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 α=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 α=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:

$$1/2\ \{1-1/6[S_C(1.0) + 4\ S_C(2.5) + S_C(4.0)]\}$$

$$+\quad 1/2\ \{1-1/6[S_I(1.0) + 4\ S_I(2.5) + S_I(4.0)]\}.$$

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 ($\geq$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

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.

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