

Health Outcomes in Heart Failure Treatment Technology Studies

Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

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State of Evidence Generation

- Currently, assessments of medical technologies are made, but evidentiary questions remain for CMS with respect to the clinically meaningful health outcomes for Medicare beneficiaries.
- Health outcomes are a key feature of heart failure technology research for Medicare coverage.
- In the future, implementation of the 21st Century Cures Act¹ and more use of the Expedited Access Pathway² may result in CMS receiving more frequent requests for coverage.
 - Increased focus on the need of patients for new and innovative medical products, medical technologies
 - Breakthrough therapies receiving market authorization based on less long-term data with greater reliance upon intermediate and surrogate outcomes.

1. 21 U.S.C. §360e-3. (2017)

2. <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>

HF Treatment Technology Research

Studies increasingly utilizing endpoints described in EAP Guidance²:

Intermediate endpoints

- Exercise tolerance and symptoms;
- Heart failure hospitalization rate

Surrogate endpoints

with a pathophysiologic pathway leading to the clinical outcome (e.g., left ventricular hypertrophy and congestive heart failure)

2. <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>

Heart Failure Study Endpoint Work

- European Society of Cardiology Heart Failure Association consensus document
 - Clinical outcome endpoints in heart failure trials³
- International Consortium for Health Outcomes Measurement (ICHOM)⁴
 - patient representatives, clinician leaders; registry leaders
 - developed Standard Sets, comprehensive yet parsimonious sets of outcomes and case-mix variables
 - recommend that all providers track

3. European Journal of Heart Failure (2013) 15, 1082–1094

4. ICHOM Heart Failure Data Collection Reference Guide Version 1.2 Revised 12/13/16 4

Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document

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Provides group recommendations for moving towards consensus:

- Mortality endpoints
- Heart Failure Hospitalization
- Recurrent morbid event endpoints
- Clinical Endpoints
- Safety Endpoints

ICHOM HF Standard Set

- Focus on patient-centered results;
- Internationally-agreed upon method for measuring each of these outcomes;
- Includes baseline conditions and risk factors;
- High-level treatment variables to allow stratification of outcomes by major treatment types;
- A comprehensive data dictionary;
- Scoring guides for patient-reported outcomes

Patient Population	Measure	Supporting Information	Timing	Suggested Data Sources
Functional				
All patients	Maximum level of physical exertion			
	Symptom control: SOB	Tracked with KCCQ-12 and NYHA		Patient and clinician-reported
	Symptom control: Fatigue and tiredness		Tracked ongoing except at acute admissions	
	Living independently/self-care	Tracked with PROMIS and KCCQ-12		Patient-reported
	Employment			
	Peripheral oedema	Tracked with KCCQ-12		Clinician-reported
	Symptom control: Disturbed sleep			
Psychosocial				
All patients	Health-related Quality of Life	Tracked with KCCQ-12	Tracked ongoing except at acute admissions	Patient-reported
	Depression and anxiety	Tracked with PHQ-2		
	Confidence/self-esteem	Tracked with KCCQ-12		
Burden of care				
All patients	Medication side-effects	Yes/No		Clinician-reported
	Financial burden	Yes/No		
	Complications of treatment	Due to device, medication and/or hospitalization	Tracked ongoing except at acute admissions	
	Number of hospital appointments	N/A		Administrative data
	Number of hospital readmissions	N/A		
	Length of stay	Date of admission and discharge		
Survival				
All patients	Mortality	N/A	Tracked ongoing	Administrative data



ICHOM
HEART FAILURE
DATA COLLECTION
REFERENCE GUIDE

Version 1.2
Revised: December 13th, 2016

Meeting Purpose

Obtain MEDCAC recommendations regarding the

- **ideal health outcomes in research studies of heart failure treatment technologies and**
- **appropriate follow-up duration**

which should be of interest to CMS

Voting 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?

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Intermediate High
Confidence Confidence

* CMS recognizes the importance of mortality as a meaningful primary health outcome of interest in research studies. We are seeking input on what additional outcomes should be considered

Question #1 - 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.

Voting 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)?

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Intermediate High
Confidence Confidence Confidence

Question #2 - 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.

Voting 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?

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Intermediate High
Confidence Confidence Confidence

Voting 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?

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low **Intermediate** **High**
Confidence **Confidence**

Question #4 - 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.

Question #4 - Discussion (cont'd)

- 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.

Additional Discussion Topics

- Please discuss health outcomes of interest and appropriate follow-up duration in studies of technologies designed for diagnosis of acute decompensation of heart failure.
- With the health outcomes and information that we have discussed today, how confident are you that there will be enough accurate information provided to patients for them to make informed decisions?
- Please discuss how studies can be designed to accurately capture patient preferences and how their preferences can best be considered and operationalized once the study has concluded.

References

1. 21 U.S.C. §360e-3. (2017)
2. Food and Drug Administration Center for Devices and Radiological Health and Center for Biologics Evaluation and Research (2015). Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions (FDA Maryland).
3. Zannad, F., et al. (2013). "Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document." *Eur J Heart Fail* 15(10): 1082-1094.
4. International Consortium for Health Outcomes Measurement (ICHOM) Heart Failure Data Collection Reference Guide Version 1.2 Revised 12/13/16