FDA Medical Device Development Tool (MDDT) Qualification Package for the Minnesota Living with Heart Failure Questionnaire (MLHFQ)

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Table of Contents

I. Description of the MDDT

a. Content

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was designed in 1984 by Thomas S. Rector, PhD and Jay N. Cohn, MD in the Cardiovascular Division at the University of Minnesota as a measure of heart failure as indicated by its adverse effects on patients' lives, *aka* heart failure related quality of life.[1] The contents of the MLHFQ were identified by patients who were experiencing heart failure when they completed a comprehensive Sickness Impact Profile, review of other studies of the effects of heart failure as perceived by patients, and by several experienced clinicians.

The comprehensive content of the MLHFQ (Table 1) is representative of the many ways heart failure can adversely affect patients' lives. The 21 questions assess the impact of the signature physical symptoms and signs of heart failure - shortness of breath, fatigue and peripheral edema as well as commonly occurring feelings of depression. Other questions ask about the effects of heart failure on common physical/social functions including walking, climbing stairs, household work, need to rest, sleep, working to earn a living, going places away from home, doing things with family or friends, recreational activities, sexual activities and diet. Ability to concentrate and memory, and feelings of loss of self-control and being a burden to others are also included. Questions about side effects of treatments, hospital stays and costs of care are included to help measure the overall adverse impact of heart failure on patients' lives.

After a brief set of instructions (Table 2), respondents use a six-point rating scale to indicate how much each of the 21 potential adverse effects of heart failure listed on the MLHFQ have affected their ability to live as they wanted during the past month (4 weeks). The response format ranges from 0 (none or not applicable), to 1(very little) to 5 (very much). Thus, the respondent weighs each potential adverse effect of heart failure using the same scale. The simple sum of the responses that ranges from 0 to 105 is a measurement of heart failure severity as indicated by its adverse effect on the respondent's life during the past month. The MLHFQ scores increase with the adverse impact of heart failure on the respondent's life. The MLHFQ can be used to measure whether a treatment for heart failure improves subjects' quality of life by reducing the adverse effects of heart failure.

Table1. Minnesota Living with Heart Failure Questionnaire.

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Table 2. Instructions for Completing the MLHFQ.

1. Subjects should respond to the questionnaire prior to other assessments and interactions that may bias their responses. You might tell the respondent that you would like to get his or her opinion before doing a medical assessment.

2. Ample, uninterrupted time should be provided for the subject to complete the questionnaire. Subjects should answer the questions without being influenced by others such as their spouse or family members who may have different perspectives than the subjects.

3. We recommend that you use the first question to give the respondent more detailed instructions as follows.
    a. Read the introductory paragraph at the top of the questionnaire.
    b. Read the first question with the respondent – "Did your heart failure prevent you living as you wanted during the last month (4 weeks) by causing swelling in your ankles or legs?"

        - If you did not have any ankle or leg swelling during the past month (4 weeks) you should circle the zero (0) after this question.
        - If you did have swelling that was caused by a sprained ankle or some other cause that you are sure was not related to heart failure, you should circle the zero (0) after this question.
        - If you had swelling that might be related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do or feeling the way you would like to feel. In other words, how much did the swelling affect your life? Circle either the 0, 1, 2, 3, 4 or 5 to indicate how much the swelling affected your life during the past month – zero (0) means not at all, one (1) means very little and five (5) very much.

4. Ask the respondent to read and respond to all 21 questions. The entire questionnaire may be read directly to the respondent if one is careful not to influence responses by verbal or physical cues.

5. Check to make sure the respondent has responded to each question. If a question does not apply to the respondent they should circle the zero (0). Make sure there is only one answer clearly marked for each question.

b. Importance to Patients

The clinical concept being measured by the MLHFQ is the adverse impact of heart failure on patients' lives. Undoubtedly the adverse effects of heart failure are one of the most important reasons why patients with heart failure seek medical care for relief (the other main reason being to prolong their life). The MLHFQ was developed to measure (offer a reliable approach to assign a valid numerical score) to this clinically important concept to be better able to assess from the patients' perspective whether medical treatments reduce or prevent the adverse effects of heart failure on their lives. Selection of the MLHFQ contents began with the most common patient-reported signs and symptoms of heart failure - shortness of breath, fatigue (tiredness or low energy in more lay terms) and fluid retention (e.g. swelling in the ankles or feet). Additional content was selected to extend the patients' assessment to consider other important ways heart failure could adversely impact their lives. Additional content was identified using the comprehensive Sickness Impact Profile (SIP) to survey (self-administered in lieu of interviewing) 45 patients with symptomatic heart failure undergoing an exercise stress test at the University of Minnesota or Minneapolis VA hospitals.[1] Each of the 136 items on the SIP is scored based on the ratings of 25 judges who used a 15-point scale ranging from minimally to maximally dysfunctional. The SIP completed by patients with heart failure identified work, recreation and pastimes, home management, sleep and rest, alertness, ambulation, social interactions and eating as most impacted. These findings have been confirmed by baseline SIP questionnaires completed by 367 subjects with symptomatic heart failure that were enrolled in a randomized controlled trial in the mid 1990's.[2] A systematic review of 14 qualitative studies of predominantly older people (total n=267) published from 1997 to 2007 also indicated that distressing symptoms, physical limitations, social and role dysfunction along with negative emotions, cognitive impairment, feelings of loss of control and being a burden to others were major issues when living with heart failure.[3] Guyatt et al asked 88 patients with a clinical diagnosis of heart failure to rate the importance of 123 ways their lives may have been affected by their heart disease.[4] Based on frequency and patients' ratings of importance, shortness of breath while walking around or upstairs or hills, being fatigued, tired or having low energy, being worried, depressed or a burden to others were among the most important ways their lives were adversely affected. Difficulties with sleep, usual social activities, forgetfulness and concentration were also rated as important. A patient generated index completed by 58 patients with a diagnosis of heart failure also indicated that walking, stairs and inclines, tiredness, sleepiness, problems with daily activities, social life, hobbies and interests and independence were important problems.[5] Another 53 patients with symptomatic heart failure who completed the 32 item Memorial Symptom Assessment Scale – Heart Failure rated shortness of breath, lack of energy, feeling drowsy, feeling sad, lack of appetite, difficulty sleeping, problems with sexual interest or activity and swelling of legs or arms among the most burdensome.[6] These and many other studies (not summarized here) that have been done over the years strongly support the importance of the MLHFQ contents to patients with heart failure. Certainly when heart failure is severe enough to require hospitalization the patients' lives can be adversely affected in many ways and preventing hospital admissions is often an important study endpoint. Finally the costs and side effects of a treatment could have important adverse effects on the ability of patients to live as

they want and need to be weighed against any reductions in the adverse effects of heart failure *per se*.

We are not aware of any evidence to suggest or reason to think the adverse effects of the symptoms, functional limitations and psychological reactions to living with heart failure have changed over the years. Indeed, as previously summarized subsequent studies have repeatedly confirmed this notion. Undoubtedly, hospitalizations, costs and side effects of treatments continue to be important concerns for some patients.

c. Principle and Method of Measurement

The method of measurement uses the responses to the questions on the MLHFQ as indicators of the severity of the latent cardiac dysfunction (heart failure) and its many systemic effects such as renal dysfunction and muscle abnormalities.[7] The questions on MLHFQ serve as direct or indirect indicators of the severity of the latent pathophysiologic aspects of a subject's heart failure that are logically the underlying targets of treatments. However, the severity of the symptoms and sequela of heart failure and their effects on daily lives cannot be ascertained using only objective pathophysiologic measurements.

Although some of the MLHFQ questions ask about hospital admissions, medical costs, working to earn living, sexual activities and other problems that aren't always applicable to all respondents, they were included in the measure because they may represent a substantial adverse effect on the respondent's life when they do apply. Likewise, whenever side effects of a treatment for heart failure adversely affect a patient's life it is important to consider the adverse effect of the treatment along with the adverse effects of the heart failure being treated.[8]

The inclusion of indicators that are important potential adverse effects of heart failure but that aren't always applicable to all respondents can introduce variation in the MLHFQ scores that is difficult to model using traditional psychometric factor or Rasch analysis.[9-12] Nevertheless, the use of indicators with varying applicability to respondents is consistent with the concept that the adverse effects of heart failure of the same severity can vary with respondents' lifestyles, socioeconomic circumstances andcomorbidities . A recent bi-factor analysis of pooled data collected during 5 clinical trials and 3 observational studies (21 countries, 3,847 subjects) confirmed that the MLHFQ questions reflect a single latent construct with a high internal consistency, and that separation into the physical, emotional, social and health care domains that have been identified by traditional factor analyses adds little to the precision of the measurement while increasing the complexity inherent in analyzing clinical trials with multiple endpoints.[13] Over decades of use, a number of clinical trials of treatments for heart failure and psychometric evaluations of the MLHFQ have reported on the internal consistency of the MLHFQ indicators, i.e. the responses to all 21 questions. As summarized in Table 3 Cronbach's alpha has been reliably high despite the inclusion of measurement indicators of varying applicability.

Table 3. Internal Consistency of MLHFQ in Various Studies.

Study‡	Number of Respondents	MLHFQ scores†	Cronbach's α
Pimobendan RCT[9]	197	47 (28, 61)	0.94
Studies of Left Ventricular Dysfunction Trial[14]	135 (NYHA I) 123 (NYHA II-III)	31 ± 25 44 ± 26	0.95 0.94
Evaluation in hospital clinics[15]	211	45 ± 27	0.95
Nine clinical trials[16]	1,136	52 ± 25	0.92
Four RCT of care [10]	638	51 ± 23	0.91
Prior to cardiac valve surgery[17]	50	40 ± 27	0.96
I-PRESERVE RCT[18]	3,605	42 (28, 58)	0.92
International Quality of Life Outcomes Database[13]	3,847	36 ± 22	0.92

‡ Reference number. †mean ± standard deviation or median (interquartiles).
RCT – randomized controlled clinical trial. NYHA – New York Heart Association classification.

Clinimetrics: The MLHFQ is based more on a traditional clinimetric perspective than a psychometric measurement model for measuring an unobservable or latent attribute.[19] Patients can observe and report how much possible adverse effects of heart failure are adversely affecting their lives. Some of the MLHFQ items such as shortness of breath and fatigue are direct or indirect causes of other MLHFQ items. [7,20] Thus the correlations between MLHFQ items and the high internal consistency of the MLHFQ (see Cronbach alphas in Table 3) may not be entirely driven by some unspecified latent construct. Selection of MLHFQ items was based on clinical experience and evidence that an item can be an important adverse effect of heart failure rather than the psychometric approach based on item correlations and homogeneity in reflecting some latent construct.[20] The emotional items, social items, costs of care, hospitalizations and side effects of treatments haven't always loaded on the factors that includes the key signs and symptoms of heart failure (shortness of breath, fatigue and swelling).[10,17] Nevertheless all items were retained because they could be related to having heart failure and could be important adverse effects for a substantial proportion of patients.

Unlike clinicians, patients cannot directly observe the abnormal cardiac structure, hemodynamics and neurohormones that are components of the clinical syndrome of heart failure. From the patients' perspective, the complex pathophysiology of heart failure is latent. Therefore the items on MLHFQ could be considered to be patient-reported indicators or manifestations of the underlying pathophysiology of heart failure. The consistently high Cronbach's alpha supports the notion that the contents of the MLHFQ are an internally consistent set of indicators of some phenomenon, presumably the complex pathophysiology of heart failure. However it's not clear that these indicators closely reflect the severity of the pathophysiology. The natural history of heart failure is one of periodically worsening signs and symptoms in the presence of relatively stable pathophysiology. There are a number of aggravating factors such as increased sodium consumption, lapses in adherence to prescription medications, acute illnesses such as the flu and changes in the condition(s) that led to the heart failure such as ischemic or

valvular heart disease or hypertension. Patients with so-called diastolic (preserved ejection fraction) or systolic (reduced ejection fraction) heart failure perceive similar signs, symptoms and impairments due to heart failure despite differences in the pathophysiology as indicated by the differences in ejection fractions.[14,18,21,22] Changes in perceptions of shortness of breath and fatigue are not strongly related to hemodynamic measurements.[23,24] In fact, there are no established pathophysiologic markers of what the MLHFQ measures (see later section about the ejection fraction). Contrary to ideal psychometric indicators, some of the MLHFQ items such as eating and fluid retention as indicated by swelling can increase levels of natriuretic peptides, and treatments administered during a hospitalization such as beta-blockers and cardiac resynchronization devices can improve left ventricular ejection fractions. Thus the MLHFQ is not necessarily a homogenous set of patient-reported indicators of the latent (and complex) pathophysiology of heart failure. It is a clinical measure comprised of multiple and somewhat heterogeneous potential adverse effects of heart failure on patients' lives.

The MLHFQ scoring algorithm is based on a clinical assessment that seeks to measure (assign a reliable and valid numerical score) the adverse effects of heart failure on a patient's life to guide care and assess care outcomes. Patients can observe and rate adverse effects of heart failure. Each potentially important adverse effect listed on the MLHFQ is weighed by the patient using the same response scale so clinicians could easily determine which, if any, of the items on the MLHFQ were most bothersome and therefore should be the target of treatments. In effect each subject assigns personal weights to the MLHFQ items that are summed for a total score representing how much heart failure adversely affected that patient's life during the past 4 weeks rather than using external weights and complicated scoring algorithms that may not represent any particular subject very well.

II. Context of Use

a. Disease

The MLHFQ is to be used as a measure of effectiveness in controlled clinical trials of treatments of people with heart failure with either a reduced or preserved ejection fraction.

b. Stage of Device Development

The MLHFQ may be used in any type of controlled clinical trial of a treatment for heart failure including early stage studies, pivotal clinical studies to support a claim that a treatment can prevent or reduce the adverse impact of heart failure on subjects' lives, or post-marketing studies to support label changes.

c. Specific Role of the MDDT

The two primary clinical goals of treating heart failure are 1) to improve the quality of patients' lives by reducing the adverse impact of heart failure and, 2) to prolong patients' lives. The role of the MLHFQ is to determine whether a treatment helps achieve the first goal. The MLHFQ is an ultimate, not an intermediate or surrogate endpoint. The MLHFQ may also be used as an endpoint in controlled clinical trials of treatments aiming to alter the progressive nature of heart failure. When the MLHFQ is being employed as a study endpoint, pre-enrollment scores may be used to help select subjects according to the impact of heart failure on their lives and ability provide reliable responses.

III. Evidence to Support Qualification

a. Retest Reliability

Reliable MLHFQ data have been collected during several clinical trials and other studies (Table 4). Differences between repeated assessments of stable subjects (measurement error) were only a fraction of the total variation in MLHFQ scores in these studies. The estimated reliability of repeated MLHFQ scores in Val-HeFT was as good as the estimated reliability of more objective measurements of B-type natriuretic peptide, serum creatinine and hemoglobin, and more reliable than the assessments of the left ventricular ejection fraction and systolic blood pressure.[24]

Table 4. Retest Reliability of MLHFQ Scores.

Study‡	Number of Respondents	Time between MLHFQ Scores	Difference between MLHFQ Scores†	Reliability Estimate
Pimobendan RCT[9]	181	1 week	0 (-3, 5)	r = 0.93
Val-HeFT RCT[24]	1,912	0, 4 &12 mo	NA	r = 0.86
Outpatient clinics[5]	54	1 week	NR	icc = 0.89
Meta-analysis[25]	81 studies	NR	NR	icc = 0.84
I-PRESERVE RCT[18]	2,904	0, 6 &14 mo	NA	r = 0.80

‡Reference number. †mean ± standard deviation or median (interquartiles).

r –correlation between repeated measurements. NA – not applicable, estimate based on structural equal model of the correlations between 3 repeated measurements. NR – not reported. icc – intraclass correlation coefficient.

These studies demonstrate that it is possible to make reliable MLHFQ measurements. The reliability of the MLHFQ score can depend on how the questionnaire is administered by investigators. Respondents should be instructed on how to answer the questions including to mark the zero when a question doesn't apply. The completed questionnaires should be closely monitored to minimize missing data. Ideally, clinical trials would incorporate a baseline assessment of the retest reliability to help establish the eligibility and stability of study subjects. A baseline assessment of retest reliability can provide an estimate of the standard error of the measurements in the hands of the investigators that can be used to help interpret the study estimates of the treatment effect.

b. Validity

Convergent and Divergent

Conceptually speaking, the adverse effects of heart failure on patients' lives are mediated by the symptoms and physical limitations and their psychosocial effects. The validity of this conceptual model for the MLHFQ score has been examined in a number of studies that correlated MLHFQ scores with measures of symptoms of heart failure and other measures of the effects of heart failure on daily existence. The rows of Table 5 are in an approximate descending order of the degree of overlap in what is being measured by the MLHFQ and how much each measure represents patients' views about the adverse impact of heart failure on their lives during the past 4 weeks. Note higher MLHFQ scores indicate greater adverse effects of heart failure whereas higher scores are better for most other measures, hence the negative correlations. As summarized in Table 5 the MLHFQ scores are clearly related to clinicians' and patients' assessments of dyspnea and fatigue. The commonly used New York Heart Association (NYHA) classification is an assessment of the symptoms experienced during ordinary daily activity. Patients are assigned to NYHA Class I when their ordinary physical activities (unspecified) don't cause undue dyspnea or fatigue, Class II when they're comfortable at rest, but more strenuous ordinary activities lead to shortness of breath and/or fatigue, Class III when less strenuous ordinary activities lead to shortness of breath and/or fatigue, and Class IV when they are not able to do any physical activities without shortness of breath and or fatigue that may even be present at rest. In contrast to the NYHA classification, the MLHFQ assesses how much the symptoms of heart failure prevented the individual from doing specified activities he or she would ordinarily do as well as other adverse effects of heart failure. Although the NYHA classification is relatively crude and less reliable and comprehensive than the MLHFQ, differences of one NYHA class consistently correspond to large differences in MLHFQ scores ranging from 7 to 23 points in Table 5.

The MLHFQ scores have been strongly correlated with other reliable measures of the adverse effects of heart failure on daily existence or quality of life including the well-established generic SF-36 scores, psychological measures and several other heart failure specific measures. Indeed, the MLHFQ has been used to help validate other patient-reported measures of heart failure.

Maximal and submaximal exercise tests that have been used as endpoints in studies of treatments for heart failure are more weakly related to the MLHFQ scores as expected based on what they measure. In fact, an impetus for developing the MLHFQ was to help determine whether the increases in exercise duration or distance walked being observed in clinical trials of treatments for heart failure represented an improvement in the daily lives of subjects. The MLHFQ score is not strongly correlated with the degree of reduced systolic cardiac dysfunction as measured by the left ventricular ejection that has not been closely correlated with the severity of symptoms, functional limitations or psychosocial impact of heart failure.

Table 5. Convergent and Divergent Validation of MLHFQ Scores.

Study‡	**Commentary on 'Other' Measure**	**Relation to MLHFQ Score†**
Bennett et al[15]	The Chronic Heart Failure Questionnaire uses 16 items to measure how much of the time during the past 2 weeks patients had dyspnea (during 5 patient selected activities), fatigue (4 specified activities) and 7 specified feelings.[59] The contents and referent period of the CHQ overlap extensively with the MLHFQ, and the content of CHQ was selected based on importance to patients with heart failure.	Total score r = -0.81 Dyspnea r = -0.63 Fatigue r = -0.78 Emotional r = -0.74
Dunderdale et al[33]	The contents of the Chronic Heart Failure Assessment Tool represent 46 ways patients reported their heart failure affected their health-related quality of life. The contents of the symptom, activity, emotions and psychosocial factors include much of the same content as the shorter MLHFQ. The questions use several response formats to measure how frequently or how much of time each item of interest occurred or how much more less frequently it occurred than similar aged adults rather than how much their lives were adverse impacted. A total Chronic Heart	symptoms r = 0.73 activity levels r = 0.60 emotions r = 0.69 psychosocial r = 0.47

	Failure Assessment Tool score was not reported.	
Mannheimer et al[32]	The Cardiac Health Profile - Chronic Heart Failure asks 10 questions suggested by experienced cardiologists who asked patients how their heart failure impacted their quality of life (Are you often tired? Do your feet or calves swell? Do you get out of breath easily? Are your legs often tired? Do you sometimes fear dying? Do you have a good appetite? Has your heart problem affected your outlook on life? Are you at any time affected by a feeling of pressure in your chest? Is your heart problem more of a difficulty with varying weather, such as cold or windy weather? Are you easily tired in the afternoon?). The visual analog scale is anchored by ‘‘no never’’ and ‘‘yes always’. Scores were calculated by measuring distances from “no never” to the marks that were summed and divided by the number of items answered.	r = 0.76
O’Leary & Jones[26]	Although not specific to heart failure, the SF-36 and similar measures of physical health/function indicate the impact on daily lives. Adverse effects of physical problems comprise the majority of the MLHFQ contents, and are also interrelated with other MLHFQ content such as social function and emotional concerns. These other patient-reported measures of physical function or disability should be strongly correlated with the MLHFQ scores.	SF-36 physical function r = -0.74 SF-36 role physical r = -0.67 SF-36 vitality r = -0.66 SF-36 physical component r = -0.73
Quittan et al[27]		SF-36 physical function r = -0.60 SF-36 role physical r = -0.54 SF-36 vitality r = -0.74
Bennett et al[15]		SF-36 physical component r = -0.57
SOLVD[14]	Physical limitations scale	r = 0.75
Rose et al[36]		r = 0.71

	Physical disability measured by computer adaptive questionnaire	
SOLVD[14]	Patients are assigned by clinicians to New York Heart Association NYHA Class I when their ordinary physical activities (unspecified) don't cause undue dyspnea or fatigue, Class II when they're comfortable at rest, but more strenuous ordinary activities lead to shortness of breath and/or fatigue, Class III when less strenuous ordinary activities lead to shortness of breath and/or fatigue, and Class IV when they are not able to do any physical activities without shortness of breath and or fatigue that may even be present at rest.[67] In contrast to the NYHA classification, the MLHFQ assesses how much the symptoms of heart failure prevented the individual from doing specified activities he or she would ordinarily do as well as other adverse effects of heart failure. Despite these differences, the average MLHFQ scores should and do progressively increase with NYHA Classification. See Figure 1s under Response 6 for further analysis of this relationship.	I 31 ± 25 II/III 44 ± 26
Quittan et al[27]		I 19 ± 16 II 35 ± 24 III 44 ± 22 IV 67 ± 27
Bennett et al[15]		I 16 ± NR II 38 ± NR III 58 ± NR IV 72 ± NR
Kubo et al[29]		II 34 ± NR III 57 ± NR IV 69 ± NR
Heo et al[10]		II 41 ± 25 III/IV 53 ± 22
Witham et al[5]		I 9 ± NR II 25 ± NR III 38 ± NR
Holland et al[34]		I/II 32 ± 21 III 49 ± 21 IV 57 ± 23
Rose et al[36]		I 16 ± 15 II 38 ± 25 III/IV 45 ± 23
CIBIS II[37]		III 40 ± 20 IV 55 ± 19
AHeFT[38]		III 50 ± 25 IV 63 ± 25
Rector et al[18]		III-II difference 9 ± NR IV-III difference 16± NR

Calvert[30]		IV-III difference 14± NR
O'Leary & Jones[26]	Five of the 21 MLHFQ items concern adverse emotional or psychological effects of heart failure that are related to the fundamental physical items of the MLHFQ as well. Thus the MLHFQ scores should be correlated with other measures of emotional or psychological constructs. Although not specific to heart failure, the SF-36 measures of emotional/mental health by asking patients to rate the impact on their lives.	SF-36 role emotional r = -0.48 SF-36 mental health r = -0.41 SF-36 mental component r = -0.43 SF-36 general health perception r = -0.59
Quittan et al[27]		SF-36 role emotional r = -0.41 SF-36 mental health r = -0.62 SF-36 general health perception r = -0.65
Bennett et al[15]		SF-36 mental component r = -0.68
SOLVD[14]	Emotional distress scale	r = 0.64
Gottlieb et al[28]	Beck Depression Inventory	r = 0.64
Van den Berg-Emons et al[31]	Depression scale Anxiety scale Feelings of being disabled	r = 0.64 r = 0.59 r = 0.72
O'Leary & Jones[26] Quittan et al[27]	Although not specific to heart failure, the SF-36 measures how one's health status affects social function. The MLHFQ also contains items related to the social impact that are interrelated to the adverse physical and emotional effects of heart failure.	SF-36 social function r = -0.70 SF-36 social function r = -0.52
	Shortness of breath (dyspnea) and fatigue are the most disabling symptoms of heart failure and a key component of clinical assessment as well as the MLHFQ. Measures of the presence or severity of dyspnea and fatigue should be related to MLHFQ scores even though they don't necessarily measure the impact of these symptoms on patients' lives or less related MLHFQ content.	

SOLVD[14]	Clinicians rated the magnitude and effort of tasks that made patients feel breathless and the related functional impairment.	dyspnea r = -0.52
Heo et al[10]	When present subject's rated the severity of their dyspnea & fatigue from 1(very mild) to 10 (worse imaginable).	dyspnea + fatgue r = 0.42
Rose et al[36]	Computerized adaptive measures using banks of calibrated items. The banks of the most discriminating items contain of 20 descriptors of fatigue and 29 activities that could bring on dyspnea.	dyspnea r = 0.68 fatigue r = 0.63
Rector et al[24]	Principle component score based on 6 clinician symptom assessments (dyspnea at rest, paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion, fatigue and NYHA classification)	symptom score r = 0.64
Maurer et al[35]	Anergia was measured using a 7 item scale (not enough energy, slowed physically, doing less than usual, slowness in morning, sit around a lot, waking-up feeling tired, naps)	anergia r = 0.65
Pimobendan RCT[9]	Sum of 12-week changes in patients' ratings of dyspnea and fatigue as none, slight, moderate, severe or disabling.	Change in MLHFQ scores Better -12 (-2, -24) No Change -1 (-8, 4) Worse 3 (-1, 12)
Rector et al[18]	Patient's ratings of changes in their dyspnea after 6 months of treatment.	Change in MLHFQ scores markedly better -19 ± 21 mod. better -16 ± 16 slightly better -8 ± 14 no change -2 ± 15 slightly worse 1 ± 15 moderately worse 8 ± 20

	Patient's ratings of changes in their fatigue after 6 months of treatment.	markedly worse 12 ± 18 Change in MLHFQ scores markedly better -22 ± 22 mod. better -15 ± 16 slightly better -9 ± 15 no change -4 ± 15 slightly worse 1 ±14 moderately worse 1 ± 21 markedly worse 9 ± 23
Witham et al[5]	Patients with heart failure were asked to rate their quality of life in each of seven domains, with 10 representing quality of life exactly as they wanted to be and 0, the worst they could imagine. Patients select up to five areas of importance in their lives that were affected by their heart failure, and 2 other questions ask about areas affected by other health problems and all other non-health areas of life. Scoring is based on which areas they most want to improve.	quality of life r = -0.46
Pimobendan RCT[9]	To measure maximal exercise ability treadmill workload was increased every 2 minutes until patients stopped because of dyspnea or fatigue. The workloads may exceed those required for daily activities and those leading to difficulties in the MLHFQ. The impact of the patients' ability to exercise is not measured, hence the modest correlation with the MLHFQ scores.	r = -0.33
SOLVD[14] Quittan et al[27] Van den Berg-Emons et al[31]	Patients walked on level ground as far as they could in 6 minutes without any patient assessment of their walking ability or how any difficulty walking adversely affected their lives.	r = -0.39 r = -0.39 r = -0.30

Van den Berg-Emons et al[31]	A actigraph device was used to simply count the number of daily movements. More consistent with the MLHFQ there was also a question about the patients' dissatisfaction with their everyday activity	r = 0.20 r = 0.47
Van den Berg-Emons et al[31] Gottlieb et al[28] O'Leary & Jones[26] Quittan et al[27] SOLVD[14] Pimobendan RCT[9]	See next section for commentary on the ejection fraction	r = -0.06 r = 0.03 r = -0.22 r = -0.24 r = 0.03 r = -0.01 12-wk changes

†mean ± standard deviation or median (interquartiles).

Ejection Fraction: Several references supporting the statement that the MLHFQ score is not strongly correlated with the degree of reduced systolic cardiac dysfunction as measured by the left ventricular ejection were provided in Table 5 Convergent and Divergent Validation of MLHFQ Scores.[9,14,26-28,31] Further support can be found in Table 3, reference 18 where there was no difference in MLHF scores in subgroups with preserved ejections fractions above or below 60% and in the figure in reference 22 showing the same distribution of MLHFQ in the studies of patients with preserved and reduced ejection fractions. Support for the statement that the left ventricular ejection fraction has not been closely correlated with the severity of symptoms, functional limitations or psychosocial impact of heart failure can be found in Table II of reference 14 (r=0.04 with a measure of dyspnea, r= -0.07 with a measure of physical limitations, r = -.03 with the 6-minute walk test and r= -0.01 with a measure of emotional distress); Table 3 of reference 26 (r = -0.25 with the left ventricular dysfunction questionnaire score); Table 1 of reference 28 where the ejection fractions were the same for depressed and not depressed subjects and Table 3 showing correlations with SF-36 dimensions (r = -0.08 with physical function, r = 0.13 role physical, r = 0.06 with vitality, r = -0.03 with social function, r = 0.02 with role-emotional and r = 0.01 with mental health); and Table 3 in reference 31 (r = 0.03 with movement related to every day activity). Thus the lack of a strong correlation between the MLHFQ score and the ejection fraction that's a conceptually distinct measure of heart failure supports the divergent validity of the MLHFQ. Indeed, the MLHFQ was developed because we were not aware of any references that supported the notion that a pathophysiologic measure of systolic or diastolic heart failure is an adequate surrogate for the adverse effects on patient's daily lives.

Efficacy of Medical Device Treatments

The MLHFQ has been successfully employed in a number of randomized controlled clinical trials of devices as treatments for heart failure to determine whether or not the device's effects on

the targeted pathophysiology translated into improvements in the subjects' quality of life. The estimated magnitude of the effects of various devices were all realistic thereby supporting the validity of the MLHFQ.

The efficacy of cardiac resynchronization therapy has been firmly established using a variety of study designs with varying limitations, control groups and endpoints including the MLHFQ that consistently indicated cardiac resynchronization therapy substantially reduced (improved) the MLHFQ scores compared to no cardiac resynchronization (Table 6).[39] Not surprisingly, cardiac resynchronization therapy didn't significantly improve the MLHFQ scores of subjects that had lower scores at baseline indicating their heart failure didn't have as much of an adverse impact on their lives.

Table 6. Effects of Cardiac Resynchronization Therapy (CRT) for Heart Failure as Measured by the MLHFQ in Randomized Controlled Clinical Trials.

Study‡	**Baseline MLHFQ Scores†**	**Follow-up MLHFQ Scores†**
MUSTIC crossover comparison of 3 months of activated versus inactivated atriobiventricular pacing[40]	47 ± 22 n = 58	Active pacing 30 ± 21 Inactive pacing 43 ± 23 (n=45) P < 0.001
MIRACLE 6-month parallel group comparison of atriobiventricular pacing versus no pacing after device implantation[41]	59 ± 21 n = 453	Mean change pacing on (n=213) -18 (-22, -12) pacing off (n=193) -9 (-12, -5) P < 0.001
MIRACLE ICD 6-month parallel group comparison of atriobiventricular pacing turned on versus off; defibrillator active in both groups[42]	56 ± 23 n = 369	Mean change pacing on (n=170) -18 (-21, -14) pacing off (n=157) -11 (-16, -7) P = 0.02
COMPANION 6-month parallel 3-group comparison of atriobiventricular pacing with or without a defibrillator versus optimal medical therapy[43]	Not reported n = 1,520	Mean change medical therapy (n=207) -12 ± 23 active pacing (n=460) -25 ± 26 P < 0.001 pacing & defibrillator (n=478) -26 ± 28 P <0.001
COMPANION Exercise substudy within 6-month parallel 3-group comparison of atriobiventricular pacing with or without a defibrillator versus optimal medical therapy[44]	58 ± 23 n = 405	Mean change medical therapy (n=66) -9 pacing (n=280) -24 mean difference -15 P < 0.01
CARE-HF 3-month parallel group comparison of atriobiventricular	44 ± NR n = 813	pacing (n=409) 31 ± 22 no pacing (n=404) 40 ± 20 mean difference -10

pacing and medical therapy to medical therapy[45, 46]		P < 0.001
Higgins et al 3-month crossover & 6-month parallel comparison of CRT on or off 30 days after device (with defibrillator) implantation[47]	42 ± 24 n =490	Mean change NYHA class III/IV CRT on (n=107) -16 CRT off (n=96) -5 P = 0.02 NYHA class I/II CRT on (n=107) -1 CRT off (n=96) -4 P = 0.26
RAFT 12-month parallel comparison of CRT plus defibrillator versus defibrillator alone in subjects with atrial fibrillation[48]	38 ± 21 n = 229	Mean change CRT + ICD (n=101) -11 ± 18 ICD alone (n=95) -5 ± 21 P = 0.06
REVERSE 24-month parallel group comparison of CRT device turned on to prevent progression of asymptomatic to mildly symptomatic heart failure versus implanted CRT device turned off.[49]	26 ± 18 n = 262	Mean change CRT on (n=180) -8 ± 15 CRT off (n=82) -7 ± 15 P = 0.62

‡Reference number. †mean ± standard deviation or median (interquartiles). NR – not reported.

Results from randomized controlled clinical trials of a variety of other devices for treatment of heart failure are summarized in Table 7. All of the effects of these devices as measured by MLHFQ scores are credible given the pathophysiological effects of the devices that were studied and to what they were compared.

Table 7. Effects of Various Device Treatments for Heart Failure as Measured by the MLHFQ in Randomized Controlled Clinical Trials.

Study‡	**Baseline MLHFQ Scores†**	**Follow-up MLHFQ Scores†**
PABA-CHF 6-month parallel group comparison of pulmonary vein isolation (PVI) versus atrioventricular node ablation with biventricular pacing (Abl +BiV) to treat atrial fibrillation in patients with heart failure[50]	89 ± 12 n = 81	PVI (n=41) 60 ± 8 Abl + BiV (n=40) 82 ± 14 P < 0.001
Borggrefe et al 3-month crossover comparison of cardiac	38 ± 27 n = 164	Mean changes device on -11

contractility modulation device turned on versus off[51]		device off -9 difference -3 n = 151 P = 0.03
PEECH 8 week parallel group comparison of enhanced lower body external counter pulsation (EC) versus protocol defined medical therapy alone[52]	not reported n = 187	Mean changes 1 week after intervention stopped EC (n=77) -8.8 No EC (n=78) -3.5 P = 0.01 Mean changes 6 months after intervention stopped EC (n=79) -3.5 No EC (n=83) -2.8 P = 0.32
ESCAPE 6 month parallel group comparison of hospital care with or without pulmonary artery catheterization[53]	74 ± 18 n = 433	Effect size 1 month post discharge ~ -0.25 P = 0.05 6 months post discharge ~ -0.05 P = NS
TIME-CHF 18 month parallel group comparison of symptom versus N-terminal brain natriuretic peptide (NT-BNP) guided treatment [54]	40 ± 21 n = 491	Month 12 18 symptom 27 ± 19 27 ± 22 NT-BNP 28 ± 18 28 ± 18 P = NS
PROTECT 12 month parallel group comparison of treating to N-terminal brain natriuretic peptide (NT-BNP) goal of ≤ 1000 pg/ml versus standard care[55]	30 (14, 47) n = 151	Median changes in quarterly MLHFQ scores standard care (n=67) -5 (-18, 0) NT-BNP (n=70) -10 (-17, -7) P = 0.05 ≥10 point improvement standard care(n=76) 39% NT-BNP (n=75) 61% P = 0.03
HeartMate II 2-year parallel group comparison of a continuous versus pulsatile flow left ventricular assist device[56]	76 ± 18 n = 165	Month Continuous Pulsatile 3 37 ± 22 42 ± 23 12 34 ± 22 44 ± 23 24 30 ± 22 61 ± NR P = 0.03
NECTAR-HF 6 month parallel group study of vagal nerve stimulation device turned on versus off.[57]	43 ± 23 n = 87	on (n=63) 36 ± 21 off (n=32) 42 ± 24 mean difference in change -8 P = 0.05
HOT 6-month parallel group comparison of home oxygen therapy (15 hours/day or	60 ± 18 n = 74	oxygen (n=50) 46 ± 20 no oxygen (n=24) 49 ± 24 difference -4

nocturnal) to best medical care without oxygen. Study stopped due to poor adherence to prescribed oxygen[58]		P = 0.42
al Halabi et al meta analysis of 4 parallel 6 to 12 month comparisons of rate control using medications versus catheter ablation for atrial fibrillation in patients with heart failure[59]	89 ± 11 (n=81) 46 ± 22 (n=52) 57 ± 20 (n=41) 44 ± 19 (n=50)	Mean ablation – med difference -12 -14 -3 -18 Pooled -12 95% confidence interval -17, -7

‡Reference number.†mean ± standard deviation or median (interquartiles). NR – not reported.

Predictive Validity

The cardiac dysfunction (heart failure) and sequela that adversely affects patients' lives also increases their risks of being hospitalized and death. Therefore, the MLHFQ scores should be positively related to the risk of heart failure hospitalizations and mortality. Ideally, tests for this hypothetical relationship should control for unrelated risk factors and should not control for any other measures related to the presence or severity of the heart failure. Several less than ideal analyses summarized in Table 8 have confirmed the hypothesized positive relationship between MLHFQ scores and heart failure hospitalizations and mortality. Several of these studies also demonstrated that changes in MLHFQ scores were related to the risk of heart failure hospitalizations and or mortality.

Table 8. Relationship between MLHFQ Scores and the Risk of Heart Failure Hospitalizations and Mortality in Various Studies.

Study‡	Baseline MLHFQ Scores†	Heart Failure Hospitalizations and Mortality
EPICAL[60]	67 ± 24 n= 101	Events in first year of follow-up Deaths 24% HR¶ per10 points 1.23(1.02, 1.46) HF hospitalization or death 62% HR¶ per10 points 1.31(1.14, 1.49)
BEST[61]	MLHFQ scores rescaled to 1 to 7 3.8 ± 0.7 n= 2708	Deaths 7% HR¶ 1.46 (1.29, 1.66) HF hospitalization or death 65% HR¶ 1.40 (1.27, 1.54)
ESCAPE[62]	at admission 74 ± 17 1 month post discharge 57 ± 23	Hospitalization or death 1 to 6 months after hospital discharge ~ 60%

	n = 313	> 5 point improvement (n=213) vs > 5 point worsening(n=51) after 1 month HR* 0.30 (0.12, 0.75) > 5 point improvement (n=213) vs < 5 point change (n=49) after 1 month HR* 0.44 (0.16, 1.22)
Rodriguez et al[63]	48 ± 20 (based on 19 of 21 MLHFQ questions) n = 394	Deaths 18% HR¶ scores above median MLHFQ score = 49 versus below 2.61 (1.58, 4.30) Emergency readmissions 35% HR¶ scores above median MLHFQ score = 49 versus below 1.59 (1.13, 2.22)
A-HeFT[38]	51 ± 25 N = 1050	Deaths 8% HR* 1.01 (0.99, 1.02) HF hospitalization or death 25% HR* 1.02(1.01, 1.02) Changes over 3 months Deaths 6% HR* 1.02 (1.00, 1.03) HF hospitalization or death 27% HR* 1.01(1.01, 1.02)
I-PRESERVE[18]	43 ± 21 n = 3605	Hospitalization or death attributed to heart failure over median follow-up 4.3 years – 17% HR¶ per 5 points 1.6 (1.5, 1.7) 6-month changes in MLHFQ scores HR¶ per 5 points 1.2 (1.1, 1.3)
COACH[64]	44 ± 21 n = 661	3-year mortality 42% HR¶ per 10 points 1.12 (1.06, 1.19)

‡Reference number.†mean ± standard deviation or median (interquartiles).
¶HR ratio (95% confidence interval) unadjusted for any covariates.
*HR ratio (95% confidence interval) adjusted for varying heart failure related covariates that may have inappropriately reduced the apparent relationship to MLHFQ scores; unadjusted HR not reported.

IV. Discussion of the Strength of Evidence to Support Qualification

a. Tool Validity

In addition to the face validity of the content of the MLHFQ, the submitted validation studies provide ample evidence that the MLHFQ score measures what it purports to measure – adverse effects of heart failure on subjects' lives. The MLHFQ has been extensively validated by studies that have consistently shown that the MLHFQ score is strongly related to other measures of the symptoms, functional limitations, and social and psychological impact of heart failure on patients' lives. Furthermore, the latent pathophysiology of heart that adversely affects patients' lives also affects their longevity, and the MLHFQ scores have been repeatedly related to mortality.

b. Plausibility

The MLHFQ is based on a generally accepted conceptual model of health-related quality of life whereby a disease such as heart failure may adversely affect many aspects of an individual's life. It is certainly plausible that study subjects' ratings of widely recognized adverse effects of heart failure can be utilized as indicators to measure the ultimate treatment outcome of interest – improvement in the quality of subjects' lives.

The significant effects, or lack thereof, of various medical devices such as cardiac resynchronization therapy in the submitted randomized controlled clinical trials strongly support the veracity of the MLHFQ.

c. Extent of Prediction

The ability of a treatment to improve study subjects' quality of life by reducing the adverse impact of heart failure is the outcome of interest. Indeed, the question is whether the effects of a treatment on other study endpoints are predictive of and can serve as adequate surrogates for the outcome measured by the MLHFQ score, a direct measure of the outcome of interest.

d. Capture

The content of the MLHFQ is highly representative of the potential effects a treatment for heart failure may have on the adverse effects of heart failure including adverse effects of the treatment. Depending on the device being studied, the MLHFQ may not account for every major effect such as the effect of inappropriate defibrillator shocks. The MLHFQ has subjects weigh a number of potential adverse effects of heart failure using the same rating scale rather than being comprised of several more in-depth measurements of particular dimensions of heart failure related quality of life. Studies could supplement the MLHFQ by using more in-depth measures of particular hypothetical beneficial or adverse effects of a treatment.

V. Assessment of Advantages & Disadvantages

a. Advantages

The main advantage of using the MLHFQ as a treatment efficacy measure is that it is a direct measure of one of the two ultimate outcomes of public interest in contrast to less comprehensive intermediate or less predictive surrogate clinical endpoints. If a device is hypothesized to ameliorate the adverse effects of heart failure, much smaller studies generally would be needed to detect significant effect than to detect a significant reduction in mortality, the other ultimate outcome. The MLHFQ has been and can be used to study the effects of many types of devices aiming to treat heart failure including in several relatively small but successful crossover studies. Using the MLHFQ as a study endpoint presents little risk to study subjects. The MLHFQ is an established clinical outcome measure that has been employed in many studies worldwide.

b. Disadvantages

We are not aware of any examples of inaccurate conclusions about the efficacy of treatments for heart failure in regards to their effects on the subjects' quality of life. False positive conclusions are most likely when blinding is not possible and the control is not a similar type of device or sham. The MLHFQ does not usually stand alone as a study endpoint but serves as an ultimate confirmation of other objective intermediate or surrogate endpoints. Some have questioned the sensitivity of the MLHFQ when a treatment did not appear to have a significant effect as hoped. However, it is likely in these circumstances that the effects of the treatment on the pathophysiology of heart failure did not translate into substantial improvements in the quality of subjects' lives. The magnitude of this discrepancy depends on how effective the device truly is. False negative conclusions can be minimized by well-designed and executed studies with minimal missing data and an adequate number of subjects and statistical power to detect the hypothesized effect size.

VI. Consent to Public Disclosure and Use

The Minnesota Living with Heart Failure™ Questionnaire is copyrighted by the Regents of the University of Minnesota and can be obtained via the internet at **www.mlhfq.org** or **http://license.umn.edu/technologies/94019_minnesota-living-with-heart-failure-questionnaire**

VII. Supplemental Information

a. Patient Understanding of the MLHFQ

We are aware of only one qualitative study of how well respondents understood and interpreted the MLHFQ.[65]A Dutch translation of the MLHFQ was repeatedly self-administered by 31 subjects who had NYHA symptomatic heart failure with a history of being hospitalized. Investigators observed the respondents as they completed the questionnaire and conducted debriefing interviews. The investigators noted several linguistic differences between the original English and their Dutch versions that may have affected their findings. The investigators did not instruct the subjects on how to complete the questionnaire (see Table 2 Instructions for Completing the MLHFQ). The instructions would have avoided the problem with subjects not reading the brief instructions at the top of the MLHFQ (see Table 1) or the core question preceding the list of potential adverse effects of heart failure. Proper instruction also could have reduced instances when respondents only considered the presence and severity of a MLHFQ problem rather than how much it affected their lives. Regardless these investigators thought responses rating the severity of MLHFQ problems most likely corresponded with ratings of how much the problems adversely affected their ability to live as they wanted to live or the degree of functional impairment. Thus this type of misinterpretation doesn't raise major concerns about validity. Use of the instructions most likely would have reduced problems respondents had when an item wasn't applicable to their lives. A quick review of the questionnaire and discussion of any missing responses would also help address this potential threat to the validity of the MLHFQ. Use of the instructions would also help address respondents' lack of focus on their lives during past month (4 weeks).

This study by Hak et al also pointed out the difficulty respondents may have attributing impairments to their heart failure. Hopefully, use of the instructions (see item 3 in Table 2 Instructions for Completing the MLHFQ) would have helped them exclude problems that respondents definitely didn't think were due to their heart failure (heart condition). Respondents most likely do consider impairments that they cannot be sure were related to their heart failure, thereby increasing measurement error and decreasing the responsiveness of the MLHFQ to the effects of treatments that are specifically for heart failure. The use of multiple ways to describe a potential adverse effect seemed to create problems when respondents did not understand or ignored the word 'or'. Although the use of multiple descriptions may cause confusion, we nonetheless decided to use them because respondents may use different terms to describe phenomenon that are essentially the same. Under these circumstances no one word or phrase seemed to be universally meaningful (see conceptually similar descriptors used in the studies summarized above). Furthermore, separation into multiple questions would greatly increase redundancy and the length of the questionnaire, thus reducing willingness to use it in clinical trials and practice. In our extensive experience this issue hasn't resulted in many missing responses, and can be minimized by allowing respondents to ask for clarification if they don't understand the instructions or a question.

In summary, the MLHFQ is susceptible to some misunderstanding by respondents that could to some extent undermine its validity and responsiveness to treatments for heart failure. Given many years of use of the current version of the MLHFQ much of which is summarized in this Qualification Package we are reluctant to make major changes that would require extensive reevaluation of the MLHFQ. At this time, these issues are best addressed by proper

instruction on how to complete the MLHFQ and allowing respondents to ask for clarification of any instructions or questions they don't understand.

b. Applicable Patient Population

As described in the cited studies most of the data contained in the Qualification Package are based on patients with American College of Cardiology Foundation / American Heart Association stage C (structural heart disease with prior or current symptoms of heart failure) or stage D (refractory heart failure requiring specialized interventions).[66] Most study subjects had New York Heart Class II (slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in symptoms of heart failure), class III (marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes symptoms of heart failure) or class IV (unable to carry on any physical activity without symptoms of heart failure, or symptomatic at rest) heart failure. The MLHFQ is applicable to patients that have been given a clinical diagnosis of heart failure that is based in part on the presence of signs and symptoms of heart failure. None of the studies in the Qualification Package were primary prevention studies that enrolled ACCF/AHA stage A (at high risk for heart failure but without structural heart disease or symptoms) or substantial numbers of NYHA class I (no limitation of physical activity, ordinary physical activity does not cause symptoms of heart failure) subjects. The MLHFQ has been employed in major studies of diastolic (preserved ejection fraction) because despite differences in pathophysiology the symptoms and other adverse effects of heart failure are the same as the adverse effects seen in systolic heart failure with a reduced ejection fraction.[18] The CHARM investigators compared MLHFQ scores in groups of enrolled subjects with heart failure with preserved ejection fractions (n=1,097) or reduced ejection fraction (n=1,612).[22] The distributions of MLHFQ scores in each group were very similar as were the relationships to independent correlates including NYHA classifications. Overall and in each group identified as having a preserved or reduced ejection fraction the MLHFQ scores were not related to the ejection fractions.

c. Ceiling and Floor Effects

Table 9 summarizes available data on MLHFQ ceiling and floor effects. Most of the MLHFQ scores that were at or close to the best possible score of zero (ceiling) were from patients in NYHA class I (asymptomatic) who are typically excluded from clinical trials of treatments for heart failure. Only small percentages of NYHA class II subjects had MLHFQ scores that were at or close to zero. Only very small percentages of NYHA class III or IV subjects had MLHFQ scores that were at or close to the worse possible score of 105 (floor). The CHARM studies that enrolled 986 NYHA class II, 1,652 NYHA class III and 71 NYHA class IV subjects reported approximately 9% had MLHFQ scores < 10 and about 2% > 90.[22] The available data strongly suggest that ceiling and floor effects are not a major problem in studies of patients with NYHA class II to IV heart failure. Future studies could minimize any such problems by excluding subjects that have extreme MLHFQ scores.

Table 9. Ceiling and Floor Effects by NYHA Classification.

	NYHA Class I	NYHA Class II	NYHA Class III	NYHA Class IV

Bennett et al.[15]				
Subjects	30	82	81	17
Mean MLHFQ score	16	38	58	72
Ceiling scores < 10	43%	14%	0%	0%
Floor scores > 95	0%	0%	5%	6%
*Val-HeFT[24]				
Subjects	-	1903	1136	59
Mean MLHFQ score	-	24	44	63
Ceiling scores < 10	-	27%	7%	0%
Floor scores > 95	-	0%	0.3%	3%
Ceiling scores = 0	-	3%	0.5%	0%
Floor scores = 105	-	0%	0%	0%
*I-PRESERVE[18]				
Subjects	-	695	2402	83
Mean MLHFQ score	-	35	44	60
Ceiling scores < 10	-	10%	5%	0%
Floor scores > 95	-	0%	<0.1%	1%
Ceiling scores = 0	-	0.1%	0.6%	0%
Floor scores = 105	-	0%	< 0.1%	1%
*A-HeFT[38]				
Subjects	-	11	986	40
Mean MLHFQ score	-	39	50	65
Ceiling scores < 10	-	9%	2%	2%
Floor scores > 95	-	0%	5%	12%
Ceiling scores = 0	-	0%	0.3%	0%
Floor scores = 105	-	0%	0%	2%

*Unpublished information from referenced studies; – indicates 0 to only 3 such subjects included.

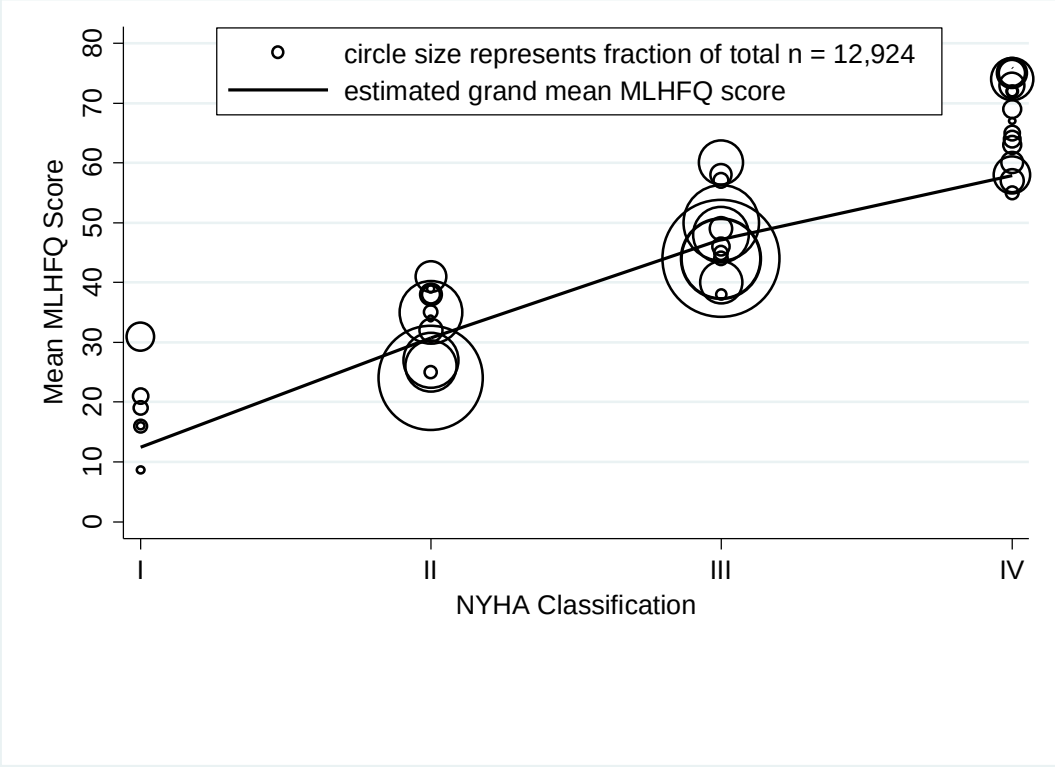
d. Responsiveness to Heart Failure Progression

After the clinical diagnosis of heart failure has been established, a typical course influenced by medical therapies is one of compensation (stable signs and symptoms) for the given severity of cardiac dysfunction (left ventricular ejection fraction, indices of cardiac diastolic dysfunction and so forth) with episodic decompensation due to aggravating factors such as increased sodium consumption, lapses in medication use and the onset or worsening of concurrent medical conditions such as pneumonia, ischemic heart disease, hypertension and cardiac valve disease. The MLHFQ is more a measure of the level of decompensation than the severity of the pathophysiology of heart failure. We aren't aware of any data concerning the progression from ACCF/AHA stage A (at high risk for heart failure but without structural heart disease or symptoms) to stage B (structural heart disease but without signs or symptoms of heart failure). The MLHFQ isn't applicable when subjects don't have a clinical diagnosis of heart failure. The effects of progression from stage C heart failure (structural heart disease with prior or current symptoms of heart failure) to stage D (refractory heart failure requiring specialized interventions) can be gleaned from studies of left ventricular assist devices (mean

baseline MLHFQ scores 76[56], 75[67], 75[68] and 73[69]) compared to device studies of less advanced heart failure (predominantly NYHA class II and III) where the mean baseline MLHFQ sores in Tables 6 and 7 range from 30 to 60. Note a few of the studies listed in Tables 6 and 7 enrolled predominantly NYHA class IV patients that were either hospitalized for heart failure (ESCAPE study[53]) or being treated for atrial fibrillation (PABA-CHF study[50]), a well-known aggravating factor.

Figure 1 shows progressive worsening (increase) in mean MLHFQ scores corresponding to worsening NYHA classifications (a measure of compensation as judged by symptoms experienced during ordinary physical activities). Figure 1 is based on data extracted from 19 studies.[5,14-16, 18,22, 24, 27, 29, 34, 36-38, 40, 53, 56, 67-69]. Grand means were estimated by regressing the extracted mean MLHFQ scores (n=47) on the NYHA classifications while adjusting for variation in studies that may have had varying approaches to NYHA classifications and approaches to administering the MLHFQ and handling of missing data. Each extracted mean MLHFQ score was weighted by the number of subjects it represented, and the analysis was clustered by study to estimate robust standard errors and confidence intervals. The adjusted mean MLHFQ scores (95% confidence interval) for NYHA classes I to IV, respectively were 12 (7 to 18), 31 (26 to 35), 47 (44 to 50) and 58 (47 to 69). The R^2 from a similar least squares regression model with the NYHA class as the only independent variable was 0.85, thus indicating that the MLHFQ scores and NYHA classifications are strongly related.

Figure1. Average MLHFQ Scores by NYHA Classification.



e. Meaningful Intra-Patient Change

Although we and others have tried to determine the smallest improvement in MLHFQ scores that would be meaningful to at least some patients, not necessarily all, we are not convinced that there is a satisfactory answer to this question. We administered the MLHFQ to 101 patients during a clinic visit.[70] Their MLHFQ scores covered a wide distribution with a median score of 54 (quartiles 34 and 74). Then the patients were told his or her questionnaire score and that this score represents how his or her life had been adversely affected during the past month. Next we asked; if a medication would improve your score by ____ (amounted varied down or up in 5 point increments starting at a 20 point improvement), would you be willing to take a medication if the medication had no costs or adverse effects? Seventy-two said they would take the medication if it would improve their score by 5 points. The same number of patients would take the medication if the benefit was a 2 out of 100 chance of living longer. Thus, a 5 point improvement was deemed to be important by the majority of these subjects. We did not ask about improvements of less than 5 points. Others examined changes in MLHFQ scores among a subgroup of 83 clinic patients who reported their dyspnea, fatigue and emotional status and overall condition had improved or worsened by 2 or 3 points (*aka* 'minimally' on a 7-point scale) during the past month.[71] Their mean change in the MLHFQ score over time (no specific treatment) was 4.8. Thus a 5-point change in the MLHFQ score was considered to be a minimal change by the majority of these subjects, but we do not know how many subjects felt a so-called minimal change would be worthwhile. The mean difference between NYHA classes estimated in Figure 1 was more than 10-points. The majority of clinicians most likely would consider an improvement that corresponds to one NYHA class or even less worthwhile. Indeed, many clinicians would prescribe a treatment that had no side effects or costs if it offers any likelihood of reducing the adverse effects of heart failure on a patient's life.

Given limited evidence on the amount of change in the LHFQ score that's meaningful to a substantial proportion of patients with heart failure perhaps one should categorize the change scores into 6 groups of $\pm < 5$, $\pm$ 5 to 10 and $\pm >10$ to describe the differences in the percentages of treatment and control groups that fall into each category. In addition, study subjects could be asked whether or not they thought there was a meaningful, important or worthwhile improvement in their daily lives. It is then possible to examine the distribution of change scores in the group that says there was. One could also determine how well the MLHFQ change scores discriminate the treatment and control groups using a c-statistic to represent the probability that an individual would have a better change score using the experimental treatment than the control intervention.

f. Recall Period

The 4-week recall period was used to allow enough time for patients to actually experience more than very short-term or less memorable changes in how their heart failure adversely affected their daily lives. We have not done patient interview or focus groups to support our conjecture that respondents most likely consider the present or past few days unless a more memorable severe decompensation such as hospitalization occurred within the past few weeks to month.[61] The 4-week recall is intended to capture more of these episodic adverse experiences that a much shorter recall period would more likely miss. There's no need to collect the MLHFQ more frequently than every four weeks. Collecting these data more

frequently is not advised to avoid capturing some of the same information captured by previous administrations.

g. Missing Data

Arbitrary criteria for 'useable' questionnaire data such as not more than 5%, 10%, 20% or even 50% (with multiple imputation) missing responses are often employed in the literature. A percentage or pattern of missing responses that assuredly wouldn't compromise the integrity (unbiased comparison, uncompromised statistical power) when the MLHFQ is employed as a study endpoint has not been established. Study sponsors and investigators who employ a questionnaire as a study endpoint need to make a concerted effort to minimize missing data including proper instruction of investigators and respondents and frequent monitoring of incoming data with remedial action when warranted. Studies that have 'high' percentages of missing responses raise concerns about whether subjects were properly instructed and whether the incoming data were closely monitored. The problem of missing responses needs to be discussed before signing off on a sponsor's study protocol that should include plans to analyze and report the extent, patterns, and proposed method of imputation and perhaps sensitivity analysis that would provide some post hoc assurances that the missing data in a study did not compromise the study's integrity.

Certainly some of the studies cited herein did not appear to check the questionnaires for missing responses as recommended. These problems did not occur in the studies that properly instructed the investigators on administering the MLHFQ, (e.g. see references 9 and 38). It is well known that questions that are sexual in nature tend to have higher rates of missing values.[72] Contrary to typical methods of questionnaire development these particularly problematic questions were retained even though that might not apply to many retired elderly subjects with heart failure because in our experience they can be very important when they do apply such as in younger patients with heart failure. Thus the extent of this problem may depend in part on the characteristics of the study subjects. A sensitivity analysis of study data that omitted a particular question(s) with an alarming percentage of missing values from all questionnaires would provide some insight into their potential effect of the missing values on the study comparison.

Many of the questionable imputation methods (mean response, carry forward, etc.) for missing data that have been used by the investigators have been based on the questionable assumption that the missing values were missing at random. It is very difficult to identify which missing values were not random. The missing at random assumption should be questioned whenever missing values are related to other study variables such as the subject's age, gender, comorbidities, etc. A method of multiple imputation that incorporates variables that are associated with the responses (missing or not) would be an acceptable approach when responses might not be missing at random. The MLHFQ does not have a pre-specified method for imputing missing values other than assigning a zero when a response to an item is known to be missing because the item did notapply to the patient when the MLHFQ was completed. Otherwise some sort of modern multiple imputation procedure may be the best approach to unbiasedly handling missing responses. Logically the imputation model should include other non-missing responses that are available before and after the form with missing values. In addition, the imputed values may be less biased when other available measures of

heart failure signs, symptoms, physical function and treatments as well as patient characteristics such as age are included in the imputation model.

Deaths are not uncommon in clinical trials of patients with end stage heart failure. Users should pre-specify how data that are completely missing due to deaths will be handled. More frequent data collection may provide scores that are close to the time of death that could be carried forward as reasonable estimates.

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