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Centers for Medicare and Medicaid Services
Center for Clinical Standards and Quality
Coverage and Analysis Group
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Via electronic submission to MedCACpresentations@cms.hhs.gov

Dear Ms. Syrek Jensen,

Abbott appreciates the opportunity to provide comments on key questions for the MEDCAC Panel as it relates to "Health Outcomes in Heart Failure Treatment Technology Studies." Abbott is a global health care company devoted to improving life through the development of products and technologies that span the breadth of health care. With a portfolio of leading, science-based offerings in diagnostics, medical devices, nutritionals and branded generic pharmaceuticals, Abbott serves people in more than 150 countries and employs approximately 94,000 people. With the recent acquisition of St. Jude Medical, Abbott now provides a number of technologies to manage and treat heart failure. The letter reflects our comments on CMS's questions posed to the MEDCAC panel.

Background

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood. Cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to congestion and/or edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema, dyspnea, or fatigue. The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from metabolic abnormalities. These problems lead to impaired left ventricular (LV) function arising from either an abnormality with relaxation or strength of contraction. Findings from the ADHERE registry of over 100,000 hospital admissions for HF suggests that about 50% of patients with acutely decompensated HF have preserved ejection fraction (EF). This is important because only ambulatory hemodynamic monitoring is proven to be a successful strategy for patients with HF and preserved EF (HFpEF), while many other

interventions have failed to change meaningful outcomes in this group. Further clinical trials and appropriate endpoint selection for HFpEF patients is critically important.

Well over 90% of patients admitted to the hospital for heart failure have symptoms of congestion which results from excess volume accumulation and increased LV filling pressures. While many clinical trials testing several interventions focused on the acutely decompensated patient after hospitalization have been completed, none changed medium term or long-term outcomes. This led the HF community to focus more closely on preventing decompensation instead of simply reacting to the already decompensated patient. These investigations discovered that the process of decompensation is a complex, but predictable long-term process that occurs over several weeks before the traditional markers of symptom development and changes in daily weight occur. It also became clear that the process of decompensation further injures the heart muscle, vasculature and activates adverse neural and hormonal responses. Each decompensation event causes progression of the patient's HF syndrome and increases the probability of death, transplant or need for mechanical circulatory support (MCS).

The complexity and progressive nature of clinical HF requires a thoughtful approach in choosing endpoints appropriate for the patient's place in their HF "journey". For example, endpoints in recent clinical trials enrolling ambulatory patients with chronic HF have evolved to focus on preventing decompensation and, traditionally, this was quantified by measuring an intervention's impact on adjudicated HF hospitalizations. While mortality is an important endpoint and improved survival is important to document, the direct relationship between HF hospitalization and death in this group makes the former an appropriate and needed primary endpoint in clinical trials.

For patients who progress to advanced status, characterized by congestion and poor systemic perfusion, transplant and mechanical circulatory support are approaches for appropriate candidates which are proven to dramatically improve long-term survival. In fact, only 25% of medically managed Advanced HF patients in the REMATCH trial were alive after 1 year. This is in stark contrast to the most recent MCS trials which demonstrate over 70% two year survival in patients receiving left ventricular assist devices (LVAD). Therefore, focusing on mortality compared to non-LVAD medical strategies in Advanced HF patients would seem unethical and difficult to perform. Appropriate endpoints for LVAD and transplant trials should focus on specific aspects of the new pathophysiology created by the intervention. Particularly important, in this regard, is to improve patient experience with the intervention, quality of life and functional capacity, while decreasing complications associated with immunosuppression or iatrogenic coagulopathies. However, quality of life measurements designed for ambulatory non-advanced patients may not reflect the needs for patients who have received transplantation or LVAD's. This important issue has encouraged development of novel instruments to measure quality of life or even functional capacity.

In summary, improving the patient experience in modern HF clinical trials must focus on endpoints that are appropriate for the patient's disease state. In particular, the endpoint of properly adjudicated HF hospitalizations is critically important to evaluate novel HF interventions. This aligns with CMS' campaign to reduce preventable readmissions within 30

days of an index hospitalization and societal calls for improved quality of HF care delivery, such as the American Heart Association's "Rise Above Heart Failure" campaign to reduce HF hospitalizations. Quality of life measurements are needed as endpoints since they describe improvement in patient experience, but the measurements should be appropriate for the pathophysiology of the patients underlying disease process. Functional capacity assessment is important, but traditional measures, such as 6 minute hall walk test or metabolic stress testing, have significant limitations. Finally, the composite of intermediate or surrogate endpoints (e.g. NT-pro BNP) with function assessment and quality of life measurements is now an approved endpoint in the FDA expedited access for premarket approval policy and should be considered by CMS to align the regulatory goals of improving the process for novel technology development with coverage decision-making.

This background is important when considering the questions CMS has posed on the appropriateness of specific endpoints in HF trials. We now provide a detailed assessment of each of these questions.

1. Definition of "Endpoint"

Before providing a viewpoint on the choice of endpoints, it is necessary to ensure alignment on the definition of terms such as primary endpoints and surrogate endpoints. These definitions are well laid out in a 2012 publication by Fleming and Powers[1] in *Statistics in Medicine*. The main points from this publication are summarized below:

A primary endpoint should have the characteristics of being a *well-defined and reliable* measure that assesses important aspects of patient health status. A key step in assessing these properties is to evaluate content validity, which is "*the extent to which an instrument measures the important aspects of concepts most significant and relevant to the patient's condition and its treatment"*. Other considerations are as follows:

- Effects on many important aspects of patient health status can best be assessed by using patient reported outcomes (PROs), defined to be "*any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*".
- The endpoint should be sensitive to the effect of the intervention.
- The endpoint should be readily measurable and interpretable.
- The endpoint should be "*a clinical event relevant to the patient*" or that "*measures directly how a patient feels, functions or survives*". An endpoint that satisfies this requirement is a clinically meaningful endpoint.

A surrogate endpoint is an outcome measure "*used as a substitute for a clinically meaningful endpoint… changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint"*. Validating a surrogate endpoint requires providing an evidence based justification, often from randomized controlled trials,

that achievement of substantial effects on the surrogate endpoint reliably predicts achievement of clinically important effects on a clinically meaningful endpoint.

2. Our Comments on CMS's Questions

Technologies to treat HF target specific subgroups or specific aspects of patient experience. Therefore, a "one-size fits all" strategy cannot exist for HF clinical trials, and a great deal is based on severity and manifestations of the disease.

HF hospitalizations or equivalents:

Abbott is very confident that HF hospitalizations or equivalents either as a standalone endpoint or as part of a composite that includes mortality is a clinically meaningful health outcome for chronic HF patients. As mentioned above, appropriately adjudicated HF hospitalizations quantify patient decompensation, which is associated with poor quality of life and higher mortality. It is critically important to recognize that decompensation leading to intensification of diuretic therapy or withdrawal of neurohormonal intervention causes further progression of the patient's disease that tends to be unrecoverable. Preventing hospitalization for acute decompensation is clearly associated with improved quality of life and improved survival. The following datasets from clinical studies support these contentions:

This is based on the following research:

- Reduction in HF hospitalization is associated with a reduction in mortality.[2,3,4]
- Reduction in HF hospitalization is congruent with patient preference and improves quality of life (QoL).[5]
- Risk of mortality is increased with any decompensation, regardless of the site of therapy delivery. (Outpatient intensification of HF therapies, emergency department visits with IV medication use and HF hospitalization).[6]
- HF hospitalizations are a significant source of health economic burden for heart failure patients and payers.[7,8]
- HF hospitalizations were successfully used as a primary endpoint in most HF device[9] trials, and as a component of a composite in both device[10] and drug trials.[11]
- The Heart Failure Association of the European Society of Cardiology (HFA-ESC) convened a group of experts who note that HF hospitalization is clinically meaningful to patients, physicians, and regulators, and that it correlates with disease progression and prognosis.[12]
- The Mitral Valve Academic Research Consortium has also recognized that HF hospitalization is a clinically meaningful measure of morbidity, and therefore, may be used as a primary endpoint in device trials for mitral valve repair and replacement technologies.[13]
- It has been noted that limitations exist for HF hospitalizations such as inconsistent definitions across trials and difficulty in adjudication. Furthermore, the threshold for hospitalization is highly variable, and may be driven by external factors unrelated to the patient's clinical status. These limitations may be mitigated by inclusion of both HF hospitalizations and HF hospitalization equivalents in the endpoint and by standardizing definitions of HF hospitalization and HF hospitalization equivalents across trials.

Furthermore, all-cause hospitalizations should be reported to ensure that the therapy does not increase other hospitalizations.

In summary, staying out of the hospital is clearly the patient's preference and is associated with improved quality of life. From a pathophysiologic perspective, HF hospitalizations are linked to irreversible progression of the patient's underlying disease process. Therefore, preventing decompensation leading to hospitalizations aligns with patient preference, CMS mandates and Cardiovascular Societal guidelines, recommendations and public awareness campaigns. Therapies and technologies that lower HF hospitalizations are valuable and should be a prioritized outcome for HF clinical trials evaluating novel technologies.

Surrogate endpoints

We are confident that surrogate or intermediate endpoints (such as reduction in mitral regurgitation, cardiac remodeling, ejection fraction, or biomarkers) are valuable endpoints. Metrics like changes in biomarkers or changes in LV volume are mechanistic endpoints and should be incorporated as secondary surrogate endpoints to provide an explanation for observed improvements in the primary endpoint. Surrogate intermediate endpoints provide valuable insights into the clinical status of patients and provide predictive value to complement primary health outcomes. Furthermore, combining intermediate and surrogate endpoints (such as NT-pro BNP, 6 minute walk distance and quality of life measures) in clinical trials for heart failure patients with reduced ejection fraction is an approved endpoint in the FDA Expedited Access for Premarket Approval process, which should align with coverage and reimbursement for novel technologies. In particular,

- Reduction in mitral regurgitation is particularly important for therapies for treating functional MR.[14]
- Reversal of adverse ventricular remodeling correlates directly with improved survival[15]
- Acutely improving ejection fraction in patients with cardiogenic shock undergoing temporary mechanical circulatory support may be an appropriate primary endpoint evaluating this strategy. For ambulatory chronic patients with HF, ejection fraction may be less robust in defining the disease and reflecting clinical status.[16]
- Biomarkers (e.g., BNP, NT-pro BNP, ST2) have strong prognostic value, both at baseline and the change over time in response to novel therapies.[17]

Quality of life (QoL)

QoL measures are meaningful for HF research, but the appropriateness of the tool considered varies by disease state and the technology being tested. Measurement of patient experience may provide a perspective not readily available from patient safety and clinical measures. Various domains of patient experience are reflected in standard QoL measures. Specifically, patient experience domains are: functional limitation, impact on daily activities, impact on emotional well-being, impact on psychological health and impact on social function.[18]

The most used and validated instruments of HF specific quality of life measures (KCCQ, MLWHFQ) are important patient reported outcomes (PROs) that should be captured as endpoints for the following reasons:

- KCCQ and MLWHFQ are the most widely studied and validated measures of quality of life in chronic heart failure.[19]
- A low KCCQ is an independent predictor of poor prognosis in patients with HF.[20]
- MLWHFQ is an independent predictor of cardiac events, death, and future hospitalizations.[21]
- KCCQ and MLWHFQ significantly improve when using successful device-based therapies for HF.[10,22]
- KCCQ and MLWHFQ measure the severity of symptoms to quantify quality of life. Improving the quality of life gained is a patient preferred outcome and in many surveys super cedes patients' desire for prolonging survival.[12]
- In addition to KCCQ and MLWHFQ, we are confident that using non-HF specific PROs such as SF-36 or EQ5D are useful endpoints to provide valid economic analyses and additional assessment of patient well-being. Although CMS does not consider costs when evaluating coverage decisions, we believe that these measures complement HF research, but they should not be standalone primary endpoints.
- Finally, QoL instruments should be developed for specific disease states. For example, both the KCCQ and MLWHFQ instruments are specific for ambulatory patients with chronic heart failure. Their applicability to patients with long-term LVAD therapy or transplant may be limited as issues impacting these groups' QoL may be significantly different. We recognize that most advanced therapy trials have used these instruments, but the unique needs of patients with LVAD's or transplant illustrate how critical it is to appropriately choose and develop QoL assessments.

Due to the subjective nature of these endpoints, every attempt must be made to keep patients and assessors blinded to the treatment received. Additionally, due to the potential for missing data, analyses must be pre-specified to address missing data, particularly due to informative censoring (such as due to death).

Functional assessments

As heart failure can manifest itself as exercise intolerance, our position is that functional assessments are appropriate for either of the following: as primary or as secondary or descriptive endpoints or as a component of a composite endpoint as described by FDA (FDA-2014-D-0363). The same level of rigor should be applied to measures of functional capacity, as with quality of life measures (blinding of patients and assessors, pre-specification of analyses to address missing data). Abbott believes that while the 6 minute walk test may be a valuable endpoint for some HF technologies (e.g., ventricular assist devices), careful expert evaluation of $VO2_{max}$ with assurance that submaximal tests (i.e. RER <1.1) can be interpreted by expert core laboratories may be an important means to evaluate functional improvement in HF clinical trials. Significant limitations to metabolic stress testing, however, when not performed in expert centers or interpreted by core laboratories limits the appropriateness as a primary or secondary endpoint in clinical trials. Co-morbid conditions, such as arthritic disease, neuropathy, lung

disease or other exercise limiting disorders may produce selection bias in trials designed to evaluate an impact on metabolic stress testing.

- The 6 minute walk test is simple to conduct and is a good physiological measure of functional capacity and exercise tolerance. This test is a useful prognostic marker of subsequent cardiac death in patients with mild to moderate HF[23]. Functional capacity assessed with this test significantly improves in HF patients receiving LVAD support[24,25] and cardiac resynchronization therapy[26].
- $VO2_{max}$, another marker for functional capacity and exercise intolerance, is a good marker of exercise capacity and a predictor of all-cause mortality or all-cause hospitalization[27], and a clinical predictor for the need for advanced therapies (such as a heart transplant[28]). However, this endpoint may have challenges when used as a primary endpoint. The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, which is the largest multi-center, randomized, controlled trial of exercise training in Heart Failure, utilized a composite of HF hospitalizations and mortality and not $VO2_{max}$ as a primary endpoint or a secondary endpoint[29]. In this study, changes in $VO2_{max}$ (and other measures of cardiopulmonary testing) over time were evaluated as potential mediators. Specifically, this trial demonstrated that for each 6% increase in $VO2_{max}$ over 3 months there was a 5% lower risk for the primary outcome of all-cause mortality and all-cause hospitalization, a 4% lower risk for the secondary end point of time to cardiovascular mortality or cardiovascular hospitalizations, an 8% lower risk for cardiovascular mortality or HF hospitalizations, and a 7% decreased risk for all-cause mortality after accounting for other significant predictors. As mentioned above, metabolic stress testing must be performed with appropriate methods, including use or an expert core laboratory to interpret submaximal tests and statistical analyses to account for missing data.

    - Although $VO2_{max}$ has been shown be a good marker of exercise capacity, it has inherent physiological challenges when utilized as an endpoint for HF therapies, as $VO2_{Max}$ may be impacted by factors outside of those treated by the specific HF technology[23].

Other Considerations: Use of Real World Evidence (RWE)

There is significant value in using RWE to provide a more complete understanding of the benefits and risks to Medicare patients when using a medical device. The FDA has called for investigating novel opportunities to leverage RWE with medical devices approvals in evaluating a comprehensive assessment of post-approval generalizability to complement clinical trial results.[30] RWE comes in many forms from industry (e.g., patient data tracking), institutions (e.g., electronic health record), public sources (e.g., CMS and private payers claims data, public registries), and patients (e.g., wearable devices). Randomized clinical trials provide early insight to device efficacy and safety to gain regulatory approval and payer consideration for coverage. RWE provides an opportunity to work with FDA and CMS to build valid comparator groups from databases (e.g. concurrent control, patients as their own historical control) to

continually capture evidence to complement clinical trials. With HF technologies, comparator cohorts can be determined both prospectively and retrospectively to evaluate HF hospitalizations, health-care utilization and provide insight into utilization of both inpatient and outpatient services that have a direct impact on quality of life and patient health outcomes. Recent examples of FDA and CMS collaboration on use of RWE has been seen with industry and physician society alignment on creation of the Transcatheter Valve Therapy (TVT) Registry for transcatheter aortic valve replacement (TAVR) and transcatheter mitral valve replacement (TMVR) procedures.[31] Abbott strongly supports incorporating RWE as an opportunity to generalize and validate findings from randomized clinical trials and a way for CMS to collect long term data to better support coverage with evidence development decisions.

3. Conclusions

In recent years, the treatment of heart failure in the US has changed due to the ability to treat many decompensation episodes in an outpatient or observation setting. While in the past, patients may have been hospitalized to treat acute episodes, today other settings are equally capable of providing effective treatment. These changes impact clinical trial design, and therefore we believe it is appropriate to include HF hospitalization equivalents in addition to HF hospitalizations. In addition, the inclusion of functional improvement measures, when appropriate, can provide an alternate, but equally important measure, of the effectiveness of device therapy in these patients. Abbott strongly believes that a "one-size fits all" strategy cannot exist for HF clinical trials. Furthermore, trials studying feature enhancements may not require the same endpoint as a study on a new, innovative device.

In summary, our recommendations to CMS's key questions are provided below:

- HF hospitalizations and HF hospitalization equivalents are valid and appropriate primary endpoints for HF clinical trials either as a standalone endpoint or as part of a composite that includes mortality.
- Surrogate or intermediate endpoints (such as reduction in mitral regurgitation, cardiac remodeling, ejection fraction, or biomarkers) are valuable and should be included as secondary endpoints.
- Functional assessments are appropriate as the following: primary or as secondary or descriptive endpoints, or as a composite evaluation consistent with FDA approval process.
- There should be an appropriate follow-up duration for QoL measurements and they are an important part of an innovative trial design. Follow-up duration is an important consideration for novel devices or therapy strategies and should be disease-state specific.
- CMS should consider use of real-world evidence as appropriate in complementing clinical trials and providing greater opportunities for data collection for coverage with evidence decisions.

- FDA and CMS should seek alignment on the appropriate endpoints for regulatory (safety and effectiveness) and coverage (improvement in Medicare beneficiaries' health outcomes) decisions.

Abbott is committed to developing, studying and continuously improving medical device technologies in the heart failure population. Abbott is also committed to the continuous surveillance of safety of our products throughout the product life-cycle. Abbott believes that improving quality of care for CMS beneficiaries, including reduction in HF hospitalizations, is critically important in assessing HF technologies.

If you have questions, please reach out to me at 781-221-8716 or via email at RBostic@sjm.com or Phil Adamson M.D. (Medical Director and Vice President of Medical Affairs) at 512-286-4526 or via email at padamson02@sjm.com.

Sincerely,

Robin R. Bostic
Global VP, Health Economics and Reimbursement

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