MEDICAL DEVICE DEVELOPMENT TOOL (MDDT) QUALIFICATION
DECISION SUMMARY FOR
KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

BACKGROUND

MDDT NAME: KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

SUBMISSION NUMBER: MDDT020

DATE OF SUBMISSION: JANUARY 19, 2016

CONTACT: JOHN SPERTUS, MD, MPH
SAINT LUKE'S MID AMERICA HEART INSTITUTE
4401 WORNALL ROAD
KANSAS CITY, MO 64111
EMAIL: SPERTUSJ@UMKC.EDU

TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period.

The KCCQ tool quantifies the following six (6) distinct domains and two (2) summary scores:

- **KCCQ Symptom Domain** quantifies the frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An overall symptom score is generally used in analyses; subscale scores for both frequency and severity are also available.

- **KCCQ Physical Function Domain** measures the limitations patients experience, due to their heart failure symptoms, in performing routine activities. Activities are common, gender-neutral, and generalizable across cultures, while also capturing a range of exertional requirements.

- **KCCQ Quality of Life Domain** is designed to reflect patients' assessment of their quality of life, given the current status of their heart failure.

- **KCCQ Social Limitation Domain** quantifies the extent to which heart failure symptoms impair patients' ability to interact in a number of gender-neutral social activities.

- **KCCQ Self-efficacy Domain** quantifies patients' perceptions of how to prevent heart failure exacerbations and manage complications when they arise. This scale is not included in the summary scores.

- **KCCQ Symptom Stability Domain** measures recent changes in patients' symptoms; their shortness of breath, fatigue or swelling. It is compares patients frequency of heart failure symptoms at the time of completing the KCCQ with their frequency 2 weeks ago. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of a study and shortly thereafter, as a measure of the acute response to treatment. This domain is not included in the summary scores.

- **Clinical Summary Score** includes total symptom and physical function scores to correspond with NYHA Classification.

- **Overall Summary Score** includes the total symptom, physical function, social limitations and quality of life scores.

Note: KCCQ Qualification includes only the Symptom, Physical Limitation, Social Limitation, Quality of Life (QOL) domains and the Overall Summary Score.

KCCQ responses are provided along a rating scale continuum with equal spacing from worst to best. On average, the 23-item version takes 4-6 minutes to complete. The concepts quantified in the KCCQ are designed to be relevant and appreciable by all heart failure patients specified in the qualified context of use. The Flesch Reading Ease is 76 and the Flesch-Kincaid Grade level is 6.7. The tool can be used to evaluate the effectiveness of a heart failure medical device studied in a clinical study.

QUALIFIED CONTEXT OF USE

The paper self -administered version of the 23-item KCCQ questionnaire is used for quantifying patients' health status, including the symptoms (frequency and burden), physical and social limitations, and quality of life impact due to the heart failure syndrome. The instrument can be used in feasibility and pivotal studies of patients with symptomatic heart failure (e.g. AHA/ACC Stages of Heart Failure C and D, or NYHA II-IV).

The KCCQ instrument may be used by medical device companies and sponsor-investigators for evaluation of safety and effectiveness for heart failure medical devices to support regulatory submissions. The KCCQ instrument, specifically the Symptom Domain Score, Physical Limitation Domain Score, Social Limitation Domain Score, Quality of Life Domain Score and Overall Summary Score, can be used as a component of a composite primary endpoint or secondary endpoint in a feasibility or pivotal clinical trial evaluating heart failure medical devices. The instrument can be used in superiority and non-inferiority trials evaluating out-patients or in-patients with heart failure syndrome. For in-patient studies, post-discharge outcomes could be helpful to define the health status benefits of treatment.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

Published literature on previous clinical studies as well as unpublished concept elucidation and

cognitive interview study reports were submitted as evidence to support the qualification of the MDDT for the qualified context of use. Proprietary data including interview logs, secondary analyses of clinical study data and a missing data analysis were also submitted to support the validity of the MDDT. The scientific evidence provided in the qualification package demonstrates the validity and reliability of the MDDT to quantify a patient's perception of their overall health status, including heart failure symptoms, social and physical limitations, and QOL. The evidence to support the KCCQ validity submitted is as follows:

Validity Evidence Based on Content

The concepts of interest that the KCCQ measures is supported by evidence based on qualitative concept elucidation studies and cognitive debriefing exercises in heart failure patients that assessed item generation, data collection methods, the instrument administration model, recall period, response options, instrument format, instructions, patient understanding, scoring, as well as respondent and administrator burden. Additional studies were conducted by other investigators who performed further validation to support the KCCQ concepts.[1,2]

Validity Evidence Based on the Construct

Validation studies presented by Green, Porter, Bresnahan, and Spertus (2000) and Spertus, Peterson, and Conard (2005) were cited to provide evidence of correlation between the KCCQ domains and other heart failure constructs, such as the 6 minute walk test, NYHA class, and Short Form 36 (SF-36). A summary of the construct validity assessments of the KCCQ qualified domains are presented in Table 1. [3,4]

Table 1. Summary of Construct Validity Assessments of the KCCQ[3,4]

Domain	Reference Measure	Statistics	Validity Type, Analysis
Physical Function	1) 6 minute walk test, 2) NYHA class, 3) SF-36 physical 4) MLHFQ physical	1) r = 0.48** 2) r = -0.65** 3) r = 0.84** 4) r = 0.65**	Convergent validity, r=Spearman correlation coefficient
Symptom	NYHA class (I, II, III, IV)	Mean score difference: F=51.3** Linear trend: F=142.2**	Convergent Validity ANOVA
Social Limitation	1) NYHA class 2) SF-36 social scale	1) r = 0.62 ** 2) r = -0.57 **	Convergent validity Correlation
Quality of life	1) SF-36 general health 2) NYHA	1) r = 0.45 ** 2) r = -0.64 **	Convergent validity Correlation
KCCQ Overall Summary	1) NYHA class 2) Survival or hospitalization	1) Mean score difference: F=41.9** Linear trend: F=156.8** 2) Mean score difference: 34.1 vs. 52.1**	Convergent and discriminant validity ANOVA, 2-sample t-test

r=Spearman correlation coefficient; F=F statistics; $p<0.01$; **$p\leq0.001$; ***$p\leq0.0001$; MLHFQ=Minnesota Living with Heart Failure Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; SF-36 = Short from-36; NYHA = New York Heart Association.

Reliability

Green et al. (2000) was cited to provide evidence of the KCCQ reliability. Both test-retest reliability and internal consistency reliability tests were presented in the validation study. A summary of the test-retest results presented in the publication is shown in Table 2.

Table 2. Test-Retest Reliability of the Qualified KCCQ Domains among Stable Patients[3]

KCCQ Domain	Baseline Mean ± SD	6-Week Mean ± SD	Difference Mean ± SD	P-value	ICC
Physical limitation	63.4 ± 26.3	64.4 ± 25.9	1.1 ± 16.4	0.25	0.80
Symptoms	69.1 ± 23.8	69.9 ± 24.1	0.8 ± 15.1	0.33	0.80
Social limitation	56.5 ± 30.5	58.9 ± 29.7	2.4 ± 19.2	0.03	0.79
Quality of life	58.6 ± 27.5	59.4 ± 26.3	0.9 ± 17.2	0.37	0.79
Overall Summary Score	62.1 ± 24.0	63.4 ± 23.8	1.3 ± 11.8	0.04	0.88

ICC=Interclass correlation coefficient

The internal reliability assessed by Green et al. (2000) of the qualified domains was > 0.70. The Cronbach's alpha for each qualified domain is listed below in Table 3.

Table 3. Internal Consistency of Qualified KCCQ Domains[3]

Domain	Cronbach's alpha
Physical Limitation	0.90
Total Symptom Score	0.88
Social Limitation	0.86
Quality of Life	0.78
Overall Summary Score	0.95

Responsiveness

Two observational studies of different patient cohorts provided evidence that the KCCQ was responsive to changes in heart failure status over time (Green et al., 2000 and Spertus et al., 2005). The evidence indicated that the KCCQ is equally sensitive to gains and losses in the measurement of concepts of interests for the population specified in the qualified context of use when compared to other, similar measures.

Extent of Prediction

Prognostic association between KCCQ Overall Summary Score and hospitalization or death was described in the cited literature included in the qualification package.[5-7] Controlling for other indicators and measures of heart failure, low KCCQ Overall Summary Scores were consistently associated with poor prognosis after 1 year. The populations studied consisted of patients with heart failure after acute myocardial infarction, patients undergoing transcatheter aortic valve replacement (TAVR) and patients with an ischemic heart failure etiology.

DISCUSSION OF THE EVIDENCE STRENGTH TO SUPPORT QUALIFICATION

The KCCQ has an extensive history of use in clinical trials evaluating heart failure medical devices to inform regulatory decisions. This experience was considered during the review in

addition to the data submitted in the Qualification Package and was used as evidence to support the Agency's decision to qualify the KCCQ as a MDDT. The developer also submitted evidence that includes peer-reviewed publications and unpublished and proprietary data, which demonstrated that the KCCQ tool was valid and reliable for the qualified context of use. Along with other evidence, the correspondence between KCCQ scores and other measures of heart failure, including hospitalization and survival were good indicators of the accuracy of the scores.[3-7] The overall score of the KCCQ was shown to predict hospitalization and mortality, as well as differential risk based on cut scores. Similarly, there were a number of examples of the match between KCCQ scores and NYHA classifications and between change scores and physician ratings of change. The multiple sources and types of evidence provide confidence in the accuracy of the scores. Evidence of the reliability was provided as both test-retest reliability and internal consistency. All of the reported reliabilities support the precision of the scores. The KCCQ captures the 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 robust approach to measuring the impact of heart failure on symptoms, function of patients and quality of life. 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 KCCQ 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, the MDDT has been extensively studied for validity and predictive ability; therefore 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; and 4) potential bias due to care provider participation in the KCCQ administration. 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. 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 or a component of a composite endpoint can further mitigate concern of a placebo device effect, as the data will be considered along with other 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, evaluating a missing data analysis performed by the developer to assess the handling of missing data and its impact on scoring, and recommending that non-care providers (e.g., administration staff) distribute the instrument to the patient 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 its extensive validation 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 submitted materials and correspondence to clinical outcomes in numerous pivotal heart failure medical device trials in the past provide sufficient evidence to support the validity and reliability of the KCCQ for the qualified context of use.

REFERENCES

1. Gwalteny C, Slagel A, Martin M, Ariely R, Brede Y, "Hearing the voice of the heart falilure patient: Key experienced identified in qualitative interviews," *British Journal of Cardiology*, 19:e1-7 (2012).

2. Pierson RF, Traina S, Braan L, Bushnell SM, McCarrier K, Martin ML, " The Most Frequently Reported Symptoms of Heart Failure, their Impacts on Daily Life, and Why these Matter with Respect to Clinical Outcomes*," 21st Annual Conference International Society for Quality of Life Research*, Poster 1017 (2014).

3. Green CP, Porter CB, Bresnahan DR, Spertus JA, "Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure," *J Am Coll Cardiol*, 35:1245-5 (2000).

4. Spertus J, Peterson E, Conard MW, et al., "Monitoring clinical changes in patients with heart failure: a comparison of methods," *Am Heart J*, 150:707-15 (2005).

5. Heidenreich PA, Spertus JA, Jones PG, et al., "Health status identifies heart failure outpatients at risk for hospitalization or death," *J Am Coll Cardiol,* 47(4):752-756 (2006).

6. Soto GE, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic Value of Health Status in Patients With Heart Failure After Acute Myocardial Infarction. *Circulation,* 110(5):546-551 (2004).

7. Arnold SV, Spertus JA, Vemulapalli S, et al., "Association of Patient-Reported Health Status With Long-Term Mortality After Transcatheter Aortic Valve Replacement: Report From the STS/ACC TVT Registry," *Circulation Cardiovascular Interventions*, 8(12) (2015).

CONTACT INFORMATION FOR ACCESS TO TOOL

FOR ACCESS TO THE KCCQ, PLEASE CONTACT:
JOHN SPERTUS, MD, MPH
SAINT LUKE'S MID AMERICA HEART INSTITUTE
4401 WORNALL ROAD
KANSAS CITY, MO 64111
EMAIL: SPERTUSJ@UMKC.EDU