MEDICAL DEVICE DEVELOPMENT TOOL (MDDT) QUALIFICATION DECISION SUMMARY FOR MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE (MLHFQ)

BACKGROUND

MDDT NAME: MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE (MLHFQ)

SUBMISSION NUMBER: MDDT026

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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a 21-item paper self-administered questionnaire designed as a measure of heart failure, as indicated by its adverse effects on patients' lives. The MLHFQ quantifies a single overall score as a measure of the impact of heart failure on the patient's life. The items capture the ways heart failure and treatments can affect the following dimensions of patients' quality of life: 1) physical symptoms and signs of heart failure, 2) common physical/social functions, 3) psychosocial and cognitive function, and 4) overall adverse impact on quality of life. The total score of MLHFQ alone was considered for qualification, exclusive of any separate dimensions or subscales.

After going through a brief set of instructions, respondents use a six-point rating scale, from none or not applicable to very much, to indicate how much each of the 21 potential adverse effects of heart failure listed on the MLHFQ affect their ability to live as they wanted during the previous 4 weeks (approximately 1 month).

QUALIFIED CONTEXT OF USE

The paper self-administered version of the MLHFQ can be used to determine whether a device treatment is effective for improving patients' quality of life by reducing the adverse impact of heart failure. The instrument can be used as a secondary endpoint in feasibility and pivotal studies of outpatients with symptomatic (NYHA class II and III) heart failure. The 21-item instrument is completed by patients after they have been properly instructed by study staff. Study staff should be properly trained to instruct the patient and if needed, administer the questionnaire, according to pre-set administration instructions. The MLHFQ instrument may be used by medical device companies and sponsor-investigators in controlled clinical trials designed to test superiority or non-inferiority of medical devices in support of regulatory submissions.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

Much of the evidence submitted to support the qualification of the MLHFQ comes from its long history of use in medical device and pharmaceutical clinical studies, as well as additional publications evaluating the psychometric and statistical properties of the score. Primarily

quantitative in nature, the publications support the reliability and validity of the MLHFQ total score in the populations sampled in the studies. In summary, the evidence provided in the qualification package supports the use of the MLHFQ score to evaluate a patient's perception of the impact of heart failure on his/her life over the previous 4 weeks. The evidence submitted in support of the MLHFQ qualification is summarized as follows:

Validity Evidence Based on Content

The items and concepts included in the MLHFQ were initially determined and supported utilizing expert opinion and a survey of symptomatic heart failure patients.[1,2] Subsequent studies provided additional support for the importance of the items and concepts included in the questionnaire to patients experiencing heart failure.[3-7] In addition to the relevance of the item content, evidence of a single measured construct supports the use of a single summary score.[8] An unpublished reanalysis of published data[9-12] provided robust evidence of low levels of ceiling and floor effects in NYHA classes II and III. Expert opinion was utilized to justify the 4-week recall period, with no input from patients.

Validity Evidence Based on the Construct

Evidence of the relationships between the MLHFQ and other assessments of heart failure, including other patient-reported outcomes (PROs), clinician rating scales, and performance outcomes, were submitted.[9,13-20] The strength and the direction of the relationships were evaluated. Table 1 shows that within studies, the differences in MLHFQ scores are associated with the differences in NYHA classification. Across studies there is some variation in mean scores by class.

Table 1. Mean MLHFQ scores by NYHA Class and Study

Published Paper	NYHA Class I	NYHA Class II	NYHA Class III	NYHA Class IV
Gorkin et al[14]	31±25	44±26		--
Quittan et al[18]	19±16	35±24	44±22	67±27
Bennet et al[9 NR]	16	38	58	72
Kubo et al[21 NR]	--	34	57	69
Heo et al[22]	--	41±25		53±22
Witham et al[6 NR]	9	25	38	--
Holland et al[23]	32±21		49±21	57±23
Rose et al[24]	16±15	38±25		45±23
Gallanagh et al[25]	--	--	40±20	55±19
Carson et al[12]	--	--	50±25	63±25
Means±Standard Deviations; NYHA = New York Heart Association. NR=Standard Deviations Not Reported.				

Reliability

The reliability of the MLHFQ has been assessed in several publications. Test-retest reliability and consistency was assessed in stable patients in four individual studies and one meta-analysis. Despite wide variation in the time between administrations, the MLHFQ showed strong test-retest reliability in all studies, as shown in Table 2.

Table 2. Test-Retest Reliability of the MLHFQ across studies

Published Paper	Sample Size	Administration Time from Baseline	Reliability Estimate
Rector et al.[19]	181	1 week	r = 0.93
Rector et al.[10]	1,912	4 & 12 Months*	r = 0.86
Witham et al.[6]	54	1 Week	ICC = 0.89
Garin et al.[26]	81 Studies	NR	ICC = 0.84
Rector et al.[11]	2,904	6 & 14 Months*	r = 0.80
r=Pearson correlation coefficient; ICC=Interclass correlation coefficient; NR=Not reported; * =based on longitudinal structural equation model estimates			

Reliability was also assessed utilizing Cronbach's Coefficient Alpha in eight studies. As shown in the table below, the reliability was > 0.90 in every study referenced.

Table 3. Internal Consistency of the MLHFQ

Published Paper	Sample Size	Scores Mean±SD	Cronbach's Alpha
Rector et al.[19]	197	47 (28, 61)*	0.94
Gorkin et al.[14]	135 (NYHA I)	31±25	0.95
Gorkin et al.[14]	123 (NYHA II-III)	44±26	0.94
Bennett et al.[9]	211	45±27	0.95
Riegel et al.[27]	1,136	52±25	0.92
Heo et al.[22]	638	51±23	0.91
Supino et al.[28]	50	40±27	0.96
Rector et al.[11]	3,605	42 (28, 58)*	0.92
Garin et al. [8]	3,847	36±22	0.92
*= median (interquartile)			

Responsiveness

Evidence from clinical studies involving medical devices was submitted to support the responsiveness of the MLHFQ. Studies involving cardiac resynchronization therapy[29-38] provided robust evidence supporting the responsiveness, while other device and pharmaceutical treatments for heart failure were not as consistently clear.[39-46] In all of the studies cited and where information was available, the large majority of patients were of NYHA Class II and III. The results are considered most robust in these patients.

Extent of Prediction

The extent of the prognostic association between the MLHFQ and hospitalization or death was described in the cited literature included in the qualification package.[11,12,47-51] An increase in MLHFQ scores were consistently associated with an increase in likelihoods of death, as well as hospitalization or death, regardless of adjustment for covariates. Since the majority of patients in these studies were NYHA class II or III, the evidence provides support for qualification in this specific population.

DISCUSSION OF THE EVIDENCE STRENGTH TO SUPPORT QUALIFICATION

The MLHFQ has an extensive history of use in clinical trials evaluating medical devices for the treatment of heart failure and other heart failure therapies. This history and CDRH's experience with the questionnaire were considered during the review of the data submitted in the Qualification Package. The developer submitted evidence that included peer-reviewed publications and reanalysis of previously published data, which demonstrated that the MLHFQ was valid and reliable for the qualified context of use. Along with other evidence, the correspondence between MLHFQ scores and other measures of heart failure, including both hospitalization and survival were strong evidence for the utility of the MLHFQ scores.[11,12,47-51] There were a number of examples that showed an association between MLHFQ scores and NYHA classifications. Moreover, the MLHFQ's widespread use in trials provided confirmation of responsiveness due to treatment, while other studies showed the reproducibility of scores in stable patients. In addition to the test-retest reliability, the reliability as measured by Cronbach's Alpha was consistently high across submitted studies, supporting the precision of the scores. The multiple sources and types of evidence provide confidence in the accuracy and meaning of the scores. The MLHFQ captures important aspects of treatment effectiveness from the patient's perspective in a reliable and reproducible manner.

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

Assessments of Advantages of Using the MDDT:

The main advantage of using the MDDT is that it provides a reproducible approach to measuring the impact of heart failure on multiple dimensions of patients' quality of life listed in the "Tool Description and Principle of Operation" section. The MDDT has already been used in numerous heart failure device clinical trials reviewed by CDRH. Therefore, CDRH has experience in evaluating and interpreting the MLHFQ results in clinical trials. The MDDT has the potential to impact multiple device development programs in the area of heart failure as the Agency considers the patient's perspective in rendering regulatory decisions. As discussed in the "Strength of Evidence" section, data from studies supporting the MDDT's validity and predictive ability suggest that it has a high likelihood of an advantage for use in clinical investigations of heart failure devices.

Assessments of Disadvantages of Using the MDDT:

The following disadvantages of using the MDDT were identified: 1) the inability to measure all important outcomes in heart failure patients; 2) potential susceptibility of a placebo device effect; 3) potential impact of missing data; 4) potential bias due to care provider participation in the MLHFQ administration; 5) potential inaccurate responses due to failure to read the instructions or the core question preceding the list of adverse effects; and 6) potential bias due to memory effects related to the 4 week recall period. When specific patient populations are used, such as the heart failure populations described in the context of use, the inability to measure all important outcomes in heart failure patients can be mitigated through the MLHFQ's use as a secondary endpoint. The study design, such as the use of randomized trials, can assist in addressing placebo device effect or minimizing the impact of missing data. Additionally, limiting use of the MDDT as a secondary endpoint can further mitigate concern of a placebo device effect and memory effects related to the 4 week recall period, as the data will be considered along with primary endpoint data.

Risk mitigation has been performed to address the disadvantages listed above. These mitigations included specifying the patient population in the context of use, recommending that non-care providers (e.g., administration staff) distribute the instrument to the patient and staff administering the MLHFQ be properly trained, and utilizing the included administration instructions, to ensure patient understanding of instructions to minimize unintentional bias.

Additional Factors for Assessing Advantages and Disadvantages of Using the MDDT:
There is minimal uncertainty associated with the MDDT with respect to the specified context of use based on the submitted evidence and documented history of use in clinical trials. The MDDT can be used to facilitate development and regulatory evaluation of heart failure technologies.

CONCLUSIONS

The materials submitted for qualification included numerous published studies utilizing the MLHFQ, encompassing a variety of medical device and other trials for the treatment of heart failure. These materials provide support for the use of the MLHFQ within the specified context of use.

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