# Input on MEDCAC Voting Questions

***Health Outcomes in Heart Failure Treatment Technology Studies***

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## Background

We are a group of cardiologists who specialize in heart failure with preserved ejection fraction (HFpEF), also known as diastolic heart failure. We provide clinical care and conduct clinical trials in HFpEF patients, and each of us has a long-standing clinical and research interest in HFpEF. Here we seek to provide input to the MEDCAC panel on the questions below, specifically with regards to HFpEF.

**Question #1:** How confident are you that the following are standalone, meaningful primary health outcomes in research studies of heart failure treatment technologies:

a. Heart failure hospitalization;
b. Heart failure hospitalization or heart failure hospitalization equivalent events (i.e., outpatient IV therapy for heart failure);
c. Total Hospitalizations?

**Response:** We believe that HF hospitalizations, HF hospitalization equivalents, and total hospitalizations are all important endpoints in research studies of HF treatment devices from both an efficacy and safety standpoint. However, not all devices will involve a mechanism that reduces hospitalizations. Therefore, combining hospitalization endpoints with functional endpoints (i.e., exercise capacity) and/or quality of life endpoints is important in patients with HF.

HF hospitalizations are clearly associated with poor outcomes and high costs to the healthcare system.[1] However, as reviewed in a recent paper by Butler et al., there are no uniform admission criteria for HF hospitalization, and the decision to hospitalize is quite subjective.[2] Furthermore, in the current healthcare environment, there is pressure to avoid HF hospitalization as it is a quality metric by which hospitals are

judged.[3,4] Thus, patients with worsening HF are often treated in alternate healthcare settings, with risk profiles that are comparable to hospitalized HF patients.[5] Finally, although current HF hospitalizations in clinical trials are typically analyzed in a time-to-first-event fashion, recurrent hospitalizations may be a more important indicator of increased risk; thus recurrent events analyses may be more appropriate for HF clinical trials.[6]

Besides the aforementioned issues regarding HF hospitalizations, patients with HFpEF often have multiple comorbidities with several competing risks for hospitalization and death.[7] Thus, while HF hospitalizations (and total hospitalizations) are important aspects of the patient journey to evaluate in HF clinical trials, we believe that due to the limitations outlined above, exercise capacity and quality of life outcomes should be included in conjunction with hospitalizations in device trials for HFpEF. Given the limited therapeutic options for HFpEF and the pressing unmet need to improve exercise capacity and quality of life (QOL) in HFpEF, strong consideration should be given to coverage of medical devices that are shown to improve these endpoints in HFpEF clinical trials.

**Discussion:**

- For each health outcome with greater than or equal to intermediate confidence (≥ 2.5), please discuss the appropriate length of follow-up post-heart failure intervention for assessing this outcome;
- Please discuss important considerations when assessing the merits of composite outcomes in research studies of heart failure treatment technologies which include the combination of mortality, heart failure hospitalization, or heart failure hospitalization equivalent events.

**Response:** For all of the aforementioned outcomes, we believe that 6 months follow-up is appropriate for assessing device- and procedure-related safety and efficacy. In our experience, lengths of follow-up beyond 6 months can be problematic due to mounting competing risks from the multiple (average = 5.5) comorbidities that are typically present in older HF patients, particularly those with HFpEF, the dominant form of HF in older individuals.[8] The 6-month time frame is particularly appropriate for trials where physical function and QOL outcomes are primary outcomes. There are several historical cardiovascular device precedents for 6-month endpoint, such as with cardiac re-synchronization therapy where a 6-month quality of life primary endpoint was supported by later preservation of clinical benefit with an acceptable safety profile. Ultimately, a 6-month follow-up timeframe balances what is meaningful for patients (i.e., they would want to see benefit early after device placement), and yet is long enough to show some durability of the treatment effect. Longer follow-up to 12 months is appropriate for trials where hospitalization events are the primary outcome.

Composite outcomes may not be ideal for most HF devices because the required sample size may be quite large which is often problematic for clinical trials of HF devices. An alternate analytic approach such as the Finkelstein-Schoenfeld method,[9] which incorporates multiple endpoints, is preferable. This method is also advantageous because it can combine multiple endpoints of interest, such as mortality, hospitalizations, and exercise capacity and/or quality of life metrics into a single

composite event and requires a smaller number of patients than a large-scale outcomes-driven HF clinical trial.

**Question #2:** How confident are you that surrogate and intermediate endpoints are predictive of standalone, meaningful primary health outcomes (e.g., reduction in mitral regurgitation, cardiac remodeling, ejection fraction, or biomarkers) in clinical research studies of heart failure treatment technologies for:

a. Heart failure with preserved ejection fraction;
b. Heart failure secondary to mitral regurgitation where the focus of therapy is mitral valve repair/ replacement;
c. Heart failure with reduced ejection fraction (e.g., cardiac remodeling, ejection fraction)?

**Response:** In HFpEF, biomarkers (e.g., B-type natriuretic peptide) and cardiac remodeling (e.g., left atrial size) may be of limited utility given the general lack of prior studies demonstrating that a change in one or more of these parameters is associated with improved hard endpoints, health-related quality of life, and/or exercise capacity. At the very least, the intermediate endpoint should be related to the mechanism of the device. Nevertheless, for Phase 3 trials, we believe that endpoints that are not simply surrogates and rather are indicative of the patient journey are of utmost importance. Thus, for Phase 3 clinical trials of HFpEF devices, we advocate health-related QOL, exercise capacity, and/or HF hospitalizations as the most important endpoints.

It is important to note that physical function measures (e.g., KCCQ physical functioning component, 6MWT, peak $VO_2$) are **not** surrogate or intermediate endpoints but rather *clinically meaningful endpoints.* Thus, we believe that these endpoints are far better than the examples given above (mitral regurgitation severity, LV remodeling, ejection fraction, biomarkers), which are not clinically meaningful by themselves.

Some have stated that physical function studies are merely surrogate endpoints for clinical events (death, hospitalization). Indeed, peak $VO_2$ and 6MWT are strong, independent predictors of cardiovascular events and death in HF patients.[10] However, unlike other "surrogate" and "intermediate" endpoints, these measures are clinically meaningful in their own right, above and beyond, and indeed independent of, any impact on clinical endpoints.

In conclusion, physical function measures are valid, clinically meaningful, primary outcomes for clinical trials in HF, and especially in HFpEF trials which often enroll elderly patients in whom quality of life is often more important than quantity of life.

**Discussion:**

- If greater than or equal to intermediate confidence (≥ 2.5), please identify the specific surrogate or intermediate endpoints and associated disease or therapy which you believe are sufficiently predictive of meaningful health outcomes.
- Please discuss how these intermediate and surrogate endpoints meaningfully contribute towards the evidence base for heart failure treatment technologies.
- Please discuss important factors to consider when assessing the utility of surrogate and intermediate endpoints.

**Response:** For HFpEF, the surrogate/intermediate endpoints must be matched to the device being tested. For example, for a clinical trial of an interatrial shunt device (which decompresses the left atrium), an exercise pulmonary capillary wedge pressure (PCWP; a surrogate for left atrial pressure) outcome measure for a phase 2 trial would be appropriate.[11] Although patients with HFpEF often have several pathophysiologic abnormalities (both cardiac and extra-cardiac), elevated PCWP during exercise is central to the pathogenesis of the HFpEF syndrome,[12] and workload-corrected PCWP correlates with symptoms and outcomes.[13] Thus, if we were to pick a single intermediate surrogate endpoint in general in HFpEF, exercise PCWP would likely be high on the list. However, as stated above, the intermediate endpoint should really be tailored to the device being tested, particularly in HFpEF, where there is less data (compared to HFrEF) on intermediate endpoints and how those endpoints relate to outcomes that are more closely associated with the patient journey.

**Question #3:** How confident are you that quality of life measures [e.g., Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living With Heart Failure Questionnaire (MLWHFQ):

a. Are adequate measures which reflect the patient experience;
b. Should be included as the standalone, meaningful primary health outcomes in research studies;
c. Should be included as a composite standalone, meaningful primary health outcomes in research studies?

**Response:**

Quality of life measures, particularly the KCCQ, reflect the patient experience in HFpEF.[14] The KCCQ, the most widely accepted measure of health-related QOL in patients with HF, is valid and reliable. It is a 23-item self-administered questionnaire that quantifies physical function, symptoms, social function, self-efficacy, and QOL in patients with HF. Scores range from 0-100; higher scores indicate better function. The KCCQ score is an independent predictor of clinical outcomes such as hospitalization and mortality in outpatients with HF,[15,16] and those recently hospitalized for ADHF.[17] It is a reliable and valid measure in HF patients, more sensitive to change than other measures of QOL in various popuations, specifically including HFpEF.[18-20] The KCCQ has been validated as an endpoint specifically in HFpEF[14]. In addition, in the NEAT-HFpEF trial,[21] KCCQ worsening was concordant with a reduction in physical activity (as measured by accelerometry) in the isosorbide arm. In the SOCRATES-Preserved trial (Pieske B, et al. Eur Heart J [in press]), a dose-dependent improvement in KCCQ was seen with increasing doses of vericiguat (sGC stimulator). Finally, Kitzman et al.[19] demonstrated in HFpEF that KCCQ was more reliable and sensitive to changes compared to MLWHF, and KCCQ correlated better with change in other clinically meaningful endpoints.

The KCCQ is also reliable, valid, and responsive in patients with comorbidities.[22] A change in score of as little as 5 points is clinically significant and is associated with changes in clinical status[20] and physical function. A one standard deviation change in 6-minute walk distance correlates with a 5-point change in KCCQ.[23,24] A 5-point change in KCCQ is associated with all-cause mortality, CV death and hospitalization in patients

with HF complicating acute myocardial infarction.[25]

We believe that patient reported outcomes such as the KCCQ are key metrics that evaluate the patient journey in HF clinical trials. They can be used as standalone measures as a primary endpoint, as long as adequate safety endpoints are measured (i.e., no excess in hospitalizations or death in patients getting active treatment). The KCCQ can also be successfully combined with other endpoints such exercise capacity and/or HF hospitalization.

**Question #4:** How confident are you that functional assessments [e.g., 6 min walk test (6MWT), VO2max, ventilator threshold]:

a. Are adequate measures which reflect the patient experience;
b. Should be included as the standalone, meaningful primary health outcomes in research studies;
c. Should be included as a composite standalone, meaningful primary health outcomes in research studies?

**Response:** The 6MWT is a well-established, clinically meaningful outcome measure in HF. Reduced physical function during normal activities is inherent in the definition of HF and is the primary manifestation of chronic HF, even when patients are well-compensated and stable, and is a major cause of their severely reduced QOL.[26,27] The 6MWT is a standardized, valid, reproducible measure of physical function in patients with a wide range of physical function.[10,28-33] It is responsive to interventions and has been utilized as a key outcome in many trials of HF, including specifically in HFpEF.[11,19,21,28-30,32,34-42] The 6MWT has become established as a key, pivotal outcome for testing pharmacological interventions in patients with pulmonary arterial hypertension, including as the primary outcome in many phase III clinical trials that led to US FDA approval of multiple medications for treatment of this disorder.[33]

The 6MWT was developed and validated by Guyatt et al as an alternative to maximal exercise testing specifically in HF patients.[43] Rather than testing maximal exercise, an activity that is a rare in modern daily life, the 6MWT examines performance in a very common daily activity by measuring the distance the patient is able to traverse in 6 minutes while walking in a hallway or large room. As such, 6MWT is accepted as a clinically meaningful outcome that is highly relevant to everyday life. In HF patients, 6MWT correlates with measures of QOL and key clinical outcomes, including hospitalization and death.[10,30,44-46] In the landmark HF-ACTION trial, the 6MWT was at least as predictive of clinical events as maximal cardiopulmonary exercise testing during long-term followup after an intervention in a large group of patients with HF with reduced EF.[10]

Standardized protocols optimize standardization and reliability of the 6MWT by including verbatim instructions for patients and detailed instructions for staff.[28,43] Since it requires no special equipment or facilities, the 6MWT can be performed in a wide range of settings, thereby enabling recruitment and follow-up of a representative patient population. The 6MWT is also feasible and safe in a wide range of HF patients, not only outpatients, but even in elderly frail patients during a hospitalization for acute decompensated HF.[47]

Functional status can also be measured by peak exercise oxygen consumption

($VO_2$). Peak $VO_2$ allows for direct objective measurement of maximal as well as submaximal exercise tolerance, and is associated with both functional ability to perform activities of daily living as well as outcomes. However, peak $VO_2$ testing is not widely available, and difficult to implement as an endpoint in large multi-center trials. Small and medium size trials, with an experienced core laboratory, can reliably perform and interpret peak $VO_2$ testing. Thus, if a HF clinical trial involving a device is able to demonstrate a benefit in terms of peak $VO_2$, that would be clear evidence of the beneficial effects of the device.

**Discussion:**

- Please discuss whether additional patient-reported measurement [e.g., Short Form-36 (SF-36), EuroQol five dimensions questionnaire (EQ5D)] should be considered to capture burdens associated with the heart failure therapy under study.
- Please discuss the appropriate length of follow-up post-heart failure intervention for assessing patient-reported measurements.
- For some studies of heart failure treatment technologies it may not be practical for patients to be blinded. Please discuss the impact of unblinded study participants on patient-reported measurements and functional assessments.
- Please discuss how to best consider the impact of adverse events associated with heart failure technologies while balancing the potential for improvements to meaningful health outcomes.
- Please discuss how to balance the benefits and harms of therapies which may improve near-term patient-reported health outcome assessments or clinical measurements (e.g., 6 MWT or symptoms) but may decrease length of life.

**Response:** We believe the KCCQ is the primary tool to capture disease-specific dimensions of QOL in HF patients. Though less well validated specifically in HF, additional patient-reported measurements such as the SF-36 and EQ5D can be usual as adjunctive measures to assess more general QOL (SF-36) as well as patient burden and cost (EQ5D). These can also be helpful in HF clinical trials to show consistency of results, though KCCQ should be the primary measure. We believe that an appropriate length of follow-up for patient-reported measurements for HF devices tested in clinical trials is 6 months, because this time frame balances what is meaningful for patients (i.e., they would want to see benefit early after device placement), and yet is long enough to show some durability of the treatment effect. HF device trials must clearly show that the clinical benefits of the device outweigh any safety concerns of the device and/or reduced length of life. The Finkelstein-Schoenfeld approach is one example of a way to combine near-term patient-reported health outcomes with safety endpoints. Another method is early device approval based on patient-reported outcomes (particularly for HFpEF where there is a general lack of efficacious therapy) with post-marketing follow-up to ensure that there is no excess of adverse events. It is important to note that in time trade-off studies of HF in general, patients with HF often choose quality of life over quantity of life. Preliminary time trade-off data from the Northwestern University HFpEF Program show that > 75% of HFpEF patients value quality of life over quantity of life.[48]

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