress and problems in the relevant areas of the study. It will consist of the Executive Committee and the chairs of the subcommittees.

4.8.4 Subcommittees

The Steering Committee will establish subcommittees to develop and monitor various aspects of the study. The subcommittee members will include regional center investigators, DCRI staff, NHLBI Project Office staff, and others as necessary. Chairs and members are nominated by members of the Steering Committee and selected by the Executive Committee. The subcommittees will develop recommendations and proposals for Steering Committee review and decision.

The following subcommittees will be established:

4.8.4.1 Endpoint Subcommittee

The Endpoint Subcommittee will be in charge of standardizing endpoint definitions and adjudicating specific endpoints for the trial.

The main roles and responsibilities of the Endpoints Subcommittee are:

- To agree on standard definitions for the endpoints of mortality and hospitalization.
- To standardize adjudication procedures for assessing these endpoints.
- To summarize above definitions and procedures in an Endpoint Manual.
- To provide an independent and blinded assessment of mode of death and hospitalizations according to the Endpoint Manual definitions and procedures.

4.8.4.2 Ancillary Studies Subcommittee

The Ancillary Studies Subcommittee will be responsible for reviewing specific proposals for substudies, except studies using genetic material. Studies using genetic material will be reviewed and approved by the Genetic Subcommittee. Ancillary and sub-study proposals involving economic or quality of life topics will be reviewed by the ancillary study subcommittee. The committee may request the EQOL committee to review proposals. The subcommittee will make recommendations to the Steering Committee regarding which studies should be pursued. Due to the need for coordination with the main study, one member of the Coordinating Center and NHLBI teams will serve on the Ancillary Study Subcommittee. Database analysis of the main trial data will be the responsibility of the publication committee.

The main roles and responsibilities of the Ancillary Studies Subcommittee are:

- To develop procedures for submission of ancillary and sub-study proposals to the subcommittee.
- To review, prioritize, and approve all ancillary and sub-study applications. Ancillary Subcommittee is to consider funding cycle for NIH and other funding organizations when evaluating proposals. In addition, it will need to evaluate the number of patients and centers required for each proposal and the commitment of participating centers in assigning priority.
- To facilitate approved ancillary and sub-study applications for funding from external sources.
- To serve as a liaison between ancillary and sub-study investigators and the Steering Committee.
- To maintain a master directory of all ancillary and substudy proposals and projects, including those reviewed by the Genetic Subcommittee.
- To review and report on the conduct of approved ancillary and sub-studies.

4.8.4.3 Quality Assurance Subcommittee

The Quality Assurance Subcommittee will be responsible for assuring that the quality of clinical trial data, particularly exercise testing, meets the standard set in the protocol and manual of

operations and will be usable for analysis. The subcommittee will include the Coordinating Center project leader and statistician. The Quality Assurance subcommittee will not be responsible for assuring the quality of the intervention, which falls under the Intervention subcommittee.

The main roles and responsibilities of the Quality Assurance Subcommittee are:

- To develop and write procedures for all measurements, including a Manual of Procedures.
- To oversee clinical site training for data collection.
- To develop and implement methods to maintain the exercise testing standards for the study.
- To review core laboratory processes on an ongoing basis.
- To regularly review the quality of data acquisition at HF-ACTION investigative sites and inform the Executive Committee of consistent variance from established guidelines at any clinical site.
- To recommend corrective action for any consistent variance from testing standards at any clinical site to the Executive Committee.

4.8.4.4 Intervention Subcommittee

The overall objective of the Intervention Subcommittee is to develop and oversee implementation of the study intervention, assuring that patients in the HF-ACTION trial receive the study intervention throughout the trial. These objectives will be discharged by site certification, monitoring, education.

The main roles and responsibilities of the Intervention Subcommittee are:

- To develop and write the operational details of implementing the study intervention, including patient education, for both intervention and usual care arms (to include the Intervention Manual of Procedures).
- To oversee clinical site training for implementation of the intervention.
- To develop and implement methods for maintaining the exercise training standards for the study.
- To regularly review the exercise training data from HF-ACTION investigative sites and inform the Executive Committee of consistent variance from established training guidelines at any clinical site.
- To recommend corrective action for any consistent variance from training standards at any clinical site to the Executive Committee.

4.8.4.5 Medical Therapy Subcommittee

The overall objective of the Medical Therapy Subcommittee is to oversee the background medical therapy (pharmacological and non-pharmacological, except patient education) that patients in the HF-ACTION trial receive throughout the trial. The primary goal is for patients enrolled in the trial to receive treatments that meet the national heart failure guidelines so that the results of the HF-ACTION study are seen as beneficial in addition to best-medical practice.

The main roles and responsibilities of the Medical Therapy Subcommittee are:

- To develop and write the operational details of implementing the background medical therapy for both intervention and usual care arms.
- To review advances in medical therapy that might necessitate modification of the standardized medical regimen during the trial and recommend adoption of changes that appear appropriate to the Steering Committee.
- To inform the Executive Committee regarding the potential need to include new pharmacological and non-pharmacological therapies for the management of HF, LV systolic dysfunction, and CAD. Final approval of these changes will be made by the Steering Committee.
- To review Coordinating Center data reflecting clinical site compliance with the standards of therapy given during the trial.
- To recommend corrective action for any consistent variance from medical therapy standards at any clinical site to the Executive Committee.

4.8.4.6 Design and Analysis Subcommittee

The overall objective of the Design and Analysis Subcommittee is to evaluate and periodically review the enrollment criteria, endpoints, and analysis plan for the study.

The main roles and responsibilities of the Design and Analysis Subcommittee are:

- To develop, evaluate, recommend changes to, and periodically review the study enrollment criteria, in coordination with the Recruitment and Retention Subcommittee.
- To develop, evaluate, and recommend changes to the study endpoints, in coordination with the Endpoint Subcommittee.
- To develop, evaluate, and recommend changes to the study analysis plan.
- To submit amendments to the Executive Committee for presentation to the Steering Committee. All amendments must be approved by the Steering Committee.
- To finalize the Endpoint Subcommittee's endpoint definitions.

4.8.4.7 Recruitment and Retention Subcommittee

The Recruitment and Retention Subcommittee will focus on meeting recruitment goals and maintaining high trial retention and exercise adherence. This subcommittee will work closely with the Intervention Subcommittee and the Adherence intervention team.

The main roles and responsibilities of the Recruitment and Retention Subcommittee are:

- To develop adherence and retention interventions for patients in the exercise training arm. The interventions will be included in the final protocol that receives Steering Committee approval.
- To develop motivational tools to promote enrollment at regional centers.
- To propose remedies to overcome barriers to the recruitment of minorities, women, and elderly subjects encountered during the trial.

- To work with regional center hub investigators to promote enrollment at hub center and aligned regional centers.
- To regularly review enrollment retention and adherence data from HF-ACTION investigative sites and inform the Executive Committee of consistent variance from established study goals and guidelines at any clinical site. The subcommittee will pay particular attention to the retention of minority, gender, and elderly subjects.
- To review submitted proposals for logistical assistance.
- To recommend corrective action for any consistent variance from enrollment, retention, and adherence goals at any clinical site to the Executive Committee.
- To work with regional centers and their satellite centers to maintain high levels of retention and adherence.
- To recommend any changes to the adherence and retention intervention based on review of trial data or new methods developed outside of the study.

4.8.4.8 Publications Subcommittee

The Publications Subcommittee will be responsible for reviewing proposals for papers made by investigators and recommending a priority listing of these proposals to the Steering Committee. The subcommittee will have the overall objective of insuring that all interested HF-ACTION trial investigators receive equal access and fairness in performing all scientific work for which they are qualified.

The main roles and responsibilities of the Publications Subcommittee are:

- To create and monitor a manuscript publication policy.
- To approve general trial press releases.
- To approve secondary database analyses of the main trial databases (not ancillary studies) and assign priority to each proposal from investigators. This includes early database analyses.
- To recommend authorship of publications and presentations.
- To review and recommend manuscripts to the Steering Committee prior to publication.
- To insure that NHLBI approval procedures are followed.

4.8.4.9 Economic and Quality of Life Subcommittee

The Economic and Quality of Life (EQOL) subcommittee will be in charge of reviewing the HF-ACTION EQOL study progress and identified issues. The subcommittee members will include the PI of the EQOL substudy. The EQOL substudy PI will provide a report to this subcommittee from the EQOL substudy executive committee.

The main roles and responsibilities of the EQOL Subcommittee are:

- To review and approve the final EQOL protocol and analysis plan.

- To regularly review EQOL data from HF-ACTION investigative sites and inform the Executive Committee of consistent variance from established study guidelines at any clinical site.
- To recommend corrective action for any consistent variance from EQOL goals at any clinical site to the Executive Committee.
- To be available at the request of the Ancillary Study Subcommittee to review ancillary studies and substudies involving economics and/or quality of life for the HF-ACTION study.

4.8.4.10 Genetic Subcommittee

The Genetic Subcommittee will be in charge of developing HF-ACTION genetic bank, identifying issues with collection, storage, and distribution of genetic material, and reviewing proposals for use of the genetic material for ancillary studies. The subcommittee members will be responsible for developing an HF-ACTION genetic study manual that includes all procedures.

The main roles and responsibilities of the Genetic Subcommittee are:

- To develop genetic substudy protocol that includes procedures for collection, storage, and distribution of genetic material.
- To develop the consent form for collection of genetic material.
- To develop procedures for submission of genetic ancillary and sub-study proposals to the subcommittee.
- To review, prioritize, and approve all genetic ancillary and sub-study applications. The committee will be responsible for informing the Ancillary Study Subcommittee of all applications under review and approved.
- To facilitate approved genetic ancillary and sub-study applications for funding from external sources.
- To serve as a liaison between genetic ancillary and sub-study investigators and the Steering Committee.
- To review and report on the conduct of approved genetic ancillary studies.

4.8.4.11 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be composed of individuals independent of the NHLBI, the study management organizations, and the investigators. The NHLBI Director approves the membership and the DSMB is advisory to the NHLBI. A nationally recognized member of the cardiovascular community with experience in oversight of cardiovascular clinical trials will chair the DSMB, comprised of experts in relevant biomedical fields including cardiology, cardiac rehabilitation, exercise physiology, quality of life and economics, biostatistics, and bioethics.

The main roles and responsibilities of the DSMB are:

- To initially review the study protocol and commission a specific regular process for evaluation of HF-ACTION trial data.

- To approve a monitoring plan for potential study discontinuation.
- To review data at least annually during the study.
- To recommend approval of protocol modifications, if warranted.
- To advise the NHLBI directly regarding recommendations for trial modification or early trial cessation.

The efficacy and safety analyses will be performed semi-blinded (i.e., treatments A and B) by the Statistical PI at the Coordinating Center. The Coordinating Center statistician will possess a copy of the treatment codes for unblinding purposes if deemed necessary by the DSMB. **The NHLBI may amend the study or stop it early, should this be deemed necessary based upon DSMB recommendation.** The chairman of the DSMB will discuss the recommendations of the DSMB with the NHLBI Executive Secretary (an NHLBI staff scientist appointment by the NHLBI), who will inform the Executive Committee. Any final decision to discontinue the HF-ACTION trial will be made by the NHLBI.

The DSMB will meet either in person or by teleconference during the planning phase and in the last half of the first year of enrollment, and at least annually for the duration of the study. The DSMB Executive Secretary will convey the DSMB recommendations to the Executive Committee after each DSMB meeting.

5 Data Management

5.1 Data Collection

5.1.1 Data Forms

Data collection forms used in this study are described in the manual of operations with summaries of their content and purpose. The front page of each form will identify the date and version of the form, and provide brief summary instructions for data collection. The subject's study number and initials will be included on every page of each form. The study subject number will reflect both a site specific code and the subject's sequence number for that site. **The baseline form and the final visit form will require the signature of the site's principal investigator with the date of completion. Satellite investigator signature is not sufficient.**

5.1.2 Manual of Operations

The manual of operations will provide more detail regarding study objectives, scope, design, and operational policies and procedures than the clinical protocol. The manual will include detailed instructions for completing study forms, including baseline health status assessments, and instructions for handling and transferring data forms to the Coordinating Center. The follow-up schedule and description of follow-up data and endpoint data will also be covered in the manual.

The operations manual will also describe the data management system, the flow of data forms, quality control measures, data queries, who and where to call for assistance, and other operational procedures employed at the Coordinating Center.

The manual will also include a specific section on the appropriate procedures for echocardiography, exercise testing and exercise training.

5.1.3 HF-ACTION Trial Website

The HF-ACTION trial website will provide printable updated versions of the protocol and manual of operations. Also included on the website will be a complete directory of participating investigators and study coordinators at all clinical sites. The website will provide a rich source of current information to investigators with secure access.

A separate free website that complies with federal regulation will be available to the public. It will include a general description of the trial, publications from the trial and contact information for participating centers if a person is interested in participating in the study.

5.2 Database Management and Quality Control

Database management and quality control for this study are the responsibility of the Duke Clinical Research Institute, Durham, NC, USA. Structured data elements from the CRFs will be entered into the HF-ACTION database and reviewed using double data entry for verification. **Selected events will be coded using MedDRA.** Information entered into the database will be systematically checked by data management staff, using error messages generated from validation programs and database listings. Obvious errors will be corrected by data management center personnel. Other errors, omissions, or questions will be entered on data query forms, which will be returned to the investigational site for resolution. After the investigator response is received at the data management center, the resolutions will be entered into the database. A copy of the signed data query form will be kept with the CRFs. Quality control audits of all key safety and efficacy data in the database will be made at designated times during the study. All clinical site patient-related reimbursement will be prompted by completion of data forms with appropriate responses to all data elements.

6 Statistical Plan

6.1 Sample Size Determination—Overview

Several design factors and research objectives have been considered in developing appropriate sample size estimates for this study. First, patient enrollment has been determined so there would be sufficient clinical endpoints to provide a high degree of confidence (high power) of detecting clinically important treatment differences in the primary endpoint of all-cause mortality or hospitalization. Second, the sample size requirements for detecting meaningful treatment differences in important secondary endpoints have also been considered. Third, we considered it important for the overall sample to be large enough to permit a prudent examination of selected subgroups of patients where exercise training might be particularly advantageous, or where the question of a treatment benefit from exercise training is particularly relevant. Important pre-specified subgroups of interest in this study include ischemic vs. non-ischemic cardiomyopathy, the elderly (age ≥ 70 years), and female patients. Finally, the sample size has been determined to provide a reasonable level of confidence of detecting therapeutic effects even in the event that current projections of event rates or treatment differences or compliance to therapy prove to be optimistic.

6.1.1 Sample Size and Power Considerations

The event rate for the primary endpoint is based on a number of trials that have enrolled similar NYHA classes of heart failure patients. The PRAISE trial enrolled primarily NYHA class III and IV patients, who had an event rate for mortality or cardiovascular morbidity of 42% over a median 13.8 months (Packer 1996). Cardiovascular morbidity was defined as a 24-hour admission for any of the following: acute pulmonary edema, cardiogenic shock, acute myocardial infarction, or ventricular arrhythmia causing hemodynamic compromise. Another estimate of the expected rate of mortality or cardiovascular morbidity can be found in the SOLVD study (The SOLVD Investigators 1991). At 36 months, the median follow-up time for the trial, the rate of mortality or admission for heart failure for the enalapril cohort was 43%. Of note, admission was defined as being due to heart failure if the discharge code for the primary diagnosis was heart failure. In V-HeFT II, the sum of the rates of mortality and hospitalization for the treatment of HF was 51.7% over a 2.5-year median follow-up period, but the authors did not provide the rate of death or hospitalization as a combined endpoint (Cohn 1991). The ATLAS trial recently showed a rate for all-cause mortality or morbidity (admission) of 79.5% over about 3 years in patients taking high-dose ACE inhibitors (Packer 1999).

Since the HF-ACTION protocol strongly recommends beta-blocker use, we have incorporated the results of two beta blocker trials (MERIT and CIBIS II) into our sample size assumptions (CIBIS-II Investigators and Committees 1999, Merit-HF Study Group 1999). The patients enrolled in HF-ACTION will be predominantly NYHA class II and III, similar to the MERIT-HF population. Although CIBIS II claimed to have enrolled predominantly class III patients, the mortality rate suggests the inclusion of a substantial number of class II patients. The mortality rate in MERIT for the treatment arm was 7.2% with mean follow-up of 1 year. The annual mortality rate for the control arm in MERIT was 11%. The annual mortality rate in CIBIS II for the treatment arm was 8.8%. The hospitalization rate for CIBIS was 33% over a mean follow-up of 1.3 years. Assuming hospitalizations were evenly distributed over the follow-up period, the annual hospitalization rate would be 25.4%. The estimated control annual hospitalization rate in CIBIS II is 30.0%. Unfortunately, there has been no hospitalization rates reported for MERIT.

We have used the mortality rates from both CIBIS II and MERIT and the hospitalization rates reported in CIBIS II, with a slight adjustment downward to account for the likely higher percentage of class II patients. The estimated annual event rate projected for the composite primary endpoint in HF-ACTION, all-cause mortality and all-cause hospitalization, is 30% in the standard care group.

In the absence of detailed life-table follow-up data on patients similar to those who will be enrolled in this trial, the following approach was used for calculating sample size. For a specified baseline outcome rate in the standard care (control) group (e.g., an overall event rate at 1 year of 30%), event rates at other time points during follow-up were estimated by assuming an exponential survival distribution (for example, if the event rate at one year was 30%, the rate at 2 years would be 51%). We then postulated that in the intervention (exercise training) arm, there would be a specific reduction of the control rate (e.g., a 20% reduction at 2 years). Event rates for the intervention group at various time points during follow-up were also estimated assuming an exponential distribution. Since the two groups will be compared (with respect to the length of time that patients are event-free) using the log-rank test (Kalbfleisch 1980), or equivalently, the Cox proportional hazards model (Cox 1972, Breslow 1974, Kalbfleisch 1980), the one-tailed formula of

Schoenfeld (Schoenfeld 1983) was modified to calculate sample size requirements based on the use of two-tailed tests.

Schoenfeld's method is based on first calculating the total number of events required in the combined treatment groups. By estimating the proportion of patients who will have an event by the end of the study, the total number of patients required for the trial can be determined. The necessary number of events depends on the level of power desired, the significance level (which we have chosen to be $\alpha=0.05$), and the ratio of the hazard function for patients receiving exercise training to the hazard function for patients in the control arm. Using exponential distributions to approximate survival in the two treatment groups (as described above), the hazard functions are particularly simple (constant over time), and thus an estimate of the hazard ratio is easily obtained. For example, if the primary event rate at 2 years was 50% in the control arm, and if this rate was reduced by 20% in the intervention arm (to 40.0%), characterizing survival over time in the two groups using exponential distributions produces an intervention versus control hazard ratio of 0.737. Once the hazard ratio, the level of significance, the desired power, and the proportion of patients allocated to each treatment are specified, equation 1 in Schoenfeld (1983) can be used to calculate the required number of events. If we specify $\alpha=0.05$, power=0.90, equal allocation of patients to treatment groups, and use the hazard ratio of 0.737 from the example above, the required number of events for a two-group comparison is 452.

The proportion of patients who will experience an event during the patient follow-up period can be estimated using the method of Schoenfeld (1983). If we designate $S_C(t)$ and $S_I(t)$ to represent survival at time t in the control and intervention groups, respectively, and if we assume patient accrual will occur over a period of 3 years with follow-up extending 1 more year after enrollment is completed, the proportion of patients who will have an event by the end of the follow-up period is estimated by the following expression:

$$\begin{aligned} & 1/2 \{1-1/6[S_C(1.0) + 4 S_C(2.5) + S_C(4.0)]\} \\ + & 1/2 \{1-1/6[S_I(1.0) + 4 S_I(2.5) + S_I(4.0)]\}. \end{aligned}$$

With the combination of parameters used in the example above (90% power for detecting a 20% reduction assuming a two-year control rate of 50%), the value of this expression (and hence the expected proportion of events) is 0.510. The total number of patients required for a two-arm study would thus be $452/0.510=888$, or 444 in each group.

If either the magnitude of the treatment benefit or the control group event rate is smaller, the sample size requirements are increased. For example, if the event rate at 2 years in the conventionally treated (control) arm is 50% or higher, 794 patients *per arm* would be required to provide a high level of power (≥ 0.90) for detecting a 15% improvement (as calculated above). If the event rate at 2 years in the control patients was only 35%, approximately 1400 patients per arm would be required to provide 90% power for detecting a 15% reduction.

A key issue in determining an adequate sample size for this trial is the magnitude of the reduction in events we could realistically expect to achieve in the intervention arm compared to the control arm. It is reasonable to postulate that with full compliance to the intervention, an effective treatment in this population could reduce the rate of events by 20%. A reduction of this magnitude would be highly significant from a clinical and public health standpoint, given the large population of patients in this country and throughout the world who suffer from moderately severe heart failure. Compared to the conventionally treated patients, we hypothesize, therefore, that in the

intervention arm, the event rate at 2 years will be reduced by approximately 20% *if the patients actually comply with the exercise intervention*. Despite the concerted efforts that will be undertaken to maintain a high level of patient compliance, some patients in the intervention arm will discontinue exercise training (dropouts), and some patients in the control arm will choose to initiate exercise training (crossovers). To compensate for the effects that dropouts and crossovers will have on the event rates, we have made the following reasonable yet conservative assumptions.

Up to 25-35% of patients in the intervention arm may discontinue the exercise training (therapy dropouts) within the first year after enrollment. Thereafter the dropout rate is assumed to be 10-15% per year. Some benefit of the intervention is expected, however, (although it may be small) for patients who drop out and thus have a shortened period of exercise training. Up to 5% per year of the control arm may initiate exercise training (crossover), which may slightly reduce the event rate in the control arm.

In prior research with elderly patients, dropout rates were <5% at 4 months; <10% at 8 months, and 16% at 14 months (Blumenthal 1991a). Admittedly, the HF-ACTION cohort is likely at increased risk for dropout; however, in clinical studies with hypertensive patients (Blumenthal 1991b) and in those with a prior infarction (Blumenthal 1988), the drop-out rates were <15%. This level of dropout does not approach the 50% rate reported in many studies. In a series of studies with overweight hypertensive patients participating in a 4-month clinical diet/exercise program at Duke's Center for Living, the drop-out rates were 35%, but these patients did not receive support and instruction in compliance-enhancing strategies as part of the study. The HF-ACTION investigators believe that the dropout rate for the HF-ACTION trial for the exercise-training arm will be about 25% in the first year and 10% annually thereafter. These assumptions concerning dropout are supported by the study performed by Kavanagh et al. in which heart failure patients participated in supervised training for 16 weeks and home exercise supplemented by supervised training sessions, very similar to the HF-ACTION study design. Patients attended 95% of the supervised training sessions in the first 16 weeks, 86% of the maintenance supervised sessions, and 78% of the home exercise sessions (Kavanagh 1996). The reason for the higher first-year rate is the evidence that a higher percentage of dropouts occur within the first 12 months in a 40-month study (Carmody 1980).

Adherence rates have been similar for patients with coronary artery disease after a myocardial infarction. In a report of initially supervised, then independent training, 82% of the patients repeated exercise testing at 1 year (Froelicher 1984). In a 1-year program, 74 patients attended 78% of the exercise sessions (Myers 1984). Similarly, 78% of 81 post-infarction patients maintained their physical activity over 4.5 years of follow-up (Marra 1985). Finally, of the 323 patients randomized to the exercise-training program of the National Exercise and Heart Disease Project, only 23% had stopped exercising after 2 years (Shaw 1981).

Despite the expected dropout described above, benefit will still be expected among exercise training patients who are randomized to exercise training, but who discontinue the intervention. As described in the background section (Section 3), exercise training is able to improve exercise duration, peak VO₂, and RR variability. In addition, norepinephrine levels were reduced by 16% after 8 weeks of training (Coats 1992). These benefits occurred in a relatively short duration ranging from 8 to 24 weeks. The results from V-HeFT I and II showed comparable results to the exercise training studies. Patients taking hydralazine and isosorbide dinitrate combination had significant improvements of their peak VO₂ by 2 months (Ziesche 1993). Patients taking enalapril in V-HeFT II had a small but significant improvement in their peak VO₂ by 6 months, but this

effect was not sustained. Enalapril has been shown to increase exercise duration significantly over placebo, over 20% in 3 studies (Joy 1987, Enalapril Congestive Heart Failure Investigators 1987, Jennings 1984). These changes were within 3 months of initiating therapy. Patients taking carvedilol have also shown significant improvements in exercise duration at submaximal intensity (239 ± 170 to 590 ± 353 sec, $p < 0.001$ versus both placebo and baseline duration) after 4 months of therapy (Metra 1994). The observed changes in exercise time from these pharmacologic interventions occurred over relatively short time periods.

As with the exercise test parameters, norepinephrine level changes are similar between exercise training studies and drug trials. In pharmaceutical studies, neurohormones have been shown to improve as early as 6 weeks from baseline. Analyses from the CONSENSUS study have shown that significant reductions in neurohormones including angiotensin II, aldosterone, and norepinephrine occurred at 6 weeks for patients treated with enalapril. A significant mortality benefit was also observed in this study for the enalapril treated group, with a mean 6 month follow-up (Swedberg 1990). Small studies of captopril in patients with heart failure have also demonstrated favorable responses on plasma norepinephrine levels, which began with acute administration and persisted during 8 weeks of follow-up (Cody 1982). Captopril has previously demonstrated a survival benefit in the SAVE trial, which persisted during 4 years of follow-up (Pfeffer 1992). Beta-blockers are also known to decrease neurohormones. Carvedilol has been shown to significantly decrease plasma norepinephrine after 4 months of therapy (Gilbert 1996).

ACE inhibitors and beta-blockers impact mortality and hospitalization as early as 6 months. In the CONSENSUS Trial (The CONSENSUS Trial Study Group 1987), NYHA class IV heart failure patients taking enalapril had a 41% reduction in mortality rate by 6 months, although the reduction at the end of 12 months was 28%. In SOLVD, predominantly NYHA class II and III heart failure patients taking enalapril had a 30% reduction in mortality at 6 months, with an even greater reduction in the combined endpoint of death or HF hospitalization. Similar early reductions in mortality were seen with hydralazine isosorbide dinitrate (Cohn 1986). During a mean follow up of 5.4 months, carvedilol has also been shown to significantly reduce mortality in the U.S. Carvedilol trials (Packer 1996).

Given that exercise training causes similar changes in exercise test parameters and neurohormone levels as specific drugs, we do not feel it is unreasonable to expect some benefit after a short duration of exercise training. We also recognize that the use of surrogate endpoints is questionable and is one of the arguments for funding this trial. Therefore, we have been very conservative in our estimate of the effect of exercise training for patients who discontinue exercising. Approximately half of the dropouts will occur by 6 months due to an expected higher dropout rate early in the study (Carmody 1980). Thus, we have estimated that dropouts will on average obtain a 5% reduction in the primary endpoint of all-cause mortality and all-cause hospitalization. A second means to argue for the 5% event rate reduction for dropouts is to amortize the expected effect of training over 24 months, a 20% reduction, over the two years. Since half of the dropouts will occur by 6 months of training, the average reduction in event rate that patients who dropout will receive is 5%, and this is assuming that the benefit of exercise training stops at the time of exercise training discontinuation instead of slowly decreasing.

With the dropout rates postulated above (25-35% within the first year and 10-15% annually thereafter), there will be approximately 40% to as high as 57.5% of patients who discontinue the intervention during the median follow-up period of 2.5 years. Assuming a 2-year event rate in the control arm of 50% (after accounting for the control patients who will initiate an exercise

program), a 20% reduction in the intervention arm in patients who maintain exercise training, and only a 5% reduction in the intervention group patients who discontinue the exercise intervention during follow-up, the projected event rate in the intervention arm would be approximately 43.9%, which translates to a 12.2% reduction, assuming 25% dropout the first year and 10% yearly thereafter. If the dropout rate is 35% during the first year and 15% annually thereafter, the projected event rate in the intervention arm will be approximately 45.2%, which corresponds to a 9.5% reduction. Similar calculations with slightly different control rates suggest that the study needs to have sufficient patients to provide adequate power for detecting a 9.5-12% reduction in the primary event rate when one takes into account dropouts and crossovers.

We note that the rate of cardiac transplantation expected over the lifetime of the trial is no greater than 5%. With the definition of our primary endpoint, we will capture these events, as most patients are hospitalized for heart failure prior to transplantation. In the analysis of mortality, the power may slightly decrease as a result of better survival expected in patients undergoing transplantation. However, this is expected to have a very minor impact on the results of this trial. The mortality data will be counted based on the ultimate survival status of the patient.

To achieve a robust sample size and provide an adequate number of patients in the trial, even under conservative assumptions about the control group event rate, the magnitude of the treatment benefit, and the dropout rate, we propose to enroll 3,000 patients. Below is a summary of what this number of patients will provide the study.

Primary endpoint (all-cause mortality or hospitalization):

1. Power >90% for detecting a treatment effect amounting to a 20% reduction in event rate if patients were compliant with the intervention based on the assumption of an annual control group event rate of 30%. If we allow for 30% non-adherence from the intervention during the first year and 12.5% annually thereafter, and for 5% cross-over to exercise per year for control patients (with crossover patients conservatively assumed to have their event rate reduced by 20%), the sample size of 3,000 patients will provide >90% power for detecting an overall 11% event-rate reduction.
2. Power >80% if we allow for 35% non-adherence during the first year and 15% annually thereafter, i.e., the power is >80% for detecting an overall 9.5% event-rate reduction. *Thus, we have excellent power for detecting the benefit expected after factoring in the effects of relatively high levels of dropouts and crossovers.*
3. Power >80% for detecting a treatment effect amounting to as little as a 16% reduction among treatment compliers, allowing for 25% non-adherence during the first year and 10% thereafter. *Thus we have good power even with a more conservative estimate of the treatment benefit.*
4. Power >80% for detecting a 20% reduction if the annual control group event rate is only 25% (rather than 30%), allowing for 30% non-adherence during the first year and 12.5% thereafter. *Thus we have good power with a more conservative estimate of the control-group event rate.*
5. Power >80% for detecting a 20% improvement in any subgroup consisting of 60% of the patients (allowing for 25% non-adherence during the first year and 10% annually thereafter), and for detecting a reduction in event rate by 25% in any subgroup consisting of at least 40% of the patients if the annual control group event rate is 30% or higher. *Thus,*

we even have good power for detecting benefit in selected subgroups if the treatment benefit in those subgroups is moderate to large.

Secondary endpoints:

6. Cardiovascular mortality or cardiovascular hospitalization: Power >80% for detecting a 25% improvement if the control group annual event rate is 20% or higher.
7. Mortality (all cause): Power >80% for detecting a 30% improvement if the control group annual death rate is 10% or higher.
8. Hospitalization (all cause): Similar to the mortality endpoint, power >80% for detecting a 30% reduction if the control group annual event rate is 10% or higher.
9. Hospitalization due to heart failure: Power >80% for detecting a 33% reduction if the control group annual event rate is 7.5% or higher.
10. Quality of Life Endpoints: The study will have >90% power for detecting outcome differences in the Kansas City Cardiomyopathy Questionnaire scale and other quality of life scales to be assessed, that are relevant and well within the range of differences observed in patients with acute or chronic heart disease.
11. Functional and Physiologic Endpoints: The study will have excellent power (>90%) for detecting clinically relevant treatment differences in the largely continuous measures consisting of exercise test parameters, distance covered in the 6-minute walk test, peak oxygen consumption, ventilatory threshold, and exercise time to an RER equal to 1.0.
12. Exercise related complications: The study will have >90% power for detecting clinically relevant exercise-related complications (Section 4.7.3.2).

6.1.2 Sample Size—Summary

In summary, 3000 patients will provide excellent power for detecting clinically relevant and realistic treatment benefits in the primary and secondary endpoints. Furthermore, this number is robust (maintains good power) even under conservative assumptions about a) the usual care group event rate, b) the magnitude of the benefit from the intervention, and c) intervention non-adherence. Therefore 3000 patients will be the target enrollment for HF-ACTION. One-half of the patients will be randomized to the arm receiving conventional therapy, and one-half will be allocated to the arm receiving exercise training.

6.2 Statistical Analysis

Statistical analysis will be performed at the Data Coordinating Center at Duke University. Although the methodological approaches and operational details of the data analysis will be coordinated by the study biostatisticians, the major analyses of the study data will be highly collaborative involving both statisticians and physicians to ensure appropriate interpretation of the data. All major treatment comparisons between the randomized groups will be performed according to the principle of “intention-to-treat”; that is, subjects will be analyzed (and endpoints attributed) according to the treatment arm to which patients are randomized, regardless of subsequent crossover or non-adherence. Statistical comparisons will be performed using two-sided significance tests. Additional perspective regarding the interpretation of the data will be provided through extensive use of confidence intervals and graphical displays.

6.2.1 Background and Demographic Characteristics

Baseline demographic and clinical variables, including risk factors, comorbidity, relevant descriptors from the history and physical examination, left ventricular function, etiology of the cardiomyopathy, past clinical events, HF functional class and baseline test results (e.g., six minute walk distance), will be summarized for each randomized arm of the study. 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.

Statistical comparisons of treatment groups with respect to baseline characteristics will be limited to selected variables and disease factors known to influence prognosis. These variables will include age, sex, race, ischemic vs. non-ischemic cardiomyopathy, previous myocardial infarction, prior revascularization, descriptors of comorbidity, HF functional class, and left ventricular function (ejection fraction). For comparisons of the treatment groups with respect to continuous baseline variables, emphasis will be given to nonparametric procedures such as the Wilcoxon rank-sum test (Lehmann 1975). Group comparisons with respect to discrete baseline variables will use the conventional chi-square test.

6.2.2 Efficacy Evaluation

Of principal interest will be the comparison of the exercise intervention arm versus the usual care arm with respect to the primary endpoint of all-cause mortality or hospitalization. The log-rank test (Kalbfleisch 1980) (sometimes called the Mantel-Haenszel test for survival data [Mantel 1966]), which is a special case of the Cox proportional hazards regression model (Cox 1972, Breslow 1974, Kalbfleisch 1980), will be the primary analytic tool for assessing outcome differences between the two treatment arms. The log-rank test (and the Cox model) can accommodate varying lengths of patient follow-up, and it uses information for each patient on the time from study entry until the occurrence of the endpoint, rather than simply enumerating the number of patients who experience an event. It also accommodates “censored” survival times, which arise because many patients will be event-free when follow-up in the study is terminated, and the length of time they will survive without an event is known only to be greater than the length of their current follow-up. The log-rank test is a well established approach for providing an overall comparison of the entire “survival” curves.

Using this procedure, the analysis strategy will be to first perform a treatment comparison that is adjusted only for the etiology of the heart failure (ischemic vs. non-ischemic). This is the factor that will be used in stratifying the randomization (based on previous studies that have shown that etiology is important for prognosis (Bart 1997) and for response to therapies (Packer 1996, CIBIS Investigators and Committees 1994, Singh 1995, The Digitalis Investigation Group 1997). This comparison will constitute the primary analysis to assess treatment effects. To supplement this analysis, the Cox model will be used to test for homogeneity of the treatment effects across the two different cardiomyopathy etiologies (ischemic vs. non-ischemic). If a significant interaction is present between treatment and type of cardiomyopathy, treatment comparisons will be performed separately in the two strata. In addition, supplementary analysis involving other covariate adjustment will be used with the Cox model. Such adjustment will be limited to a relatively small, prospectively-defined set of patient characteristics that are known a priori to have a strong prognostic relationship with the primary endpoint. This adjustment will serve as a prelude to further examination of differential treatment effects. The adjustment variables will include age,

sex, race, history of myocardial infarction, previous revascularization, ischemic cardiomyopathy vs. non-ischemic dilated cardiomyopathy, NYHA HF class, ejection fraction, and baseline use of beta-blocker and ACE inhibitor therapy. Cox model analyses may also be performed using study site as a stratification factor. If an imbalance between treatments in the use of beta blocker therapy develops during follow-up, an analysis that seeks to account or adjust for this factor will be performed using a time-dependent covariate with the Cox model. Kaplan-Meier survival estimates (Kaplan 1958) based on the primary endpoint (survival free from hospitalization) will be calculated for each treatment group to display the outcome results graphically.

If the data provide evidence of an overall difference in outcome between treatment groups, we will examine whether the therapeutic effect is similar for all patients, or whether it varies according to specific patient characteristics. In particular, we will focus on whether the relative therapeutic benefit differs according to patient age, sex, race, heart failure class, and heart failure etiology. These issues will be addressed formally with the Cox model by testing for interactions between treatment and the specific baseline variables.

Although the analysis will include an examination for treatment interactions as indicated above, treatment comparisons with respect to the primary endpoint will be performed within a few pre-specified subgroups of interest, including the more elderly patients (age >70 years), female patients and, as mentioned above, the subgroups characterized by an ischemic cardiomyopathy and by a non-ischemic cardiomyopathy. These comparisons will be carefully interpreted in conjunction with the formal interaction tests. Treatment effects for the primary endpoint as characterized by the hazard ratio (with 95% confidence intervals) will be calculated and displayed for these prospectively defined subgroups as well as for the overall study population.

6.2.2.1 Supplementary Analysis of the Primary Endpoint

In addition to the efficacy analyses outlined in Section 6.2.2 for the primary endpoint, supplementary analyses will be performed that more directly address the issue of compliance with the exercise intervention. To account for the pattern of dropouts or non-compliance with the intervention and extend the treatment evaluation beyond the important intention-to-treat analyses, we will incorporate compliance as collected by adherence measurements outlined in section 4.5.3. The analysis will use approaches such as those by Efron and Feldman (1991) in which compliance was considered as an explanatory variable. This is an area of on-going statistical research, and new developments or approaches that emerge will be incorporated into these supplementary analyses. Simple observational treatment comparisons that include only patients who complied with specified levels of the exercise protocol will be examined as supportive information, recognizing that such comparisons must be interpreted cautiously.

To supplement the conventional significance testing and confidence interval approaches that will comprise the primary analyses for this trial, we will provide additional perspective on the assessment of treatment effects using established Bayesian approaches to the analysis of clinical trial data. The application of Bayesian methods to clinical trials has recently received considerable attention in the statistical and clinical trials literature. In part, its appeal stems from the fact that what consumers of clinical trial results often want to know is the likelihood (probability) that the treatment is actually beneficial, or the likelihood that the treatment has a clinically important benefit. Such probability assessments are directly obtainable from a Bayesian analysis. Spiegelhalter et al. (1994) demonstrated how one can derive clinically useful information such as an estimate of the probability that the hazard ratio (exercise training: conventional therapy) is less

than some specified value (e.g., 0.90) and an estimate of, for example, the probability that exercise training is “clinically equivalent” to standard therapy, i.e., that the hazard ratio is within some interval close to 1.0 (such as 0.90 to 1.10). We will supplement the primary statistical presentations discussed above by computing Bayesian probabilities that exercise training is beneficial and that it has a clinically important benefit. For these computations, a flat (non-informative) prior distribution for the intervention: usual care (control) hazard ratio will be assumed. We will use readily available S-Plus functions for these calculations, or the Cambridge group’s BUGS program (Bayesian Inference Using Gibbs Sampling [Thomas 1992]) to derive a posterior distribution from a full Bayesian analysis.

6.2.2.2 Analysis of Secondary Endpoints

Secondary endpoints that will be evaluated in this trial are (1) the composite of cardiovascular mortality and cardiovascular hospitalization, (2) the composite of cardiovascular mortality and heart failure hospitalization, (3) all-cause mortality, (4) cardiovascular mortality, (5) all-cause hospitalization, (6) cardiovascular hospitalization, (7) heart failure hospitalization, (8) total myocardial infarctions, (9) total worsening heart failure events, (10) the composite of all-cause mortality and all-cause hospitalization and emergency room visit and urgent clinic visit for heart failure exacerbation, (11) physiologic endpoints, (12) cost, and (13) quality of life. Data analyses for each of these endpoints are discussed below.

6.2.2.3 Analysis of Secondary Endpoints 1, 2, 3, 4, and 10

For comparing treatments with respect to these secondary endpoints, the analyses will proceed similarly to the approach outlined for the primary endpoint, using time from enrollment until either the first occurrence of the endpoint or censoring as the response variable, and assessing treatment differences using the log-rank test and the Cox proportional hazards model. Kaplan-Meier survival curves will be computed to graphically display the survival experience of the two treatment groups as a function of time from randomization.

6.2.2.4 Analysis of Secondary Endpoints 5-9

The approach for these nonfatal secondary endpoints involves several related yet different analyses to comprehensively assess and fully characterize differences among the treatment arms with respect to these outcomes.

One characterization will be in terms of the time from randomization until patients experience the first occurrence of each individual endpoint. The methodology for analyzing censored failure-time data outlined previously for the primary endpoint will thus be applied to compare treatment groups with respect to each of these outcomes. We point out that these analyses must be interpreted cautiously, however, because nonfatal events may appear to occur with a lower incidence in one treatment group simply because that arm had a higher death rate. Obviously, after patients die, they can no longer experience one of these nonfatal outcomes. As an aid in interpreting the analysis of each endpoint alone, failure-time analyses will also be performed using a composite endpoint consisting of death in conjunction with each individual nonfatal outcome.

Another approach for analyzing these endpoints will take advantage of the fact that, when these nonfatal endpoints are individually considered as part of a composite endpoint with death, the two components of the composite endpoint (death and the nonfatal outcome) have a natural rank-ordering in terms of their severity. The treatments can thus be compared with an approach that not only uses the time until the first occurrence of one of these component outcomes, but also factors in the severity of the outcome. The approach we will employ, developed by Berridge and Whitehead (Berridge 1991), combines the Cox proportional hazards model in conjunction with an ordinal severity of event model to potentially increase power for the treatment comparisons. The severity of event portion is a continuation ratio ordinal logistic model. An extended hazard function is defined by multiplying the regular Cox hazard function by the probability of the event being of severity j from the ordinal model, where j references the various severity categories. In this analysis, death will obviously be considered as the most severe event, and the nonfatal outcome as least severe. Within this framework, one can test whether the exercise intervention prolongs the time to the first occurrence of either of these events, whether the intervention decreases the severity of the first event that occurs, or (with two degrees of freedom) whether it has either effect.

Finally, since some patients may experience one of these types of nonfatal events multiple times, a comprehensive comparison of the treatment arms with respect to these outcomes should take into account the longitudinal pattern in the repeated occurrences of such events. In clinical situations where there may be multiple events per subject, it is desirable to be able to accommodate those multiple events using time-to-event methods such as the proportional hazards model which explicitly allow for varying lengths of patient follow-up and appropriately handle censored observations. A major issue in extending proportional hazards regression models to this situation, however, is intra-subject correlation (i.e., where multiple events occur within the same patient, those events will be correlated). Fortunately, there is active, ongoing methodological research on the application of survival models to this situation (Pepe 1993, Wei 1989, Lee 1992, Therneau 1997). To provide a more comprehensive analysis of these nonfatal endpoints, we will use the proportional hazards model that can accommodate multiple events per patient. The approach makes use of cluster modifications of so-called *sandwich* estimates of the variance-covariance matrix of the regression coefficients, thus providing standard errors of the regression coefficients that take into account the correlations among multiple event times within a given patient (Wei 1989, Lee 1992, Therneau 1997). Specialized software functions for performing such analyses are available in S-PLUS (Therneau 1997).

Because of the problems already mentioned in analyzing nonfatal events alone, we will use the multiple-event methodology outlined above, which allows multiple events per patient of the same type (e.g., multiple hospitalizations), and accommodates events of different types. We will model both death and the multiple episodes of these nonfatal events using multiple-events Cox model analysis (Wei 1989, Lee 1992, Therneau 1997). By synthesizing the results from these different approaches (that is, by considering a nonfatal event such as hospitalization in terms of a single event per patient, in terms of multiple events per patient, and hospitalization combined with death), we will be able to provide a comprehensive assessment of treatment differences with respect to each nonfatal endpoint and, as part of the analyses, identify and assess other clinical factors that are associated with these important secondary outcomes.

6.2.2.5 Analysis of Physiologic Endpoints

The major physiologic endpoints of interest include changes from baseline in exercise test parameters and the six-minute walk. For continuous measures such as exercise test duration and distance walked during a six-minute walk test, treatment arms will be compared with respect to the change from baseline to the value achieved at selected, pre-specified follow-up points using the nonparametric Wilcoxon rank-sum test. The data for these comparisons obviously depend on the follow-up tests being performed. While every effort will be made to obtain complete data, a limitation of these comparisons is that patients can be included only if the tests are performed. To accommodate patients whose test data are not available because they died, parallel analyses will be performed where the dead patients are included by assigning them the lowest rank in the rank-based Wilcoxon analysis (i.e., they are given the worst outcome).

Where there are patients with missing values for other reasons (e.g., missed follow-up, patient incapacity, or refusal), analyses will be performed using the complete data cases. Parallel, comparative analyses will also be performed, however, where the missing measures are imputed using multiple imputation methods. A concerted effort will be made, however, to minimize the amount of missing data.

To extend the results of the HF ACTION trial to the practicing clinician, the investigators will define and describe functional and physiologic parameters that are clinically significant. For the purpose of this trial, we will a 15% increase in 6 minute walk, 10% increase in peak VO₂, 10% change in the VE/VCO₂ slope and 5 beat decrease in the heart rate at the end of the exercise test's second stage. These clinically meaningful parameters will allow the application of the findings of HF ACTION to the patient population with heart failure.

6.2.2.6 Analysis of Quality of Life and Cost of Care Endpoints

The important quality of life and cost of care endpoints for the quality of life and economic analyses and the analysis plans for these outcomes are addressed in detail in the EQOL Substudy manual. These endpoints include health status measures from the Medical Outcomes Study 36 Item Short Form (SF-36); quality of life as assessed by the disease-specific Kansas City Cardiomyopathy Questionnaire; a measure of depressive symptoms based on the Beck Depression index scale; and utilities assessed by patient interview using the EuroQoL.

The HF ACTION trial's sample size provides high precision for the estimates of treatment group differences in patient-reported outcomes. Statistical significance in such cases denotes non-zero differences, but not necessarily clinically meaningful ones. Therefore, we purposely selected measures that have published, validated definitions of a clinically meaningful change. Our primary outcome measure is the Kansas City Cardiomyopathy Questionnaire, for which a 5-point difference is considered clinically meaningful. Statistically significant differences below the clinically meaningful difference will be explicitly discussed in publications as not reflecting a clinical effect of treatment.

6.2.2.7 Multiple Comparisons

As a final note to the discussion of the major analyses that will be performed in this trial, we acknowledge the fact that with the primary endpoint and the various secondary endpoints that have been outlined, there is a multiplicity of analyses to be performed, which leads to 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. To attempt to adjust for the effects of the repeated significance testing that will occur as part of the interim monitoring, plus adjust for the multiplicity of endpoints analyzed, would require very small significance levels to be used for every comparison. We plan to work at the usual α -level for each of the major comparisons of the intervention arm versus the usual care arm rather than formally adjusting the significance level for every comparison. However, we will be conservative in the interpretation of the analyses, taking into account the degree of significance, and looking for consistency across endpoints. In addition, the actual p-values for each comparison will be reported (not simply whether significance is achieved) to aid in the overall interpretation. Also, the Bayesian interpretations discussed above (along with so-called credible intervals) will assist in providing an appropriate interpretation of the study results. We have also declared a primary outcome variable to help guard against the multiple testing problem.

6.2.3 Safety Evaluation

The recording and reporting of adverse events (AE) in HF-ACTION is crucial to better understand the risks and complications associated with exercise training in a population with heart failure, and to establish definitive safety standards for exercise training. These adverse events will be collected on the CRF from randomization through the follow-up period. **Deaths and SAEs resulting in hospitalizations that occur after informed consent is signed but before randomization will also be collected on the CRF.** Specific adverse events associated with the disease under study and/or resulting from exercise training will be collected and characterized by the type and the impact of the event. These types of adverse event will include not only causes for hospitalizations or death, but also events that may have a correlation with exercise training, including injuries sustained during training (sprain, falls, etc.) and symptomatic hypoglycemic episodes in diabetic patients. The impact of these adverse events will be categorized based on the following severity index: **1)** resulted in an urgent clinic visit or emergency room visit; **2)** required hospitalization; and **3)** resulted in loss of life. Those AEs unresolved at the end of the trial will be listed as ‘ongoing’.

Serious adverse events (SAEs) resulting in a death secondary to exercise training will be reported within 5 days to the coordinating center. The coordinating center will forward this information to the NHLBI and the DSMB chairperson. The coordinating center will provide a summary of mortality to the chairperson of the DSMB on a regular basis. Analysis of AE will be presented at DSMB meetings. **If it is unknown whether a SAE resulting in a death occurred while exercising or within 3 hours after exercising, this event will also be reported within 5 days to the coordinating center and forwarded to the NHLBI and DSMB chairperson.**

6.2.4 Interim Analysis

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 objective of these analyses will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either treatment arm. In addition, however, the interim monitoring will also involve a review of the usual care arm event rates, patient recruitment, compliance with the study protocol, submission of data forms, and other factors that reflect the overall progress and integrity of the study. The Data

and Safety Monitoring Board (DSMB) will carefully and confidentially review the results of the interim analyses.

We anticipate that the Data and Safety Monitoring Board will meet at approximately 6-month intervals to review the accumulating data. Prior to each meeting of the DSMB, the Data Coordinating Center will conduct the desired statistical analyses and prepare a summary report that will be carefully reviewed by the DSMB. The extracted data files and analysis programs for each DSMB report will be maintained at the Data Coordinating Center for the life of the study. Each report will describe the progress of patient enrollment, the rates of compliance with therapy, and the frequency of protocol violations.

These interim safety and efficacy reports introduce well-recognized statistical problems related to the multiplicity of statistical tests performed on an accumulating set of data (Armitage 1969, McPherson 1974). As a solution to the problem of repeated tests, we propose to adopt for use in HF-ACTION a group sequential method similar to that proposed by O'Brien and Fleming (1979) as a guide in interpreting interim analyses. This procedure requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. With this conservatism early in the trial, the critical value at the final analysis is near the "nominal" critical value. Hence sample size requirements with this procedure remain essentially the same as the conventional fixed sample size estimate. The actual method for interim monitoring that will be employed in HF-ACTION is the general approach to group sequential testing developed by Lan and DeMets (1983) for which neither the number of looks nor the increments between looks must be pre-specified. The Lan-DeMets approach requires only specification of the rate at which the Type I error (which in this trial will be $\alpha=0.05$) will be "spent." The procedure allows "spending" a small portion of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05. One such spending function generates boundaries that are nearly identical to the O'Brien-Fleming boundaries. It is this approach that we propose to use in HF-ACTION, namely two-sided, symmetric O'Brien-Fleming (1979) type boundaries generated using the flexible Lan-DeMets (1983) approach to group sequential testing. Since the number of looks and the increments between looks need not be pre-specified, it allows considerable flexibility in the monitoring process for accommodating additional comparative examinations of the data in response to concerns of the DSMB that may arise during the course of the trial. Assuming that the DSMB will conduct its first formal data review in the latter half of the first year of recruitment, and then continue those reviews approximately every 6 months thereafter through the patient recruitment period (3 years) and the follow-up phase (1 year), there will be approximately 7 reviews of the data. With 7 interim analyses approximately equally spaced in time, the Lan and DeMets "spending function" that approximates the O'Brien-Fleming stopping boundaries involves a very stringent alpha level (0.00001) for declaring significance at the first interim analysis. At the subsequent interim analyses, the required significance levels will be somewhat less stringent. The requirements for significance at each interim analysis, depending on exactly when the analysis occurs, can be computed with the Lan-DeMets methodology. The final analysis can be undertaken with a significance level of approximately 0.041, relatively close to the nominal 0.05 level.

The analytic approach that will be used at the interim analyses for assessing treatment differences will be the time-to-event analysis methods described above, except that interpretation of statistical significance associated with treatment comparisons of key study endpoints will be guided using the group sequential boundaries outlined above (O'Brien 1979, Lan 1983, Geller 1987). The appropriateness of using the log-rank test (or equivalently the Cox model) in the group sequential

framework has previously been well established (Tsiatis 1981, 1982, Gail 1982, DeMets 1985). For each of these interim analyses, the critical value of the test statistic and the corresponding p-value required for significance in that particular analysis will be presented so that significance can be assessed precisely. If significantly large and important treatment differences are observed at any of the interim analyses, the Data and Safety Monitoring Board may recommend that randomization of patients be stopped, or that the design and conduct of the trial be appropriately modified. Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the originally projected sample size. As an aid in this latter assessment, the Data Coordinating Center will supplement the group sequential analyses outlined above with calculations of conditional power based on the method of stochastic curtailment (Halperin 1982, Lan 1982, Ware 1985). This procedure evaluates the conditional probability that a particular statistical comparison will or will not be significant at the end of the trial at the α level used in the design, given the hypothesized treatment difference and the data obtained to date. Conditional power for the primary endpoint and for total mortality will be computed and provided to the DSMB as part of the interim study reports.

The Data and Safety Monitoring Board will regularly review the level of compliance of patients in the exercise training arm (overall and by site). As part of those reviews, the DSMB will assess the effect of the exercise training in improving peak VO₂ levels from their baseline values. After approximately one year of enrollment, results of the three-month exercise test will be reviewed. If patients do not show at least a 10% improvement in peak VO₂ from baseline (overall or at any individual site), this may prompt the DSMB to make specific recommendations to the Steering Committee for altering the study protocol or working with specific sites. When 12-month exercise test data are available on a suitable number of patients, the DSMB will also review those results and provide appropriate feedback to the Steering Committee. Twelve-month VO₂ scores should be improved by at least 8% compared to baseline to be indicative of compliance with the home exercise training protocol.

The DSMB will be particularly valuable in advising the study leaders and NHLBI of advances in the treatment of patients with HF. A number of therapeutic advances may occur during the course of the trial. The DSMB will be expected to assist in putting these advances in perspective. If protocol modifications are warranted, close consultation among the principal investigators, the DSMB, and NHLBI will be needed. In the initial meeting with the DSMB, the protocol for evaluation of data will be agreed upon.

7 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with HF-ACTION 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 **45** Code of Federal Regulations dealing with clinical studies (including **part 46** 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.

7.1 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.

Any amendments to the protocol, other than administrative ones, must be approved by this committee.

7.2 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.

Separate informed consents will be required for **national or provincial database** follow-up in eligible patients who can not be approached for randomization consent due to treating physician preference. If a patient refuses to provide consent for randomization, he or she will be offered entry into the registry and a separate registry informed consent will be provided. Once randomized, subjects will be asked to provide a separate informed consent for obtaining a blood sample for genotyping and for any other ancillary study procedures. 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.

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