



**CardioMEMS™ HF System (St. Jude Medical) and Sacubitril/Valsartan (Entresto™, Novartis)
for Management of Congestive Heart Failure:
Effectiveness, Value, and Value-Based Price Benchmarks**

Summary of Public Comments Received on Initial Draft Report and ICER Response

The Institute for Clinical and Economic Review (ICER) values the opportunity to receive and respond to public comment on its work products by interested stakeholders. There were 19 sets of stakeholder comments submitted in response to the initial draft CTAF report on the CardioMEMS™ HF system and sacubitril/valsartan (Entresto) for congestive heart failure (CHF) that was posted on September 11, 2015. Below is a summary of the major comments received, organized by intervention, as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

CardioMEMS

- Our assessment of the candidate population size was derived from manufacturer-supplied data on the percentage of annual hospitalizations in which patients would be in NYHA Class III following discharge. It was pointed out in public comments that the original calculations did not consider the fact that some patients are hospitalized multiple times in a given year; accordingly, we have revised our estimate to reflect the number of unique hospitalized Class III patients in a given year. An estimate was provided in public comment, but this was based on Canadian data and a 10-year follow-up period.¹ We opted to use data from a US-based observational study instead, which suggested a rate of 1.57 hospitalizations per hospitalized patient.² As a result, the size of the candidate population is now approximately 287,000 Class III patients annually (generating 450,000 hospitalizations), and corresponding budget impact results were generated. In addition, due to the smaller population size, our estimate of the value-based price benchmark increased (from \$7,622 to \$10,665).
- We received comments that our estimate of device uptake (25% of candidate population at 5 years) was an overestimate, citing current penetration figures in certain markets and mentioning that patient selection is a relatively intensive process. However, we also received comments indicating that pulmonary artery pressure monitoring will soon become the standard of care. Our methodology attempts to estimate “unmanaged” uptake patterns without consideration of potential payer or provider policies that might be instituted to restrict use. We have therefore retained our uptake estimate of 25%.
- Multiple stakeholders commented on our assessment of the presence/absence of data on CHF-related and/or all-cause mortality. We have clarified our description of the CHAMPION trial³ to make clear that this trial was powered to detect differences in CHF-related hospitalizations. We maintain, however, that rigorous evidence of a mortality reduction in CardioMEMS would

increase our level of certainty in net health benefit. In addition, post-hoc analyses of mortality data from CHAMPION have been presented at several clinical meetings, and the manufacturer describes “strong favorable trends for reduced mortality” in their submission to the Centers for Medicare & Medicaid Services (CMS) for add-on payment status.⁴

- We were criticized for not considering the FDA’s summary conclusions, which acknowledged the limitations of the additional analyses performed by the manufacturer but found the consistency of their findings to indicate a positive treatment effect in reducing CHF-related hospitalizations. However, stakeholder comments did not include the FDA’s statement indicating that the magnitude of this positive effect remains unclear. We re-evaluated our assessment of the evidence and decided that the potential clinical benefits of the device as well as its current safety profile should increase our level of certainty. Given the study limitations already described, we retain our belief that further study could result in shifts in the magnitude of benefit, with a small possibility of “negative” net benefit (e.g., comparable clinical benefit and small risk of harm from an invasive treatment). We have therefore revised our evidence rating from “Insufficient” to “Promising but Inconclusive”.
- Comments were also received that we had excluded recent randomized trials on specific alternative methods of CHF management (e.g., telemonitoring, discharge planning, home visits). We have clarified our description of the systematic reviews we used, added mention of the recent randomized trials, and have described more clearly which types of interventions have shown clinical benefit.
- Several stakeholders suggested we incorporate a paper recently accepted by *The Lancet* into our review; this paper summarized 13 months of post-trial experience in the former treatment and control groups from CHAMPION. While it is ICER’s general policy not to consider studies unless published or officially “in press”, we note that these same analyses are already summarized in the manufacturer’s resubmission of data to the FDA and are already discussed in our report.

Sacubitril/Valsartan (Entresto)

- We were asked to revisit our estimate of the proportion of prevalent CHF that would be Class I (i.e., not eligible for Entresto), as the only Class I patients included in the PARADIGM-HF trial were those who improved from Class II to Class I after beginning the run-in phase. Proportions from two US-based observational studies were suggested. We opted to use the proportion of Class I (25.1%) from the Resource Utilization Among Congestive Heart Failure (REACH) Study,⁵ as CHF patients in this study were identified in all relevant settings of care (i.e., primary care, specialty clinic, emergency department/inpatient settings).
- We also received comments that the widely-cited estimate of CHF prevalence in the US (5.7 million) was outdated. We identified another often-cited study with a 2015 projected prevalence of 6.2 million,⁶ which we have now employed in our calculations.

- As a result of these two changes, the candidate population size for Entresto declined from 2.6 million to 2.2 million, the number treated by year 5 declined from 1.95 to 1.67 million, and new corresponding budget impact results have been generated. With the smaller expected population size, our value-based price benchmark has consequently increased from \$3,779 per year to \$4,168.
- Our approach to assessing budget impact and calculating the value-based price benchmark was criticized for not capturing all of the potential benefits of Entresto that would be realized during long-term use. While we agree that a long-term horizon is appropriate to capture the totality of clinical benefits for chronic therapies, it is also the case that health systems must budget for the introduction of multiple new technologies every year.
- A request was made to add the phrase “and reduced ejection fraction” to each of the voting questions relevant to Entresto. We have made this change.

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Public Comments Received on “CardioMEMS™ HF System (St. Jude Medical) and Sacubitril/Valsartan (Entresto™, Novartis) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks” by September 25, 2015

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8. **Lynne Warner Stevenson, MD**, Professor of Medicine / Director, Heart Failure Program / Director, Heart Failure, VAD, Transplant Training Program, Brigham and Women’s Hospital / Harvard University, Boston, MA
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18. **Rosemary P. Peterson, MD, FACC**, Heart Failure and Transplant Cardiologist, CHI-Franciscan, Tacoma, WA
19. **Christi Shaw**, Head, US General Medicines / President, Novartis Pharmaceuticals Corporation and **Cathryn Clary, MD, MBA**, Head, US Clinical Development and Medical Affairs, Novartis Pharmaceutical Corporation, East Hanover, NJ

To whom it may concern:

I am writing with respect to the St. Jude CardioMEMS device. While I have spoken regarding the device in the past I did so in an education to our community of physicians. It appears there were some concerns that was raised by CTAF regarding the innovative technology. I hope I can explain my reasoning for the device. First I am a board certified Cardiologist and Interventional Cardiologist trained at both UCLA and the University of Texas in Houston. I did receive extensive training at both UCLA and the Texas Heart Institute in Congestive Heart Failure as well as heart transplantation. As Chairman of Quality Management at Huntington Hospital in Pasadena, Ca I have no worked extensively with our physicians in optimizing care for CHF

Some concerns in reports I have viewed revolve around mortality. The CHAMPION trial was not powered nor ever intended to establish mortality benefit. Does that then automatically call into question the device? My answer is absolutely not. The cost of CHF is enormous. The major expenditure is hospital admissions (Yancy CW, et al. Circulation 2013). A major reason for such is that patients discharged home are still volume overloaded despite feeling better. (Lala A, et al. JCF 2013) Thus the CardioMEMS device is important the hospital plan of care. In fact while demonstrating the reduced hospital readmissions and improved quality of life scores the CHAMPION trial did demonstrate an important point. The biggest change from standard therapy was that CardioMEMS patients had further changes in therapy. This indicated physicians and patients work together to become more aggressive in titrating and adding therapies that are designed to be of instrumental benefit in CHF. In fact this was seen in both CHF with reduced ejection fraction as well as those with preserved ejection fraction, a population that is much understudied yet represents that majority of the CHF population. I for one have become much more aggressive in titrating therapies and have noticed in my population that they love the idea of continued monitoring over their care on a daily basis.

This brings to an important point that was mentioned in reports. The device is only as good as the patient and physician. The patients must be proactive and do their daily checks. This is much like daily weights, however in my population the patients are much more reliable with CardioMEMS. Also the physician and his group must respond to the data. This is the key point. The CardioMEMS is not useful unless you are proactive.

As Chairman of Quality at a major private hospital that is well respected we are constantly reviewing our systems. While mortality may be important it is not the only thing. I have come to respect the triple aim of therapy; 1) Provide high quality of Care 2) At an affordable cost and 3) With better patient satisfaction. If we focus on these goals the value of care will benefit and so too will our patients

Sincerely

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TO: ICER
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RE: CTAF Draft Report- CardioMEMS HF System

As the Medical Director of a very busy heart failure program and as co-author of the CHAMPION trial Lancet manuscript, I read with great disappointment the above mentioned CTAF report. I will begin my comments with the statement in the report which reads as follows: “We judge there to be low certainty of a small net benefit for the CardioMEMS HF System compared to alternative management in patients with CHF. There is low certainty because while the CHAMPION trial’s results indicated that patients receiving active monitoring experienced fewer hospitalizations with the CardioMEMS HF System, many questions remain, including the device’s impact on mortality, its performance in a setting without the enhanced nurse communication experienced in the trial, and whether the device would provide clinical benefit over the more intensive CHF care-management programs described above. In addition, the device has only been evaluated in a single trial of 550 patients. We believe there is a reasonable chance that CardioMEMS would not confer incremental benefit in all subsequent studies or settings. Therefore, we judge the current body of evidence to be “insufficient”, or a rating of “I” using the ICER Evidence Rating framework.” Page ES5 of Report.

I respectfully disagree with the draft findings related to the CardioMEMS HF System. The clinical assessment expressed by CTAF focused primarily on three areas: the opinions of the FDA Advisory Panels, impact on mortality and alternative treatment options. Although CTAF included 6 peer-reviewed publications relevant to its assessment, some important literature that was not cited pertains to the fact that recurrent hospitalizations for acutely decompensated heart failure worsen outcomes independent of age and renal function (1,2). Therefore the reduction in heart failure (HF) related hospitalizations by pulmonary artery pressure (PAP) guided therapy is extremely important not only to society, but to individual patients as well.

The CTAF report focuses extensively on the opinions expressed by the 2013 FDA Advisory Panel Committee. However, the CTAF report does not include relevant findings of the FDA related to the FDA Advisory Panel Committee: “Regarding the 2nd Panel Meeting, FDA disagrees with the Panel Vote that there is not reasonable assurance that the device is effective. FDA acknowledges that, when taken individually, each analysis has its limitations. However, when considering the totality of effectiveness data, the consistency of the results indicate a positive treatment effect in reducing HF-related hospitalizations. This positive treatment effect seen in the Open Access (Part 2) of the study also agrees with the positive treatment effect seen in the Randomized Access (Part 1)”. And again, “The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. It is important to consider the totality of effectiveness data presented. Although each analysis on its own has its flaws and limitations, the consistency and concordance of the results indicate a positive treatment effect in reducing HFR hospitalizations”

The CTAF report appears to inappropriately discount the agreed upon statistical plan developed by the FDA and CardioMEMS to evaluate several aspects of the trial to further confirm efficacy of hemodynamic guided care, which ultimately led to FDA disagreeing with the FDA Advisory Panel Committee’s opinions and granting FDA approval.

- Independent third party audit, conducted by two independent heart failure cardiologists, included an evaluation of concordance of communications between nurses and investigative sites found little, if any, impact on treatment patterns.
- Longitudinal analyses concluded that when pressure information was provided to investigators for the first time in former control patients, HF hospitalization rates decreased to levels comparable to the HF hospitalization rates in Treatment group patients whose PA pressures were available throughout the study. The Open Access period was characterized by no communication between the sponsor and sites.
- A propensity analysis was performed to evaluate the outcomes of Treatment group patients who were not the subject of a sponsor communication to outcomes in an equally matched group of control patients. This analysis demonstrated lower hospitalizations in the treatment group when compared to equally matched control patients. The management of these patients occurred without sponsor reminders.

It is also important to note that a careful evaluation of the medication changes occurring in the 2 arms of the trial, showed several important facts:

- Medication changes occurred twice as often in the PAP-guided therapy group than in the Control arm.
- Although diuretics were the medications most often adjusted, important changes occurred for all medication classes, including an increased proportion of patients receiving GDMT at 6 months compared to baseline.
- In the PAP-guided therapy group 56% of medication changes were made on the basis of PAP values only, in the absence of symptoms and signs of HF decompensation.

The CTAF report mentions in several places that the CardioMEMS HF System did not show a mortality difference – this is not surprising as the study was not powered to show a mortality difference. The primary endpoint was a reduction in HF hospitalizations, which was achieved. Whereas a slight, but measurable decrease in cardiovascular mortality is seen in large populations from 1986-2003, this is somewhat offset by an increase in non-cardiovascular mortality (5). During this time, however, hospitalizations for heart failure have increased nearly 300% (National Hospital Discharge Survey, CDC/NCHS and NHLBI).

The CTAF report includes information on alternative methods of CHF management for contextual purposes. However, we have concerns regarding the manner in which the CTAF report represents these options. Analysis of alternative management strategies was not conducted in a similar manner to the way the CardioMEMS HF System was analyzed and presented, “We did not systematically review alternative methods of CHF management, as these were not direct comparators of CardioMEMS. However, below we present a summary of information regarding the effectiveness of such management strategies, placing that of CardioMEMS in appropriate context.” (Page 20 of Report). Several important, large, randomized controlled studies were not included in the CTAF report. Given the scope of these trials, we believe they should also be included in the data presented when evaluating these types of strategies.

- Telemonitoring in Patients with Heart Failure (Tele-HF) Trial (6)
 - 1,653 patients, randomized 1:1, 180 day primary endpoint
 - Conclusion – “Among patients recently hospitalized for heart failure, telemonitoring did not improve outcomes”
- Impact of Remote Telemedical Management on Mortality and Hospitalizations in Ambulatory Patients With Chronic Heart Failure, The Telemedical Interventional Monitoring in Heart Failure Study (TIM-HF) (7)
 - 710 patients, randomized 1:1, median follow up of 26 months
 - None of the primary endpoints (death from any cause; death from CV cause) or secondary endpoints (hospitalization for HF or death due to CV cause; any hospitalization; hospitalization

for any CV cause; HF hospitalization) were met comparing remote telemedical management to usual care

- Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure (DOT-HF) (8)
 - 335 patients, randomized 1:1, mean follow up of 14.9 months
 - Conclusion – measurement of intrathoracic impedance did not improve outcomes, and increased HF hospitalizations and outpatient visits in HF patients
- Effect of implanted device-based impedance monitoring with telemedicine alerts on mortality and morbidity in heart failure: Results from the OptiLink HF study. (9)
 - 1,002 patients tele-managed with intrathoracic impedance, randomized 1:1 with alert capabilities turned “on” or “off”
 - There was no significant difference in the primary composite end point or its components (all cause death, cardiovascular hospitalization)

In my view, there are important reasons why the CHAMPION trial succeeded and the trials summarized above failed: 1) Ill-defined and variably applied actions in response to the monitoring information, 2) Lack of instructions on the appropriate care of patients who present for evaluation owing to a device alert, 3) Difficulty in assessing whether treatment decisions result from device monitoring information or are simply a consequence of the knowledge that the patient is in the Treatment arm of the trial (bias), 4) Inadequate sample size, 5) Heterogeneous population and end-points, 6) Management based on single readings rather than trends, 7) Lack of protocol-based treatment guidelines and consequent variation between responses to the monitoring information. In the CHAMPION trial Investigators were given both target PAP values to be acted upon and guidelines on how to achieve such targets.

Another surprising statement of the CTAF Report is that the CardioMEMS device becomes irrelevant five years after implantation. I do not believe this to be true. Firstly there are no data to support this conclusion. Secondly I can attest to the fact that I regularly monitor the PAP pressures of individuals implanted in 2006 and I still make therapeutic decisions based on the hemodynamic information provided by the CardioMEMS device. Incidentally, I performed right heart catheterizations in patients implanted with the CardioMEMS device who required, for example, a vasodilator challenge, I found that nine years after implant the PAP values provided by the CardioMEMS device were still identical to those obtained by invasive hemodynamic measurements.

Another important fact is that HF-related hospitalizations are decreased by PAP-guided therapy in both HF with reduced EF (HrEF) and in patients with HF with preserved EF (HFpEF) (9). I believe this finding is extraordinarily important, not only because HFpEF patients are at least 50% of the overall HF population, but also because no single approach has been previously shown to alter the outcomes of HFpEF patients (10).

Finally the Centers for Medicare and Medicaid Services (CMS) New Technology Add-On Payment (NTAP) Designation is not included as a reference, which determined that the CardioMEMS HF System met the high threshold for the New Technology Add-On Payment (NTAP). In addition to other criteria, a technology must demonstrate that it represents “a substantial clinical improvement” over existing therapies to qualify for NTAP. CMS made this award based on similar evidence to that reviewed by the CTAF draft report, and determined that CardioMEMS met the substantial clinical improvement threshold and awarded NTAP effective October 1, 2014 (11). CMS also awarded Transitional APC Pass-Through Status, which also includes the criteria of “substantial clinical improvement”, effective January 1, 2015. (12).

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11. Fed Reg, Vol. 79, No. 163, Aug 22, 2014
12. CMS Transmittal 3156, Dec 22, 2014

Comments on the CTAF Draft Report on the CardioMEMs HF System

As a practicing, board certified Advanced Heart Failure/Transplant Cardiologist, I have many issues with the draft report as presented. I will address each by section.

Under “Controversies and Uncertainties” the document asserts that patients in the control arm of the CHAMPION trial were not given the same level of nursing care as those in the treatment arm. All patients in the CHAMPION trial were treated in organized disease management programs as outlined in the study protocol, and got what is considered beyond standard of care. As such, the nursing care provided in the treatment arm should not be considered a confounding variable when analyzing the results. There is also a question about the lack of a mortality benefit despite the reduction in hospitalizations. The study was powered to meet the primary endpoint which was reduction in heart failure hospitalizations, it was not powered to detect differences in mortality; therefore, criticism on this finding is irrelevant. If any difference in mortality had been detected as a secondary endpoint, it would only have been hypothesis generating and not a reliable finding. Furthermore, reduction in hospitalizations for heart failure is a robust and significant endpoint that has substantial cost implications and quality of life implications.

Under “Alternative Management Strategies”, the document states that several RCTs, systematic reviews and technology assessments have been done to evaluate the effectiveness of programs to reduce hospitalizations for heart failure. However, there is no summary of the studies that have been done, and the overall negative findings of those studies. The Tele-HF trial (N Engl J Med.2010;363:2301-2309) which showed that telemonitoring did not improve outcomes. The TIM-HF trial (Circulation .2011;123:1873-1880) showed no improvement in mortality or hospitalization with telemedical management and the DOT-HF trial (Circulation.2011;124:1719-1726) actually showed increased heart failure hospitalizations and outpatient visits. This section grossly mischaracterizes the other studies that have been done as somehow being better or equivalent to the results in the CHAMPION trial. The “Summary and Comment” also fails to mention that CMS determined that CardioMEMs met the high threshold for the New Technology Add On Payment (NTAP) on October 1, 2014, and was awarded APC Pass-Through Status on January 1, 2015. Both of these indicating that CardioMEMs demonstrated “substantial clinical improvement”.

Under “Other Benefits or Disadvantages”, placement of the CardioMEMS device is characterized as an anxiety provoking “surgical procedure”. Placement of the device is a minimally invasive procedure that is similar to and no more anxiety provoking than a diagnostic heart catheterization.

Under “Potential Budget Impact”, it seems strange that the group chose to use an “unmanaged” model, when all expensive technologies have strict controls in place. In addition, there are CMS mandated criteria in place for patients to qualify for the device. Uptake is overestimated in the intermediate range. From our current experience, it is clear that uptake will only be in the low range at 5 years. The device requires a fair amount of decision making regarding patient selection. Not every patient is a good candidate for the device. This would significantly alter the cost-effectiveness analysis.

From personal experience, the device has been instrumental in managing difficult to control heart failure patients who are at risk for repeat hospitalization. Remote management with CardioMEMs allows us to track trends and make medication changes before the patient even develops symptoms. By the time patients are symptomatic it is often too late to prevent a hospitalization. The CardioMEMs system is a great option, and prevents the need for repeated right heart catheterization procedures. I would strongly recommend changes to the draft report to reflect the comments above.

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September 22, 2015

To Whom It May Concern,

I am writing on behalf of the CardioMEMS™ HF System Technology. I have recently become aware that California Technology Assessment Forum (CTAF) has issued a draft report on the technology with concerns over its efficacy in heart failure patients.

The CardioMEMS HF System was approved in May, 2014. The FDA Advisory Panel reviewed data from the CHAMPION Trial demonstrating irrefutable efficacy and safety in the 550 patient cohort. The safety profile of this implantable diagnostic device is unparalleled. Among the patients included, 98.6% patients were free from device system related complications.

The CHAMPION trial was never designed to be a mortality driven trial. The efficacy endpoint was Six- Month Heart Failure Hospitalization. At six months, there was a 28% RRR in HF hospitalization. At 15 months, there was a 37% RRR in HF hospitalization. Longitudinal data from the CHAMPION trial showed the durability of the technology to maintain its benefit in managing HF.

To date, HF clinicians have lacked solid, objective patient data in the ambulatory setting to manage patients. For the last thirty years, we have used conventional office assessment, telephone surveillance, monitoring, and worsening symptomatology to acutely manage HF. The result was that by the time patients present with symptoms they have been fluid overloaded for quite some time. Hospitalization in this fragile patient population has been conclusively associated with a proportional rise in mortality.

There have been multiple peer-reviewed publications in patient populations such as those with Chronic Kidney Disease, Chronic Lung Disease, and Preserved Systolic Function (HFpEF). For the group of patients, with HFpEF there is a demonstrable reduction in HF hospitalizations. The CardioMEMS technology represents a substantial benefit for this patient population for which no current treatment regimen has proved to reduce morbidity or mortality.

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This technology represents a significant advancement for the patient population with chronic heart failure. Continued coverage of this implant is needed to impact the long term quality of life and consequences suffered by this cohort of patients.

Your continued support of advances in patient care is desperately needed.

Sincerely,

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September 23, 2015

RE: CTAF Draft Assessment of CardioMEMS HF System



Members of the CTAF Advisory Board,

Thank you for offering a period of public comment to allow us to address our concerns with the CTAF's draft assessment of the CardioMEMS HF System.

Although we support the CTAF's intent to review the effectiveness of the system, the findings wrongly judge the CardioMEMS HF System's body of evidence as "insufficient," or a rating of "I" using the ICER Evidence Rating framework. Our concern with this conclusion is that the draft report will undermine patient access to this important breakthrough for treating heart failure patients.

CardioMEMS was approved by the U.S. Food & Drug Administration in 2014 because of the clear safety, efficacy and treatment effect directly attributable to the sensor. In addition, having reviewed the published evidence, the Center for Medicare and Medicaid Services determined that the use of CardioMEMS represented a substantial clinical improvement over the current standard of care and was awarded add-on payment status in 2015. CMS reaffirmed this decision for 2016.

On top of that, a new analysis from the CHAMPION trial shows CardioMEMS provides a 43 percent reduction in HF hospitalizations and 53 percent improvement in survival of CRT/ICD class III HF patients. [An economic analysis](#) of the entire CHAMPION population demonstrates the CardioMEMS is a cost effective intervention.

What the CTAF fails to consider when judging the value of this system, is the quality of life for patients with heart disease. The CardioMEMS provides ease of compliance for patients, reductions in readmissions and less time spent in the hospital, and relief in knowing their hearts are being monitored closely for any problems. These are critical for the patient communities we serve. Heart failure is a serious problem for a large number of California residents and is a leading cause of hospitalizations.

If the CTAF's draft assessment becomes final, patients are the ones who lose. Please postpone your meeting to ensure the report is revised given its current flaws.

Sincerely,

A handwritten signature in black ink that reads 'Scott Suckow'.

Scott Suckow
Convener
California Chronic Care Coalition in San Diego County



BONNIE J. ADDARIO
LUNG CANCER
FOUNDATION

September 23, 2015

California Technology Assessment Forum (CTAF)
Draft Report on the Cardio MEMS HF System
ctaf@icer-review.org

Dear California Technology Assessment Forum (CTAF):

As a health care patient advocate representing thousands of patients in California and across the nation, I can attest that innovative medical research is invaluable for patients suffering from all chronic diseases, including lung cancer, heart disease and breast cancer. On behalf of the Bonnie J. Addario Lung Cancer Foundation, we want to ensure that the latest technology is available to all patients, whatever their diagnosis. For this reason, we question your assessment of the CardioMEMS HF System and ask that you take into account all the data and research before making a decision.

As a foundation, we have long supported the physicians and researchers that are pushing innovation forward, finding new treatment options and discovering ways to improve patient outcomes and quality of life. Our goal is to push for cures, but we cannot do so without ensuring innovation occurs on every level.

Please take into careful consideration the role innovation plays in everyday lives for victims of chronic disease. Medical advancements for any condition bring hope to all patients. It is for these reasons that we urge you to postpone your decision to ensure the report is revised using all the data and research available on this breakthrough therapy.

Sincerely,

Scott Santarella
President & CEO



RE: CTAF Draft Assessment of CardioMEMS Heart Failure System

To distinguished members of the CTAF Advisory Board,

As a pharmaceutical economist, researcher, peer-reviewed journal editor, college professor, and father of a child with a severe form of ulcerative colitis, I am writing to relay my concerns with the conclusions reached by the CTAF board with respect to CardioMEMS HF System.

While I do not present myself to be an expert in the area of heart disease and heart failure, I am a scientist and am able to discern peer-reviewed literature that evaluates outcomes and forecasts the benefits and costs of various treatment modalities. Additionally, I wholeheartedly value patients' ability to access the most innovative and breakthrough advances in medicine and medical devices.

I have learned first-hand the value of innovative treatments and technologies, as my fifteen year old daughter was recently diagnosed with ulcerative colitis. As a result of the newest innovation in pharmaceutical biologics she is able to live a relatively normal life as a teenager. If not for these innovative and breakthrough advances, I am not sure if my daughter would be able to attend school, participate in karate, perform community service, and volunteer for political campaigns as she is currently able to do, albeit sometime with difficulty. Certainly, before she began treatment on Remicade, all of these activities were suspended, and it was a monumental struggle for her to complete her freshman year of high school. Her quality of life was essentially zero, or negligible.

I hope you will take the time to reevaluate your findings before making a final decision on this system, taking into account all the data and research presented. Your careful dedication to investigate and evaluate all of the data to ensure a thoughtful decision concerning access barriers to this life-saving technology is paramount and much appreciated.

Sincerely,

Shane P. Desselle

Shane P. Desselle, RPh, PhD, FAPhA
President, Applied Pharmacy Solutions
Editor, Research in Social and Administrative Pharmacy
Professor, Touro University California College of Pharmacy

Heart & Vascular Center

Lynne Warner Stevenson, M.D.

Professor of Medicine

Director, Heart Failure Program

Director, Heart Failure / VAD / Transplant Training Program

September 24, 2015

RE: Access to the CardioMEMS HF System for Home Management of Patients at High Risk for Re-hospitalization Without New Monitoring System

Dear Review Committee,

I am writing to to add my support to the request for re-evaluation of the CardioMEMS HF System for Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting. This request is based upon additional evidence that outcomes represent a substantial clinical improvement over current treatment options, including new published analyses of the benefit in heart failure with preserved ejection fraction, heart failure with concomitant pulmonary disease, and heart failure with pulmonary hypertension. An article further demonstrating the sustained benefit when used outside a randomized trial setting has just been accepted for publication by Lancet. Evidence demonstrating the impact of this system to reduce 30 day re-admissions was recently presented at the American Heart Meetings. I founded the Ahmanson UCLA Heart Failure Center and for the past 22 years have been Director of Heart Failure and training director for the heart failure fellowship at Brigham and Women's Hospital, gaining over 30 years of experience in the management of heart failure patients. I have already experienced this advance as a game-changing technology for the care of our patients with advanced heart failure.

I have engaged in extensive research with previous devices intended to help manage heart failure patients out of the hospital. The CardioMEMS HF System is appreciably different from all other technologies tested in heart failure management, and has substantially more published clinical data demonstrating not only improved patient outcomes, but specific information as to how to use the information from the device to alter medication therapy in time to prevent many hospitalizations. The CardioMEMS HF System, approved by the FDA in May, 2014, also has a remarkable safety and reliability profile to date.

Background on the Inadequacy of Currently Available Treatment Options To Improve Outpatient Management of Heart Failure

HF affects over 5.7 million patients in the United States, resulting in over one million primary HF hospitalizations.¹ Although significant progress has been made in the treatment of HF over

¹ American Heart Association, Heart Disease and Stroke Statistics—2015 Update at e242 (2015).

the past several decades, particularly in the reduction of mortality, HF hospitalizations remain a major clinical and public health problem. Hospitalization for HF is not only associated with impaired quality of life and significant economic burden, but it is also often associated with evidence of myocardial injury and acceleration of the downhill course of affected individuals.^{2,3,4} The estimated total cost of HF in 2013 was \$30.7 billion, and it is expected to grow to \$69.7 billion by 2030, which reflects the size and dimension of this enormous clinical challenge.⁵

The primary symptoms leading to hospitalization for worsening HF are dyspnea, edema, and gastrointestinal symptoms related to elevated intra-cardiac filling pressures, which are usually caused by fluid retention.^{6,7,8,9,10} For these reasons, the 2013 American College of Cardiology (“ACC”)/AHA HF guidelines recommend that physicians evaluate volume status with each patient encounter.¹¹ Unfortunately, most of the decisions in heart failure management are made when the patient is at home. At home it is not feasible to use daily physical examination or any laboratory results to assess the patient, and we have depended on unreliable markers such as total body weight or changes in symptoms, which usually do not change soon enough to allow effective intervention to prevent hospitalization. Effort has been devoted to increase the frequency of weight and symptom reporting from home using various telemonitoring systems. Unfortunately, multicenter randomized clinical trials using rigorous telemonitoring protocols have proven ineffective to reduce HF hospitalizations either in the US or in Europe.^{12,13,14,15,16,17} In this context it is particularly noteworthy that the CardioMEMS HF System has been able to reduce hospital admissions by 37%.

² Solomon SD, et al; for the CHARM Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482-7.

³ O'Connor CM, et al. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. *Circ Heart Fail*. 2011;4:724-32.

⁴ Braga JR, et al. Outcomes and care of patients with acute heart failure syndromes and cardiac troponin elevation. *Circ Heart Fail*. 2013;6:193-202.

⁵ Dunlay SM, et al. Lifetime Costs of Medical Care After Heart Failure Diagnosis. *Circulation: Cardiovascular Quality and Outcomes*. 2011; 4:68-75

⁶ Kato M, et al. The worst symptom as defined by patients during heart failure hospitalization: implications for response to therapy. *J Card Fail*. 2012;18:524-33.

⁷ Gheorghiade M, et al. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *Am J Med*. 2006;119(Suppl 1):S3-S10.

⁸ Schiff GD, et al. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med*. 2003;114:625-30.

⁹ Cotter G, et al. Fluid overload in acute heart failure--re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail*. 2008;10:165-9.

¹⁰ Metra M, et al. The pathophysiology of acute heart failure--it is a lot about fluid accumulation. *Am Heart J*. 2008;155:1-5

¹¹ Yancy CW, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128.

¹² Chaudhry SI, et al. Telemonitoring in patients with heart failure. *N Engl J Med*. 2010 Dec 9;363(24):2301-9

¹³ Koehler F, et al; Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation*. 2011 May 3;123(17):1873-80.

¹⁴ van Veldhuisen DJ, et al; DOT-HF Investigators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation*. 2011 Oct 18;124(16):1719-26.

¹⁵ Cleland JG, et al. Noninvasive Home Telemonitoring for Patients with Heart Failure at High Risk of Recurrent Admission and Death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005 May 17;45(10):1654-64

¹⁶ Dang S, Dimmick S, et al. Evaluating the evidence base for the use of home telehealth remote monitoring in elderly with heart failure. *Telemed J E Health*. 2009. 15(8): 783-96.

¹⁷ Polisena J, et al. Home telemonitoring for congestive heart failure: a systematic review and meta-analysis. *J. Telemed Telecare*. 2010. 16(2): 68-76.

First Therapy Proven to Decrease Hospitalizations in Heart Failure With Preserved Ejection Fraction

Approximately 50% of patients hospitalized with decompensated HF have preserved left ventricular ejection fraction, also referred to as “diastolic dysfunction”. This is a particularly challenging population as they are frequently elderly with multiple co-morbidities that limit management. Despite multiple recent trials, there have previously been NO THERAPIES shown to improve any outcome for this population. The CHAMPION protocol included a pre-specified subgroup analysis based on LVEF considering patients with an ejection fraction (“EF”) $\geq 40\%$ as “preserved” EF, and a subsequent ad-hoc analysis of patients with LVEF $\geq 50\%$, to conform to 2013 guidelines providing clearer consensus on defining HF patients with preserved EF with the criteria.¹⁶

The HF hospitalization rate was significantly lower in the preserved EF treatment group compared to the control group for the six month primary endpoint of the randomized period with a relative risk reduction of HF hospitalization of 46% for LVEF $\geq 40\%$ treatment cohort, and a 50% relative risk reduction for the LVEF $\geq 50\%$ treatment cohort. The reduction in HF hospitalizations for all three groups was significant both at the six month primary end point period and the full duration of the Randomized Follow-Up period. Calculation of the number needed to treat is a remarkable 2 in order to prevent one hospitalization in heart failure with preserved ejection fraction.

Thank you for your recognition of the magnitude of the heart failure burden and review of the current evidence, which provides a comprehensive, complete, and definitive story of the importance of pulmonary artery pressures for management of chronic Class III heart failure after hospitalization, the proven protocol for using the pressure information from the Cardiomems device in time to adjust therapy and avert hospitalization, and the impact to decrease hospitalizations regardless of ejection fraction. We have currently integrated this device and pressure monitoring into our program and are very excited to see the impact on our patients reduce their symptoms of heart failure, maintain clinical stability at home, and to actually become more interested and empowered to be compliant with their medical regimen. I anticipate that the strategy of pulmonary artery pressure monitoring to guide outpatient management of heart failure will rapidly become the standard of care for the select population who has persistent Class III symptoms of heart failure despite a heart failure hospitalization during the past year.

Sincerely,

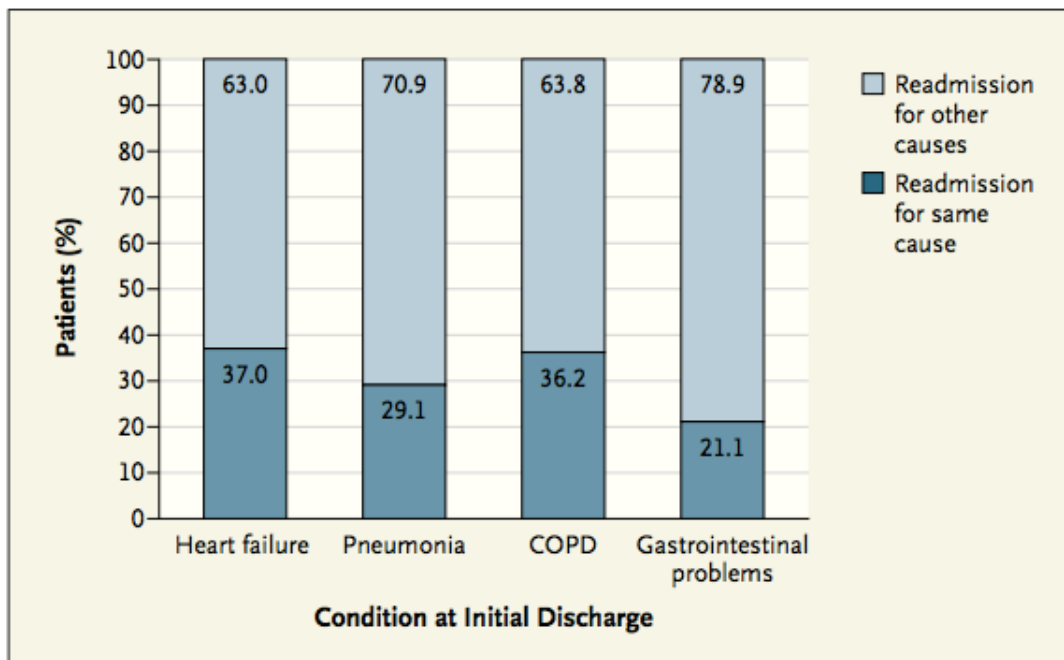
A handwritten signature in black ink, appearing to read 'Lynne Warner Stevenson', with a long, sweeping horizontal stroke at the end.

Lynne Warner Stevenson M.D.

Hospitalization for heart failure remains a major problem from several reasons. Hospitalization for HF is #1 cause of hospitalization in the MediCare population accounting for well over 500,000 hospitalizations accounting for almost 30 billion dollars. Data from Krumholtz reported in Circulation 2014 noted that there were 5.8 million admissions for HF in the population 65 years and above between 1999 and 2010.

These hospitalizations are not without consequence. In house mortality is 2-4% per admission and 30 day mortality is very high, 10-12%. Krumholtz noted in the NEJM 2014 that there appeared to be increased vulnerability to rehospitalization for many reasons in the 30 days after HF hospitalization that he termed the “ Hospital Acquired Syndrome. “ This risk includes pneumonia, cardiovascular events other than heart failure, including falls. (see Below)

PERSPECTIVE



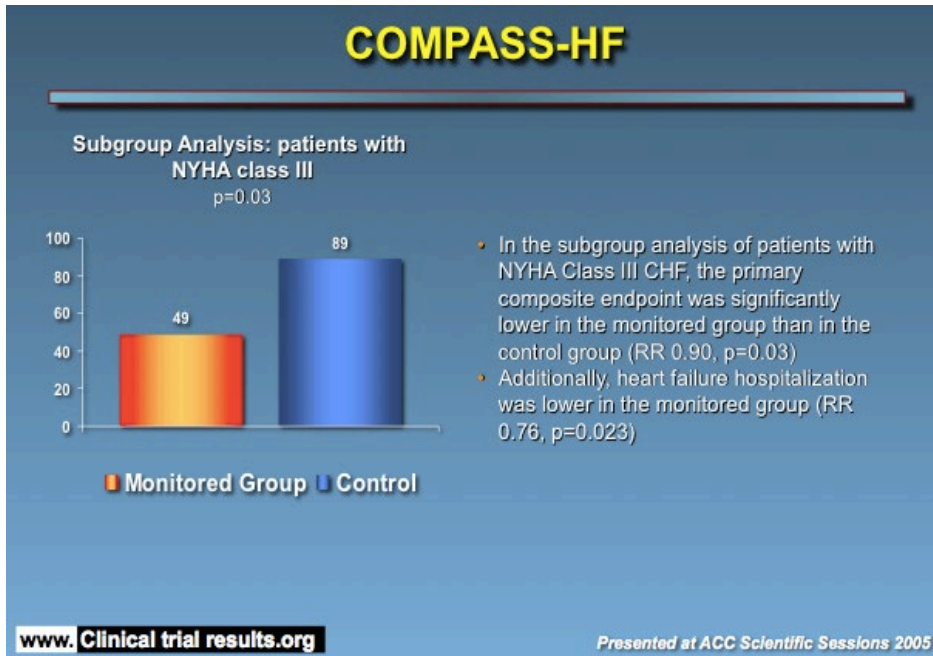
Proportions of Rehospitalizations for Causes Other Than the Condition at Initial Discharge.

Data are from Jencks et al.¹

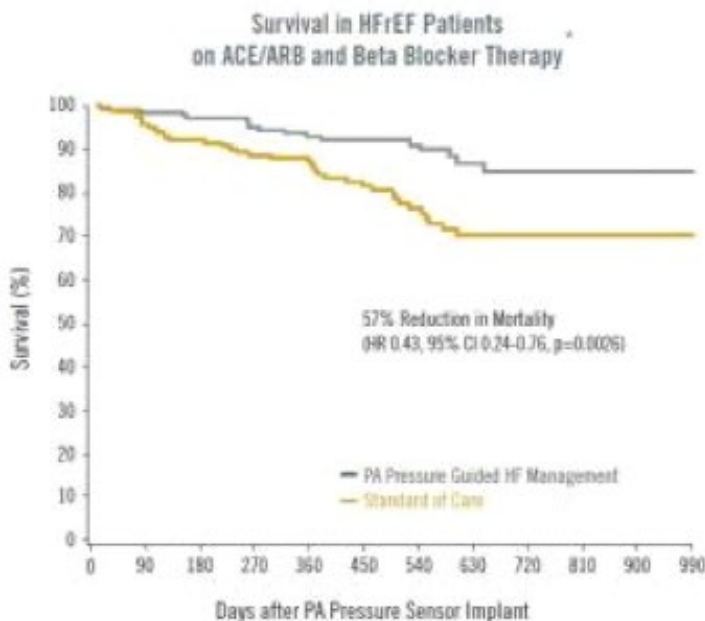
Reducing HF hospitalization has been a major but elusive goal. Heart failure clinics do work but are not widespread. Telemonitoring has not been successful. Following impedance signals is better than weights as shown by the FAST trial but patient alerts increased hospitalizations.

CTAF concentrated on Champion trial but implanted hemodynamic monitoring has been explored for 15 years. The Compass trial with the Medtronic device did not meet its primary endpoint but important lessons were learned, namely that Class III patients should be the primary focus as Class IV patients were too sick to benefit. Compass found

a 24% reduction in hospitalization in NYHA Class III patients, $p = .03$. (Reported at ACC 2005) . The Homeostasis trial using the implanted LA pressure monitor also found a benefit with monitoring. (Ritzema J, Troughton R, Melton I, et al: hemodynamically guided self-therapy in severe heart failure patients (HOMEOSTASIS) study group. Circulation 2010;121:1086-1095.)



Data presented by William Abraham at the ACC in 2015 in a post hoc analysis in patients with low EF in the Champion trial demonstrated a reduction in mortality in the actively managed group.



The estimate for numbers of implants at 5 years seems highly inflated. For example in the San Diego Metropolitan area with 3 million inhabitants, approximately 30 devices have been implanted, thus far, 1/100,000 population, giving an rough estimate of 3500 nationwide during the first year of approval. So the impact on costs seems highly inflated.

Finally the report does not address the unique needs of patients with normal ejection fraction heart failure. Fully 50% of patients admitted to hospital with heart failure have a normal ejection fraction (HFpEF). Currently there are NO evidence based therapies for these patients beyond BP control and diuretics. The Cardiomems system reduces hospitalizations in the HFpEF by 50%. Elevated PA pressures are the hallmark of the hemodynamic abnormality in these patients and the Cardiomems system is quite successful in reducing these pressures.

In summary the Cardiomems PA pressure monitoring system

- 1) Significantly reduces HF hospitalization in patients with NYHA Class III HF patients despite medical therapy. These admissions result in a period of significant morbidity and mortality and generate costs of billions of dollars. The system reduces admissions by 30% at 6 months and 38% at 15 months. This benefit is increased in patients with HFpEF where admissions are reduced by 50%. These patients currently have no therapy that is comparable to pressure monitoring in terms of benefits
- 2) The Cardiomems systems builds on data from the Medtronic Chronicle System reported in the Compass trial and the St Jude Left atrial pressure monitoring system so that several studies suggest benefit. A post hoc analysis suggests a mortality benefit in patients with a reduced ejection fraction.
- 3) The suggestion that hundreds of thousand of patients will be implanted with this device is not supported by current usage.
- 4) In our hands the device allows patients to be managed at home and reduces the need for inperson clinic visits.

Lack of support for this new and innovative technology will result in the needless hospitalization and suffering of many thousand of patients. For the first time in decade we have a therapy for HFpEF that actually works. This technology should be supported rather than marginalized.

J. Thomas Heywood
Scripps Clinic
La Jolla Ca

RE California Technology Assessment Forum (CTAF) Draft Report on the CardioMEMS HF System

Dear California Technology Assessment Forum (CTAF):

Having reviewed your preliminary draft report on the CardioMEMS, I am writing on behalf of the NAACP- California State Conference to respectfully request that you reconsider your recommendations to consider the value to patients.

Heart failure is a significant and serious problem for a large number of California residents, especially African Americans and is the leading cause of hospitalizations, readmissions and premature deaths. Cardiovascular disease is the leading cause of death in California and the primary cause of readmissions for older Americans.

Innovative and breakthrough technologies and medications are critical for the control of many chronic conditions affecting the African American community including heart disease, diabetes and more. We believe it is important that cardiologists have the ability to offer this proven technology to their patients, leading to improved outcomes, which also can help contain health care costs over time.

Please consider the clinical data that included six peer-reviewed publications relevant to its assessment. Five of six publications were considered “good” quality (highest ranking), based on the assessment criteria. We are aware that you disregarded the clinical data evaluations when conducting your assessment and ask that you reconsider that decision, and consider all relevant information before releasing the final report.

Sincerely,
Alice A. Huffman
President
NAACP – California State Conference

Submitted Electronically

September 25, 2015

**Institute for Clinical and Economic Review (ICER)
Draft Report on the CardioMEMS HF System for the Management of Congestive Heart Failure**

St. Jude Medical appreciates the opportunity to comment on the draft ICER report regarding the CardioMEMS HF System in the management of congestive heart failure. In summary, we strongly disagree with the methods and conclusions of ICER in the draft report that there is “low certainty of a small net benefit for the CardioMEMS HF System compared to alternative management in patients with CHF.” We also disagree with the proposed rating of “I” in the report and contend that the totality of the evidence warrants a significantly higher rating than this. We offer our rationale and detail comments on the draft report below.

Clinical Data Evaluated

ICER identified six published, peer-reviewed publications relevant to the CardioMEMS HF System. Inclusion of these publications is appropriate, and we agree with the Study Quality ranking provided in Table E1. We note that ICER identified five of these studies as “Good”, the highest rating possible. Subsequent to the draft report being written, an additional important study has been accepted for publication by The Lancet¹. This study prospectively collected an additional 13 months (mean) of real-world experience of utilizing PA pressure information to guide patient management in both the former treatment and control patients. During the blinded, randomized access period, Control patients in the CHAMPION Trial received excellent care with lower than anticipated event rates. Despite this, as reported, their event rates were significantly higher than the treatment group. Once patients finished the randomized access period of 18 months, PA pressures were made available to physicians in the former control group for the first time. Significant reductions in heart failure hospitalization rates in the ensuing 13 months (48% decrease, $p < 0.0001$). All of these events were prospectively adjudicated by the independent group of heart failure specialists that comprised the Clinical Events Committee of the CHAMPION Trial. During the “Open-Access Period”, former Treatment group patients continued to benefit from hemodynamic guided management with the low event rates seen during the randomization period. There were no communications between the sponsor and the investigators during this 13 month open-access period. The manuscript is in press, but we confidentially provide the document for your review.

Summary of ICER’s Clinical Evaluation

CTAF accurately reports the results of the clinical trials included in their evaluation. However, ICER raises three primary concerns with these data: 1) FDA Advisory Panel concerns of potential bias in the CHAMPION trial due to nurse communications, 2) Lack of a statistically significant mortality benefit in the CHAMPION trial, and 3) Alternative Management Strategies providing similar benefit to the CardioMEMS HF System.

Bias of Nurse Communications

ICER has seemingly discounted the outcomes reported in peer-reviewed, published literature based primarily on concerns of potential bias introduced by nurse communications as communicated by the FDA Advisory Panel. Unfortunately, the report does not include the determination by the FDA that stated, “**FDA *disagrees*** (emphasis added) **with the Panel Vote that there is not reasonable assurance that the device is effective. FDA acknowledges that, when taken individually, each analysis has its limitations. However, when considering the totality of effectiveness data, the consistency of the results indicate a positive treatment effect in**

reducing HFR hospitalizations. This positive treatment effect seen in the Open Access (Part 2) of the study also agrees with the positive treatment effect seen in the Randomized Access (Part 1)².” Please note the Open Access study referenced above is the recently published manuscript included with this letter.

ICER inappropriately discounts the agreed upon statistical plan developed by the FDA and CardioMEMS to evaluate several aspects of the trial to further confirm efficacy of hemodynamic guided care, which ultimately led to the FDA’s conclusion that the CHAMPION Trial efficacy outcome was accurate leading to FDA approval. The draft report includes a description of these analyses, but appears to rely solely on the opinion of the FDA Advisory Panel. We remind ICER that FDA advisory panels have no policy or decision-making authority. The FDA’s scientists and statisticians operate with processes that set the standard for rigor in regulatory decision-making globally and should not be trivialized. The FDA’s assessment and conclusions should be used to determine the validity of the CHAMPION Trial results.

Mortality Impact

The draft report mentions repeatedly that the CHAMPION trial did not demonstrate a statistically significant reduction in mortality. This should not be a surprise as the CHAMPION trial was neither empowered nor designed to evaluate mortality in this population. To emphasize this point, we note that the CTAF study discussed a systematic review of high-intensity disease-management programs for heart failure. In the analysis, CTAF pointed out that the reduction in mortality was from 13% in the control group to 10% in the intensive-management group, although the time point of this difference was stated directly [p 47]. The sample size required to detect this difference with 80% power is approximately 1,800 per group. Despite this, the trial did demonstrate a favorable trend in mortality reduction of 20% in the treatment group.

Alternative Management Strategies (AMS)

The draft report includes discussion of AMS in treating heart failure, however, ICER states that a systematic review wasn’t completed as they weren’t direct comparators to the CardioMEMS HF System. It is essential to compare the results of hemodynamic guided care to heart failure management outcomes achieved by traditional tools. This is the essence of the CHAMPION Trial and why this major breakthrough is both economically and clinically beneficial. We provide an appropriate systematic review for ICER to consider. We remind ICER that current management strategies result in over 1,000,000 hospitalizations for heart failure in the US. Heart failure (HF) decompensation contributes to over 3,000,000 hospitalizations. Over ½ of these hospitalizations involve patients with preserved ejection fraction heart failure, for which there are NO guidelines or consensus for care.

There are large randomized controlled trials outlining several strategies to reduce hospitalizations for patients with heart failure. Unfortunately, even intense telemonitoring of symptoms and daily weights to manage patients with heart failure does not impact HF hospitalization rates or mortality. Examples of these studies include: **Tele-HF³** – In this study of 1,653 randomized patients recently hospitalized for heart failure, intense telemonitoring of weights and symptoms did not improve outcomes; **TIM-HF⁴** – None of the primary or secondary endpoints regarding heart failure hospitalization or death were met when comparing telemonitoring to usual care; **DOT-HF⁵** – Measurement of intrathoracic impedance did not improve outcomes, and increased HF hospitalizations and outpatient visits in HF patients; **Optilink-HF⁶** –No impact of monitoring intrathoracic impedance on all cause death or cardiovascular hospitalization in 1,002 patients monitored for over 12 months. These meaningful studies demonstrate how ineffective our current tools are in managing heart failure, which should be included in ICER’s evaluation.

Centers for Medicare and Medicaid Services (CMS) Determination of Substantial Clinical Improvement

An important designation omitted in the draft report was the CMS decisions that the CardioMEMS HF system is a *substantial clinical improvement* over existing therapies. CMS awarded the CardioMEMS HF System both the New Technology Add-On Payment (NTAP)⁸ as well as Transitional APC Pass-Through Status⁹ based on evidence from the CHAMPION Trial.

Cost Effectiveness Analysis

The draft ICER report indicates that the CardioMEMS HF System has the potential to provide clinical benefit over standard approaches to CHF management, and the cost/QALY findings remained below commonly accepted cost-effectiveness thresholds. We have conducted a cost effectiveness analysis that was presented recently at a large scientific session¹⁰. This analysis calculated a comprehensive incremental cost effectiveness ratio of \$30,167 over a 5 year horizon. However, it is important to note that both analyses found the CardioMEMS HF System cost-effective utilizing commonly-accepted thresholds.

Budget Impact Analysis

The ICER analysis assumes that 450,000 patients annually are eligible for the CardioMEMS HF System. We agree that it is a challenge to make an accurate prediction of the indicated population in the US. The ICER calculation utilizes 1 million annual HF discharges multiplied by the percentage of patients estimated to be NYHA Class III per published literature. This calculation fails to consider that one discharge does not necessarily equate to a unique patient. In fact, HF patients may have multiple discharges in one year, so this traditional approach overstates the numbers of patients with a potential indication for the CardioMEMS HF System. The literature suggests that 61.3% of patients are readmitted for HF within the first year,¹² thus a more accurate assessment would be approximately 109,000 when considering individual readmission rates.

St. Jude Medical has no modeling of an “intermediate” market uptake since this level of new technology uptake has never been seen this early after introduction. The ICER analysis estimates 112,500 patients will receive the technology annually. We believe a “low” uptake still significantly overestimates annual market uptake and does not represent “real-world” expectations. We are unable to provide proprietary sales figures in this letter, but market analysts project the utilization of the CardioMEMS HF System, based on survey data and their own analyses, to be much lower.¹¹

These assumptions dramatically influence the value based benchmark calculated in the draft report. We suggest that ICER re-evaluate the assumptions utilized in calculating the benchmark. Unfortunately, based on the limited information on the calculations of the models, as well limitations of time and space to provide comments on the ICER draft report, we need to limit our suggestions on the assumptions that go into both analyses. However, we would be very willing to share more detailed comments and analyses should ICER be interested in reviewing them.

In summary, we strongly disagree with the conclusions regarding the CardioMEMS HF System included in the ICER draft report. The robust body of clinical evidence demonstrates that the CardioMEMS HF System has a statistically and clinically meaningful reduction in HF hospitalizations, which is superior to the best medical management available. The arguments put forth in the ICER draft report appear incomplete and not based on the results of the published, peer-reviewed evidence, as well as erroneous assumptions included in the budget impact analysis. As such, we urge the ICER draft report to factor in these comments, and reevaluate the rating based on the ICER Evidence Rating Framework. Thank you for the opportunity to provide comments on draft ICER report. If you have any questions or require additional information, please do not hesitate to contact me directly at (512) 286-4526 or at padamson02@sjm.com.

Sincerely,

Philip B. Adamson, MD, MSc, FACC
Medical Director, Vice President of Medical Affairs
Adjunct Associate Professor of Physiology
University of Oklahoma Health Sciences Center

References:

1. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, for the CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION trial. In-Press, Lancet
2. Source: PMA P100045: FDA Summary of Safety and Effectiveness Data, p88
3. Chaudry SI, et al, N Engl J Med 363;24 December 9, 2010
4. Koehler F, et. al, Circulation, 2011; 123: 1873-1880
5. van Veldhuisen DJ, et al, Circulation 2011; 124:1719-1726Asdf
6. Effect of implanted device-based impedance monitoring with telemedicine alerts on mortality and morbidity in heart failure: Results from the OptiLink HF study. (Böhm M, et al, ESC 2015 Congress; Abstract 5057Asdf
7. McAlister et al: J Am Coll Cardiol 2004;44:810-819
8. CMS Hospital Inpatient Prospective Payment System Final Rule, Federal Register (79 Fed Reg., No. 163) August 22, 2014.
9. CMS Transmittal 3156, December 22, 2014
10. Adamson P.B., B.R., Bauman J., Dalal N., Martinson M., Abraham W.T. Cost effectiveness assessment of pulmonary artery pressure monitoring for heart failure management. Heart Rhythm Society. 2015 12:5 SUPPL. 1 (S82). Boston, MA.
11. Credit Suisse Equity Research Report, March 19, 2015
12. Soohun C, et al, Lifetime Analysis of Hospitalizations and Survival of Patients Newly-Admitted with Heart Failure, *Circ Heart Fail.* 2012;5:414-421



RE: California Technology Assessment Forum (CTAF) Draft Report on the CardioMEMS HF System

Karen Shore PhD

Program Director, California Technology Assessment Forum (CTAF)

Institute for Clinical and Economic Review

The California Association of Area Agencies on Aging, a nonprofit organization representing California's 33 area agencies on aging and the leading voice on aging issues in California, is most concerned about CTAF's findings on the CardioMEMS device. Having carefully reviewed your preliminary draft report, our organization is deeply troubled with your draft findings, specifically the published findings which you disregard when reporting your outcomes.

CardioMEMS was approved by the U.S. Food & Drug Administration in 2014 following rigorous review of the evidence, and outcomes that clearly show safety, efficacy and treatment effect directly attributable to the sensor. In fact, the FDA states that "Access to PA pressure data provides doctors with another way to better manage a patient's heart failure and potentially reduce heart failure-related hospitalizations. Reducing heart failure hospitalizations has a direct impact on a patient's well-being."

This breakthrough medical device allows physicians to track certain heart failure patients' conditions early, and in real time, and reduces the likelihood of hospital readmission. This is not only cost-effective but improves the overall quality of life for patients.

We are deeply concerned that your inconclusive report could have a devastating impact on patients who would greatly benefit from this breakthrough medical device. Given these concerns and the flaws in your analysis, we request that the CTAF substantially revises the assessment.

We sincerely hope the CTAF will take our concerns seriously, and you will consider the livelihood of the patient and the benefits this device will have on those patients who live in constant stress because of the uncertainty of their condition.

Respectfully,

A handwritten signature in dark ink, appearing to read "Derrell Kelch", written in a cursive style.

Derrell Kelch
C4A Executive Director

RE: CTAF Draft Assessment of CardioMEMS HF System

Dear California Technology Assessment Forum Advisory Board,

On behalf of the California Senior Advocate League (CalSAL), we would like to express our concern with the conclusions drawn from the CTAF's draft assessment of the CardioMEMS HF System issued on September 11, 2015.

CalSAL represents senior communities through California, many of which could lose the benefits from the CardioMEMS system if the CTAF adopts the conclusions in the draft assessment. We urge you to consider the quality of life for senior patients in our state when finalizing your decision. Benefits to patients include ease of compliance, reduced hospital readmission and peace of mind knowing the device will detect issues before patients experience symptoms.

CardioMEMS meets the quality of life and cost effectiveness thresholds typically used when judging value. The draft report's final assessment of "value," however, does not consider this and applies an arbitrary "impact" standard that does not take the patient into account. We need new innovation to reduce the burden and cost of heart failure and CardioMEMS is an effective option for patients.

Overall, CardioMEMS provides doctors with a better way to manage a patient's heart failure and potentially reduce heart failure-related hospitalizations. The system has undergone rigorous review by the FDA, which approved the innovative device, and Medicare, which established payment for it. Above and beyond this, the quality of life the device provides to patients CalSAL serves is unprecedented.

Please redraft your assessment in order to ensure your decisions put patients first.

Sincerely,

John Kehoe, California Senior Advocates League

September 25, 2015

Panel Members
California Technology Assessment Forum

To Whom It May Concern:

I am writing to express my concerns about the ICER draft report on the CardioMEMS HF system you have under consideration. My experience with the CardioMEMS device has proven it to be a game-changer in the way my patients and I manage their heart failure. I disagree with the findings on clinical effectiveness contained in the draft report and urge you to make several key revisions in the draft report, and update your conclusions accordingly.

I began using CardioMEMS with my patients in February 2015 and have treated 18 patients. To date, our hospital has treated a total of 29 patients. My personal experience thus far, is this technology has radically changed our Heart Failure management. We have had a dramatic decrease in readmissions for CHF, in fact, since our first implant in February, only one out of the 29 patients were readmitted for heart failure, and this was clearly due to a dietary indiscretion.

Our patients are completely involved and galvanized in managing their own care in a way I have never seen before. They are committed to maintaining food diaries now, to daily weights, to knowing exactly what meds/doses they are on.

The CardioMEMS system has been an invaluable tool to me and my partners in day to day Heart failure treatment.

I look forward to its increasing use. With all the advances in CHF medical therapy, device therapy, CRT therapy, I strongly advocate for the important/individual place that CardioMEMS has secured for itself in the arsenal for CHF treatment.

The analysis in the draft report relies on opinions of the FDA Advisory Panel instead of focusing on the outcomes of published, peer-reviewed literature. The draft report ranks the quality of evidence as high, which is appropriate. However, relying on the opinions of several individuals over peer-reviewed publications in respected journals is inconsistent with an evidence review. Given the FDA approved CardioMEMS, they believe the technology to be safe and effective, thus making irrelevant the opinion of the Advisory Panel.

The draft report also includes several references to the lack of clinical effectiveness data on mortality. I'm not clear why there was an emphasis on this endpoint when the CHAMPION trial's primary endpoint was the reduction of heart failure hospitalizations.

As physicians, we clearly understand the CHAMPION trial was not powered to demonstrate an impact on mortality, but to demonstrate a statistically significant reduction in hospitalizations.

I also want to comment on the alternative strategies that are included in the draft report. These strategies have been available for quite some time, and the published clinical evidence clearly shows that these strategies do not favorably impact outcomes for heart failure patients. The draft report did not include a thorough review of the evidence of these strategies, yet uses them as a comparator to the outcomes of CardioMEMS. The evidence included in the draft report provides a skewed view of these strategies, and the report does not accurately account for the published evidence that contradicts the conclusions included in the report regarding them. I urge the report be revised to account for the full body of literature on these alternative strategies.

Finally, the Centers for Medicare and Medicaid Services (CMS) also reviewed the evidence on CardioMEMS and determined that the device represents a “substantial clinical improvement” as a part of meeting CMS’s new technology reimbursement criteria. It’s a failing that the draft report fails to mention this determination entirely.

For these reasons, I request that ICER consider these comments and revise the draft report to more accurately reflect the robust published evidence.

Sincerely,

Vyshali Rao, MD, FACC, FSCAI, FAHA
Foothill Cardiology (626) 793-4139

September 24, 2015

California Technology Assessment Forum

Congestive Heart Failure Section

Re: CARDIOMEMS PA sensor monitoring system

I am writing today in support of the CARDIOMEMS HF system which I currently use in management for my patients with stage III congestive heart failure. As a specialist board certified in advanced heart failure and cardiac transplantation, I unfortunately see the sickest heart failure patients in my area. While optimal medical therapy certainly allows for patients to have symptomatic improvement, and in some cases, recovery from cardiac muscle dysfunction, sadly, this is not universal. A small cohort of patients do exist that despite optimal, and maximally tolerated medical therapy, still struggle with symptoms of heart failure. In my practice, these mainly involve patients with diastolic heart failure, and universally, whether their CHF is either systolic or diastolic, symptoms are related to abnormal filling pressures.

Previously, for this cohort of patients who are most difficult to manage, a combined medical effort of daily weights and judicious dietary restrictions from a patient side, combined with frequent laboratory draws (to assess renal function and electrolytes), and frequent clinic visits were the mainstay for therapy. These patients were (and still are) subjected to frequent adjustments in diuretics and afterload reducing medications. Still, despite seeing some of these patients between two and four times a month in the office setting, decompensations still exist, and hospitalizations do occur for fluid overload at a rate that is far more frequent than class I or II heart failure patients.

Since having the opportunity to implant and subsequently manage my class III heart failure patients with the CARDIOMEMS system, I have found that management of their heart failure has improved dramatically. Patient compliance with monitoring and transmitting data has been better than I had initially expected. Additionally, targeting diuretics and afterload reduction medications to PA pressures has allowed for, what I believe, is a global symptomatic improvement for my patients with this therapy, and in addition, a likely reduction in hospitalization for this cohort.

I feel that this benefit extends more towards my patients with heart failure with a preserved ejection fraction, who usually have a very narrow therapeutic window between dehydration and symptomatic fluid overload.

In summary, I am definitely a supporter of the CARDIOMEMS system for a select cohort of class III heart failure patients whose fluid status is difficult to assess, dynamic, and challenging to manage from a outpatient setting. I feel in these patients, knowledge of their PA pressures and targeting medications to a specific level has made management easier on my part, and in addition, I feel my patient's symptoms to have improved.

Sincerely,

Hirsch S. Mehta, MD FACC
Advanced Heart Failure and Pulmonary Hypertension
San Diego Cardiac Center
Sharp Heart Transplant and LVAD Program



September 25, 2015

Steven D. Pearson, MD, MSc, FRCP
President, Institute For Clinical and Economic Review
One State Street
Suite 1050
Boston, MA 02109 USA

Sent via Email: ctaf@icer-review.org

RE: ICER Draft Report on CardioMEMS and Entresto for Management of Congestive Heart Failure

Dear Dr. Pearson

The Advanced Medical Technology Association (AdvaMed) is pleased to submit the following comments on the ICER Draft Report on CardioMEMS and Entresto for Management of Congestive Heart Failure and the Questions for Deliberation which were released by CTAF for the October 29, 2015 Public Meeting.

AdvaMed member companies produce the medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMed members range from the largest to the smallest medical technology innovators and companies. We are committed to ensuring patient access to life-saving and life-enhancing devices and other advanced medical technologies in the most appropriate settings.

AdvaMed wishes to provide comments on the following topics: (1) General Procedural Issues related to the ICER Draft Report on CardioMEMS and Entresto for Management of Congestive Heart Failure; and (2) Issues related to the CTAF Questions for Deliberations for the October 29, 2015 Public Meeting. Our comments specifically relate to the CardioMEMS device, and do not represent an opinion on Entresto.

I. General Procedural Issues related to the ICER Draft Report on CardioMEMS and Entresto for Management of Congestive Heart Failure

A. The New ICER Value Framework Has Not Been Sufficiently Vetted

The ICER Framework on assessing value has only recently been finalized. Thus, we believe there has not been sufficient time for stakeholder and public comment and it has not gone through any vigorous

vetting process to date. It is unclear how the framework assesses the clinical and economic impact of medical technologies/devices on health systems. Although ICER has previously evaluated drugs, it does not seem to have significant experience in evaluating medical technologies/devices. Medical devices account for only a small portion of health care spending. Additionally, advances in medical technology can increase efficiencies in care and have been demonstrated to lower health care costs over the long term.

Emphasizing short-term cost savings may create barriers to using innovative treatments that represent improvements in care but deliver their cost savings over a longer period of time. Applying the value framework to new technologies with limited time on the market may be a source of inherent bias, as there is insufficient time for physician and patient experience to evolve and be adequately captured. Importantly, this short time frame does not adequately capture the longer-term patient outcomes that factor into the cost/value equation.

B. ICER Lacks Sufficient Clinical Expertise/Participation in the Evidence Review Process

We note that two of the ICER Report's physician authors, who are not directly associated with ICER, are employees of the VA Palo Alto Health Care System and do not appear to have on-going specialty experience or certification in managing patients in the critical care setting or interventional cardiology, where devices like CardioMEMS would be most likely considered and utilized. AdvaMed is concerned that there is insufficient clinical representation on the ICER panel by clinician(s) with first-hand, practical clinical experience with the technology under review.

The patients that would require a device such as CardioMEMS tend, by definition, to have more advanced stages of CHF (NYHA Class III patients with a hospitalization in the previous 12 months). Therefore, the data analysis should be conducted by practicing clinicians with the appropriate background and experience to opine in this area. AdvaMed recommends that the ICER authors include a rotating clinical expert position that varies according to the technology being reviewed. Establishing such a position on the ICER panel would ensure representation by a clinician with direct experience with a reviewed technology, and provide ICER with invaluable insight into the practical application of the technology and its value in clinical practice. Inclusion of such clinical expertise will provide real-world input regarding the implications of a coverage and reimbursement determination during the ICER/CTAF deliberation process. The lead medical society for each technology should nominate or select the clinician, or when there is no agreement on a lead society, relevant state and national medical societies should be invited to recommend the candidates for this position.

C. ICER Should Provide Additional Transparency in the Proceedings

We also believe that transparency in the ICER evidence review process could be improved by requiring contracted research organizations to meet with interested parties prior to providing their draft reports. Such a meeting would promote the discussion of specific topics relevant to the contracted research organization's review and evaluation of submitted information and existing research. The contracted organization would have an opportunity to ask questions requiring technical expertise. Interested parties would have the opportunity to discuss the interpretation of peer-reviewed literature and provide the contractor with completed clinical research not yet in the public space. Furthermore, this meeting would ensure that the contractor understood all relevant research--thereby improving Evidence Report accuracy and obviating the need for the immediate re-review of an assessment due to newly published research.

ICER focuses heavily on the opinions expressed by the 2013 FDA Advisory Panel Committee in the CHF Draft Report. However, the ICER report does not include relevant findings made by the FDA, including the Agency's disagreement with the Advisory Panel and ultimate decision to grant CardioMEMS FDA approval. The report also fails to include relevant information, such as CMS' approval of increased payments for the technology under the new technology add-on payment (NTAP) policy (inpatient setting) and under the transitional pass-through payment policy (outpatient setting). Full disclosure of such supplemental material and events is essential in allowing the public to provide comprehensive comments on this issue.

II. CTAF "Questions for Deliberation" (October 29, 2015, Public Meeting)

The CTAF CHF "Questions for Deliberation" for the October 29, 2015 public meeting are posed in a manner that assumes the totality of evidence for CardioMEMS has been adequately presented. This may not be the case. For example, regarding alternative management strategies for CardioMEMS, we are aware that several important, large, randomized controlled studies concerning implantable device-based impedance monitoring were not included in the ICER Report. These implantable device studies should have been considered as potential alternate management strategies, and would have been more appropriate than considering "non-pharmacologic interventions" such as structured telephone support, tele-monitoring, and patient education to make indirect effectiveness comparisons for contextual purposes.

The assumption that the evidence presented in the Draft Report is complete introduces significant bias in the questions for deliberation and interferes with the validity of the responses. The questions should include a response option indicating that the responder does not have adequate information based on the Draft Report to come to a conclusion. Therefore, AdvaMed recommends that CTAF include the following fourth choice (d) for each of the questions evaluating care value/provisional health system value:

(d) Unable to Determine/Inadequate Evidence Presented

We also recommend that each question indicate that the available evidence being queried is based on the evidence specifically provided in the September 11, 2015 Draft Report.

We would be pleased to answer any questions regarding these comments. Please contact Steven J. Brotman, MD, JD, Senior Vice President, Payment and Health Care Delivery Policy, at (202) 434-7207, if we can be of further assistance.

Sincerely,

/s/

Don May
Executive Vice President,
Payment and Health Care Delivery

September 25, 2015

Advisory Panel
California Technology Assessment Forum
Re: Review of CardioMEMS HF System

Via Email: to ctaf@icer-review.org

As leading physicians and patient advocates concerned about addressing health disparities in the treatment of heart failure, we are concerned about recent efforts to reduce patient access to new, innovative technologies for the treatment and management of heart failure. In particular, we urge you to reconsider adverse coverage decisions and draft assessments relating to the CardioMEMS HF system to include consideration of the potential benefits the first-in-class wireless monitoring device offers to help reduce the disparate impact of heart failure on African Americans.

African Americans are disproportionately affected by heart failure, suffer higher death rates, poorer health outcomes overall, and develop heart failure at a younger age. Moreover, African Americans have higher hospitalization and readmission rates for heart failure and experience greater functional decline post-hospitalization for heart failure. Research also shows that many commonly used treatments for heart failure may affect African Americans and other minorities differently. Having access to treatments and technologies that can help to reduce hospitalizations, readmissions, and health decline is important for all heart failure patients, but particularly so for African Americans living with heart failure.

The CardioMEMS HF system provides cardiologists and their patients real-time data on pressure changes in the heart that provides invaluable information about the patient's health status in time to allow adjustments in treatment before an acute problem develops. Once implanted, the technology sends data on heart pressure rates to the patient's care team who monitors the data for any troubling changes. Changes in pressure often occur well before other signs of a problem are noticeable and allow the care team to respond before the patient's health status declines requiring a hospitalization. Having this information marks a major advance in our ability to reduce the toll of heart failure.

This new technology, shown to significantly reduce hospital readmissions, could provide tremendous benefit to people living with heart failure. Yet, consideration of the benefits and risks associated with improving access to African Americans in discussions of overall value and in local coverage decisions is lacking.

In contrast, the Centers for Medicare and Medicaid Services, after extensive review of the evidence, judged the CardioMEMS HF device as representing a substantial clinical improvement over the standard of care and assigning a pass through and add-on payment covering the device. That is an important recognition that shouldn't be ignored or overruled to deny patients access.

Many patients living with heart failure also have other comorbid conditions, which complicate their treatment and ability to track symptoms and warning signs on their own.

These realities make having timely information on their health status even more important to the avoidance of poor health outcomes and premature death.

We strongly believe it is important that cardiologists can exercise clinical judgment to offer this proven technology to patients who could benefit. To do so will lead to improved outcomes, which also can help in containing healthcare costs over time. Eliminating health disparities in the treatment of heart failure depends upon African Americans and their physicians having access to the best treatments and technologies that meet their needs and overcome barriers to better health.

Sincerely,

National Minority Quality Forum

<http://www.nmqf.org/>

Healthy Women

<http://www.healthywomen.org/>

Men's Health Network

<http://www.menshealthnetwork.org/>

Partnership to Fight Chronic Disease

<http://www.fightchronicdisease.org>

Retire Safe

<http://www.retiresafe.org/>

25 September 2015

To Whom It May Concern:

I have concerns about CTAFs stance on the CardioMEMS device. It cannot be evaluated along the same lines as mortality reducing medications such as Entresto. It is a monitoring device to assist with the management of this very complex and difficult to evaluate population in this country and should complement mortality reduction medications. As a society, we have decided to attempt to take the constant “revolving door” approach to heart failure to the communities and direct pulmonary artery pressure that is “real time” is an excellent method to do this in this population that has the tendency to re admit frequently. CardioMEMS is the tool that enables the patient to gain some control over his or her chronic disease. It allows the provider to intervene with the patient before the patient requires hospitalization or highly reactive care, as we have traditionally done.

We, as providers cannot be expected to “keep patients out of the hospital” if we are not empowered to utilize tools that have shown clear benefit in this manner. This device would allow us to not continue to “guess” or admit patients to the hospital for tailored therapy based on right heart data on a regular basis. Given the appropriate criteria, physicians will use this tool judiciously and where they believe the benefit exists, in the Class III patients who are frequently readmitted.

Respectfully,

Rosemary P. Peterson, MD, FACC
Heart Failure and Transplant Cardiologist
CHI-Franciscan

September 25, 2015

Dr. Dan Ollendorf
Chief Review Officer
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

Re: Suggestions for ICER/CTAF's revision of ENTRESTO draft report

Dear Dr. Ollendorf:

Novartis recommends a key revision to the pricing framework assessment which will impact the final price benchmark recommendation:

The size of the eligible population should be adjusted for New York Heart Association (NYHA) class size using the distribution in the US population, rather than the distribution in the PARADIGM-HF trial.

- In two large US observational studies (REACH and IMPROVE-HF), approximately 28% of the real-world HF population were NYHA Class I.[1, 2] The budget impact analysis is driven by the size of the population eligible for treatment with ENTRESTO. Using the NYHA class distribution found in the PARADIGM-HF trial, ICER assumes 5% of the heart failure (HF) population is ineligible for treatment.[3] Patients were not eligible for inclusion in the PARADIGM-HF trial if the patients were NYHA Class I at time of screening. However, between screening and the time of randomization, approximately 5% of patients improved to NYHA Class I after the sequential run-in periods with enalapril followed by ENTRESTO.[3] Hence, the 5% of NYHA class I patients seen in PARADIGM-HF relate to outcomes of the run-in period and do not reflect real-world prevalence. Incorporating real-world NYHA Class I data into the analysis would reduce the eligible treatment population in the health system value analysis to approximately 1.4M, and thus the price recommendation to meet the short-term thresholds would also change.

- **Recommendation:** The population eligible (NYHA Class II-IV) for treatment with ENTRESTO should reflect the real-world NYHA HF class distribution, as found in large real-world studies e.g. REACH and IMPROVE-HF; ~28% NYHA Class I (ineligible for Entresto).

ICER Draft Report: ENTRESTO

- Novartis agrees with the assessment of the burden of HF, as it is substantial for patients and the US healthcare system. Furthermore, Novartis agrees with the ICER assessment that ENTRESTO is both clinically and cost-effective and brings a long-term value to patients.
- ENTRESTO was found to be a highly cost effective therapy, with an incremental cost effectiveness ratio of \$50,915. Of note, ENTRESTO did not exceed the cost effectiveness thresholds in any of the scenarios ICER modeled in sensitivity analyses.
- ICER's pricing recommendations in the draft report are not based on ENTRESTO's long-term value and the cost-effectiveness analysis. The draft price benchmark is based on short-term budget impact and costs without accounting for full patient outcomes.
- Clinical data from the largest heart failure trial conducted in patients with reduced ejection fraction to date, PARADIGM-HF, show ENTRESTO was superior to enalapril in reducing the risk of the combined primary endpoint of cardiovascular death or hospitalization for heart failure (Hazard ratio [HR] 0.80, 95% confidence intervals [CI] 0.73-0.87, $P < 0.001$).[3]
- ENTRESTO also had significant reductions in all-cause mortality (HR 0.84, CI: 0.76-0.93, $P < 0.001$) and all-cause hospitalizations compared to enalapril (HR: 0.84; CI: 0.78-0.91; $P < 0.001$), and these clinical outcomes are not taken into account using this short-term budget impact approach to establish pricing recommendations.[3, 4]
- ENTRESTO significantly reduced the risk for sudden death (HR: 0.80, CI: 0.68-0.94, $P = 0.008$) and death due to worsening heart failure (HR: 0.79, CI: 0.64-0.98, $P = 0.034$) compared to enalapril.[5]
- The choice of enalapril, the most studied ACE inhibitor in heart failure patients, at a dose of 10 mg twice daily as active comparator was based upon the pivotal SOLVD-Treatment trial. This trial showed that compared to placebo, enalapril reduced the risk of death or HF hospitalization in a broad spectrum of HF patients, at a mean daily dose achieved of 16.6mg.[6,] This was a dose comparable with that in other major HF trials using enalapril.[7-9] The CONSENSUS trial targeted a dose of enalapril 20 mg twice daily; but only 22% of patients reached this dose, with a mean daily dose of 18.4 mg.[10] Importantly, in PARADIGM-HF, the mean daily dose (\pm SD) of enalapril was 18.9 ± 3.4 mg and the mean daily dose (\pm SD) of ENTRESTO was 375 ± 71 mg.[3]

- The PARADIGM-HF study was designed with 2 active run-in periods to: (i) maximize attainment of the target doses in each study arm during the double-blind treatment period, and (ii) provide investigator-unblinded safety information on the tolerability of ENTRESTO. [3, 8]
- ENTRESTO's effects on the primary composite endpoint (cardiovascular death or hospitalization for HF) were consistent across the wide range of subgroups examined in PARADIGM-HF. Subgroup analyses for the primary endpoint demonstrated a strong consistency across different racial groups. In particular, PARADIGM-HF enrolled 428 (5.1%) black patients[3] which is comparable or higher than other major and recent heart failure studies (CHARM-Added [5%][11], EMPHASIS [2%][12], SHIFT [0%][13]).
- ENTRESTO Voting Questions: Novartis recommends adding “and reduced ejection fraction” to each of the three voting questions where Class II-IV CHF is noted (e.g., “For patients with Class II-IV CHF and reduced ejection fraction, is the evidence adequate to...”)
- ENTRESTO is a novel agent for the treatment of patients with heart failure and reduced ejection fraction. ENTRESTO was designated for fast track review by the FDA. Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. ENTRESTO has substantial mortality, morbidity and quality of life benefits; therefore the focus of ENTRESTO's assessment should be on the positive impact it will bring to patients and their families.

Sincerely,

Christi Shaw

Christi Shaw
Head, US General Medicines
President, Novartis Pharmaceuticals Corporation

Cathryn Clary

Cathryn Clary, MD, MBA
Head, US Clinical Development and Medical Affairs
Novartis Pharmaceuticals Corporation

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