

Sponsor Executive Summary - Addendum

Prepared for the
December 8, 2011 meeting of the
Circulatory System Devices Panel

P100045

CardioMEMS *Champion*[™] HF Monitoring System
CardioMEMS, Inc.

Introduction

CardioMEMS is presenting additional information to the Advisory Panel. This additional information is an ad hoc presentation of existing information reflected within the PMA submission.

Background

FDA has raised a potential issue relating to the involvement by CardioMEMS clinical nurses and the national Principal Investigators (PIs) in providing recommendations to investigational sites regarding the management of pulmonary artery pressures for individual enrolled subjects. They have suggested that this involvement by the sponsor and PIs may have had a bearing on the results of the study and their interpretation. However, the FDA has not provided to date any evidence from the study to support a finding that either inappropriate contact was made with study site personnel or that legitimate contact with study site personnel, as outlined in the protocol, resulted in bias being introduced into the study results obtained.

Both we and the FDA are in agreement that the approved protocol allowed CardioMEMS the capability to review pulmonary artery (PA) pressure readings for the Treatment group and to alert investigators if the pressure readings were elevated. By protocol design the alerts could include both automated and manual email notices. In addition, the approved protocol did not permit CardioMEMS to review pulmonary artery (PA) pressure readings for the Control group or to provide email alerts to investigators if pressure readings were elevated for Control patients. Further, as prespecified by the protocol, both study physicians and CardioMEMS were, in fact, blinded to pressure measurements from the Control group.

As prespecified within the clinical protocol, when the PA pressures were outside of values that were setup in advance for individual patients and modifiable by investigators, each investigator was required to consider medication changes per the hemodynamic monitoring treatment guidelines in the protocol. Follow-up email contact after pressure alerts, with investigators by CardioMEMS clinical staff, enforced compliance with protocol requirements and ensured that investigators considered all treatment options to lower PA pressures, including the treatment guidelines prespecified in the clinical protocol. The FDA is concerned that similar emails were not sent regarding Control group subjects but as is evident from the study design, emails directed towards reducing PA pressure could not have been sent regarding the Control group subjects. These PA pressure reduction recommendations could have been made for Control patients only if the pressures for Control patients were monitored during the trial.

There is also agreement that investigators (or designees) ultimately made all treatment decisions and were responsible for managing enrolled subjects. The role of CardioMEMS clinical nurses and national PI's was to provide training, education, and recommendations in accordance with Appendix E, Management of Hemodynamic Parameters (Attachment A). As is appropriate, final responsibility resided with study physicians to make treatment decisions at all levels, including medication changes.

Supplementary Analysis of Sponsor Support

Standard of Care

The sponsor, steering committee and PIs took a number of steps to ensure that a uniform, high-level standard of care (clinical decision making on the basis of symptoms, weights or physical examination or other commercially available tests) was provided to all patients in the study. This effort began with the inclusion criteria for the Study requiring optimal pharmacologic therapy (OPT) for patients with systolic heart failure in keeping with the ACC / AHA Guidelines. During the Study, it included the following activities:

- Investigator regional meetings (7 meetings),
- Local investigator and PI conference calls and coordinator calls (56 calls)
- Newsletters provided to each site (47 issues)(see sample newsletter in Attachment B)
- Extensive educational materials regarding heart failure and its management were provided through a variety of formats including slide presentations, references and conference calls (a sample presentation is provided in Attachment C)
- A comprehensive training program for all investigators and sites
- Summary of heart failure medications and interactions in every patient binder (Attachment D).

These steps, along with the diligence of the investigational sites, ensured a uniform delivery of standard of care (Table 1) including medication changes, outpt IV diuretics, dietary counseling, sleep apnea treatment and discontinuation of harmful medications.

Table 1: Analysis of Standard of Care

	Treatment (270)	Control (280)
HF Medication Changes		
# Medication Changes	1064	1061
Outpatient IV Diuretics		
# Subjects (%)	23 (8.5%)	26 (9.3%)
<p>Reference: ACC/AHA Guidelines 2005</p> <p>The use of intravenous diuretics for the treatment of chronic HF is fully described. In addition, the guidelines suggest the benefit of outpatient care in preventing HF admissions.</p> <p>pg. e208 – “Many HF admissions may be prevented with good outpatient care.”</p>		
Dietary Counseling		
# Subjects (%)	27 (10.0%)	23 (8.2%)
<p>Reference: ACC/AHA Guidelines 2005</p> <p>Dietary counseling is recommended to prevent clinical deterioration of patients with HF.</p> <p>pg. e175 – “Of the general measures that should be used in patients with HF, possibly the most effective yet least utilized is close attention and follow-up. Nonadherence with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family, can reduce the likelihood of nonadherence and lead to the detection of changes in body weight or clinical status early enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration.”</p>		
Sleep Apnea Treatment		
# Subjects (%)	35 (13.0%)	44 (15.7%)
<p>Reference: ACC/AHA Guidelines 2005</p> <p>Screening for sleep apnea is a Class IIa recommendation.</p> <p>pg. e162 – “Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (Level of Evidence: C)”</p>		
Pulmonary Vasodilators e.g. Sildenafil		
# Subjects (%)	6 (2.2%)	6 (2.1%)

<p>Reference: ACC/AHA Guidelines 2005</p> <p>Evidence supporting the use of sildenafil for the treatment of HF patients is described.</p> <p>pg. e200 – "Recent studies suggest that sildenafil may produce hemodynamic benefits in patients with coronary artery disease and may act to improve some of the peripheral vascular abnormalities that characterize patients with HF."</p>		
Discontinuation of Contraindicated Medications (NSAIDs & TZDs)		
# Subjects (%)	8 (3.0%)	6 (2.1%)
<p>Reference: ACC/AHA Guidelines 2005</p> <p>Discontinuation of contraindicated medications is a Class I recommendation.</p> <p>pg. e173 – "Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs. (Level of Evidence: B))"</p> <p>Evidence suggesting the negative of effects of thiazolidinediones in NYHA Class III patients is described.</p> <p>pg. e202 – "Thiazolidinediones have been associated with increased peripheral edema and symptomatic HF in patients with underlying risk factors or known cardiovascular disease. The risk of developing edema with thiazolidinediones is dose related and is higher in diabetic patients who are taking concomitant insulin therapy... Initiation of these drugs is not recommended in patients with NYHA functional class III to IV symptoms of HF."</p>		

The high level of standard of care resulted in excellent overall outcomes for all patients in the CHAMPION Study, including for the Control group. The Control group experienced a very low 6-month HF hospitalization rate of 0.44; in relating the CHAMPION results to a similar study, the NYHA Class III group in the COMPASS trial experienced HF hospitalization rates of 0.70 in the Control arm and 0.45 in the Treatment arm. In this comparison, the CHAMPION Control group results were superior to those achieved in the COMPASS Treatment group, attesting to the efforts taken in the study to deliver a consistent high-level of care to all study subjects.

Pulmonary Artery Pressure Based Heart Failure Management

The CHAMPION Trial, as approved by the FDA, was designed by the steering committee, principal investigators, and sponsor to rigorously test the hypothesis "that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations." (Appendix E, p 1). The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical

decision making in addition to symptoms, weights or physical examination (traditional markers of volume). The protocol also explicitly states:

“The CHAMPION trial will differ from previous hemodynamic monitoring studies in that *specific recommendations* will be made to utilize pressures in heart failure management including use of diuretics and vasodilators.” (Appendix E, p 1, italics added).

These plans were based on the realization from previous studies of hemodynamic monitoring that information of the type provided by the CardioMEMS sensor has clinical value only if acted upon.

As indicated above, the protocol clearly states that specific recommendations will be made regarding pressure management. These treatment recommendations are now of concern to the FDA because they were not made for Control patients but since they were in response to elevated pulmonary pressures for specific Treatment patients, the same recommendations could not have been made for Control patients. These treatment recommendations could have been made to Control patients only if the pressures for Control patients were monitored during the trial.

Appendix E was carefully developed by the PIs and steering committee with extensive input from the FDA to provide explicit guidelines for treatment on the basis of pulmonary artery pressure. In accordance with the clinical protocol and to assure compliance with the protocol treatment guidelines, CardioMEMS nurses would send email alerts inquiring about patients with elevated pressures and the steps the site was taking to manage the pressures. These emails were triggered by persistently elevated pressures, not clinical information, and directed solely towards reducing pulmonary artery pressures; clinical status information was not available to the CardioMEMS nurses and thus there was no knowledge of clinical decompensation, impending hospitalizations or the ability to prevent them.

In some cases, specific recommendations were provided for consideration as outlined in Appendix E. These recommendations always adhered to the contents of Appendix E and the ACC / AHA Guidelines for the Management of Chronic Heart Failure referenced in Appendix E:

“In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.” (Appendix E, p 2)

Typically, they emails were designed to remind sites to follow the guidelines in Appendix E and to follow the escalation process outlined in the guidelines. For example, there were reminders to progress to nitrates as indicated on p. 1 of Appendix E:

“If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed.”

Or to consider outpatient IV diuretics as indicated in the escalation algorithm for refractory elevated pressures described below:

“Add or increase diuretic (and appropriate electrolyte replacement)

- a. Increase or add loop diuretic
- b. Change to another loop diuretic
- c. Add thiazide diuretic (with caution)
- d. *IV doses of loop diuretic*
- e. Serum electrolyte evaluation with change in baseline medication
- f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic” (Appendix E, p. 3, italics added)

In patient’s refractory to treatment, investigators were reminded to investigate other causes such as sleep apnea or secondary pulmonary hypertension, as described in the protocol: “If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated.”(Appendix E, p. 1) (ACC / AHA Guidelines for Management of Chronic Heart Failure, 2005, pg. e162, e200). These recommendations were consistent with good clinical practice and ACC / AHA guidelines.

Throughout, investigators were reminded to follow good medical practice and to consider a patient’s previous responses when making medication changes “Diuretics and vasodilators should be adjusted based on the subject’s baseline diuretic requirement, knowledge of the *subject’s prior response* to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline” (Appendix E, p. 1, italics added).

Lastly, in each category of patient management, opti-volemic, hyper-volemic, or hypo-volemic, the investigator was always reminded to consider hospital admission:

- “a. Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the use of IV therapeutic agents
- b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated” (Appendix E, p. 3)

Thus, Appendix E was developed to definitively test the hypothesis of PA pressure based HF management while assuring patient safety. The follow-up to sites from the CardioMEMS nurses was designed to assure that Appendix E was followed.

Supplemental Analyses

As part of the routine conduct of a clinical trial, a large amount of correspondence between sites and sponsor is generated and not provided as part of the PMA submission (CRFs, SAEs, patient visit reminders, etc). The FDA developed a recent interest in the follow-up email alert correspondence to the sites and all of these emails have been provided to the FDA. Please find attached the email examples

provided by the FDA in its Addendum and conformation that all of the recommendations in these emails are based upon Appendix E and the ACC / AHA Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult. (Attachment E)

In order to consider the effect of any email alerts on medication changes and study outcomes, *ad hoc* supplemental analyses were performed. The first analysis evaluated how physicians managed medication changes when email alerts were provided from CardioMEMS. These alerts took the form of either *inquiries* (requests for updates on patients) to the sites or as *recommendations* to follow the treatment escalation outlined in Appendix E of the protocol. Given the number of patients and the study duration, the number of alerts was quite small. There were 391 follow up alerts in the first 6 months or 0.25 emails / patient month. In addition, there were 360 follow-up alerts in the period after 6 months to unblinding at the study conclusion, or 0.14 emails / patient month. After unblinding, patients were followed for safety and no follow up email alerts directed towards protocol treatment strategies compliance were sent.

During the first 6 months, physicians acted on the email alert *inquiries* from CardioMEMS by changing medications 4.4% of the time. Also, physicians considered and followed the *recommendations* offered within email alerts 5.5% of the time. After 6 months and up to unblinding, physicians acted on the email alert *inquiries* from CardioMEMS 3.2% of the time and followed the *recommendations* offered within email alerts 3.5% of the time. Thus, physicians exercised clinical judgment that may have considered, but differed from email recommendations on > 90% of all occasions before and after 6 months. While the alerts served as reminders to modify PA pressures, other important factors such as signs and symptoms were considered by physicians as part of the treatment strategy. The data indicate that physicians were effectively independent in their use of the protocol recommended treatment guidelines and needed little support beyond their own review and assessment of PA pressures provided to them. The only effect from the email alerts was to serve as supportive reminders about pressure monitoring data and protocol guidelines, rather than directing physician treatment decisions.

Table 2: PA Pressure Medication Changes Secondary to Emails

	First 6 Months	After 6 Months to Unblinding	After Unblinding
	N= 270 Treatment Patients 6 Months	N= 244 Treatment Patients 9 Months	N=383 All Patients 17 Months
CardioMEMS Follow-up Emails	391	360	0
Inquiry Emails	198	229	na
Recommendation Emails	193	131	na
Emails / patient month	0.25	0.14	na

PA pressure med changes/ patient month	0.88	0.28	0.23
PA Pressure Med Changes/patient month associated with CM <i>Inquiry</i> Email	0.04 (4.4%)	0.01 (3.2%)	na
PA Pressure Med Changes/patient month associated with CM <i>Recommendation</i> Email	0.04 (5.5%)	0.02 (3.5%)	na
PA Pressure Med Changes/patient month made independently by Investigator	0.81 (90.0%)	0.25 (93.4%)	0.23 (100.0%)

The second analysis evaluated the impact from email *inquiry* and *recommendation* alerts upon patient outcomes, regardless of whether it was acted upon by the site. At 6 months, Treatment patients discussed in emails with the sites did slightly worse and after 6 months they did slightly better, suggesting no clear impact on outcomes of emails sent to the sites. Interestingly, after unblinding the entire study cohort did very well, approaching the Treatment group results pre-unblinding due to a dramatic reduction in the Control group hospitalization rates. Since no *inquiry* or *recommendation* email alerts were being sent during this time period, the sites clearly were able to provide ongoing hemodynamic management without additional reminders and were able to maintain good clinical results for patients.

Table 3: Impact of Emails on Outcomes

	Up to 6 Months [6 Month HF Rate]		After 6 Months to Unblinding [Annualized HF Rate]		After Unblinding [Annualized HF Rate]	
	Emails	No Emails	Emails	No Emails	No Emails	
Treatment Pts. (HF Hosp. Rate)	151 (0.36)	119 (0.26)	133 (0.32)	111 (0.40)	383 (0.47)	
All Pts. (HF Hosp. Rate)	Study Duration Patients [Annualized HF Rate]				Former Treatment 186 (0.46)	Former Control 197 (0.49)
	Treatment 270 (0.46)	Control 280 (0.73)				

Post Market Support

CardioMEMS will carry forward the successful elements from the CHAMPION Study to the commercial setting. All of the training materials and programs conducted during the Study will be continued. The automated and manual pressure alerts, including follow-up email alerts will be continued. In addition, as presented in the training materials submitted with the PMA, additional programs such as educational symposia on hemodynamic monitoring, web based case libraries, interactive presentations, and web based and telephone support lines will be provided. The approach of managing pressures in heart failure patients outlined in the appendix was adequately tested in this trial and can be considered a safe means to guide users in a post-market environment.

Summary

CardioMEMS and the steering committee and PIs took a number of steps to assure excellence of standard of care (SOC) heart failure management for all patients, regardless of randomization group. The numbers of SOC or non-pressure interventions including medication changes were similar between the Treatment and Control groups. The Control group outcomes matched the best of other studies, confirming rigorous heart failure management. The above findings do not support the contention of bias in the standard of care provided to the Treatment or Control groups.

The protocol, specifically Appendix E, was developed by the steering committee, PIs, and sponsor in cooperation with the FDA to definitively test the hypothesis of PA pressure based HF management while assuring patient safety. The follow-up emails to sites from the CardioMEMS nurses were designed to assure that Appendix E was followed and were completely consistent with the specific recommendations stated in Appendix E as well as ACC / AHA guidelines on heart failure management. CardioMEMS sought to achieve a high-level of compliance with its study protocol. Lack of compliance would have diminished the scientific validity of the study and ability to clearly demonstrate the benefit observed. The sponsor's ongoing involvement in supporting study physicians did not go beyond the protocol and those guidelines.

Email alerts had no discernible impact on the outcomes in the Treatment group. The investigators acted independently of the email recommendations offered for their consideration and continued to get excellent outcomes, including a dramatic improvement in the previous Control patients, when the inquiry and recommendation emails stopped completely.

APPENDIX E: MANAGEMENT OF HEMODYNAMIC PARAMETERS

The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations. The unique nature of the implanted device allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures. The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

Guidelines for managing heart failure using pulmonary artery pressures

The CHAMPION trial will differ from previous hemodynamic monitoring studies in that specific recommendations will be made to utilize pressures in heart failure management including use of diuretics and vasodilators.

Pulmonary Artery Pressure Goals:

PA Systolic	15 - 35 mmHg
PA Diastolic	8 - 20 mmHg
Mean PA pressure	10 - 25 mmHg

An elevation of pressures beyond these reference ranges should be considered a volume overloaded status. Diuretic therapy should be adjusted to reduce these pressures to within pressure goals unless the following occurs:

1. Serum creatinine increases by 20%
2. If systemic systolic blood pressure drops by 20 mmHg when changing from supine to a standing position
3. Symptomatic systemic hypotension

The above listed clinical events should be confirmed by three (3) evaluations in order to prevent withholding the appropriate treatment regimen.

If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed. If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated. If the pressures remain high after the above steps are taken, then the reference ranges may be reset for the individual patient and the new values should be considered “optivolemic”. Medication adjustments and patients’ responses must be documented prior to changing the goal ranges.

Diuretics and vasodilators should be adjusted based on the subject’s baseline diuretic requirement, knowledge of the subject’s prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline. Consultation with the national PI’s is encouraged to optimize the success of medical management of PA pressures.

A decrease in the pulmonary pressures below the established ranges should be considered a volume depletion event and diuretic therapy should be held and chronic dose should be lowered.

In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.

Opti-volemic

Opti-volemic Definitions

- Subject symptoms: minimal symptoms and minimal evidence of poor perfusion
- Invasive Hemodynamic Monitoring:
- Pulmonary artery systolic pressure 15 – 35 mmHg
- Pulmonary artery diastolic pressure 8 – 20 mmHg
- Pulmonary artery mean pressure 10 – 25 mmHg
- HF Pressure Measurement System Parameters:

The initial parameters will be set to the above values. After all guidelines for managing HF using pulmonary artery pressures as described on the previous page have been implemented and documented, the Investigator may reset the values to an acceptable range for individual subjects and establish the range in mmHg in the secure website.

Opti-volemic Treatment Recommendations

- No medication changes based on hemodynamic data obtained from the HF Pressure Measurement System
- Baseline chronic aggressive therapy (reduced LVEF)
 - a. ACE inhibitor (ARB or other vasodilator if ACE not tolerated) to target dose
 - b. Digoxin, diuretic and electrolyte replacement advised
 - c. Consider spironolactone as indicated in subjects with stable renal function and potassium handling
 - d. Nitrates to appropriate doses as tolerated
 - e. Beta-blocker administration and/or uptitration according to guidelines when subject is not hypervolemic.

If the subject has signs of poor perfusion (cold), consider other interventions, such as:

- a. Admission for monitoring and further adjustment of medical management
- b. Intravenous (IV) pharmacotherapy
- c. Increase vascular volume if still without evidence of congestion at rest
- d. Consider invasive hemodynamic monitoring for determination of Cardiac Output if indicated

Hyper-volemic

Hyper-volemic Definitions

- Subject symptoms: Congestive symptoms (wet)
- HF Pressure Measurement System Parameters: above the pre-determined opti-volemic range
- Daily trends: elevated trend data outside the pre-determined opti-volemic range
- Weekly trends: elevation in trend data

Hyper-volemic Treatment Recommendations

- Add or increase diuretic (and appropriate electrolyte replacement)
 - a. Increase or add loop diuretic
 - b. Change to another loop diuretic
 - c. Add thiazide diuretic (with caution)
 - d. IV doses of loop diuretic
 - e. Serum electrolyte evaluation with change in baseline medication
 - f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic
- Add or increase nitrates
- Start or re-educate in salt intake and fluid restriction
- If subject has signs and symptoms of poor perfusion (cold) in addition to being hyper-volemic:
 - a. Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
 - b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Hypo-volemic

Hypo-volemic Definitions

- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- HF Pressure Measurement System Parameters: below the pre-determined opti-volemic range
- Daily trends: decrease in trend data outside the pre-determined opti-volemic range
- Weekly trends: decrease in trend data

Hypo-volemic Treatment Recommendations

- Lower or discontinue diuretic
 - a. If on a thiazide diuretic with loop diuretic, lower or discontinue the dose of thiazide (and adjust electrolyte replacement)
 - b. If on only loop diuretic, lower the dose or discontinue
 - c. Consider liberalization of oral fluid restriction and salt restriction
- If postural hypotension, hold or lower vasodilators and/or oral nitrates, especially if hypotensive when sitting or supine
- If worsening renal function, hold or lower ACE/ARB dose, especially if hypotensive
- If subject had signs and symptoms of poor perfusion (cold) in addition to being hypo-volemic:
 - a. Consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring or the use of IV therapeutic agents
 - b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Recommended Frequency of HF Pressure Measurement System Review

Subject Status	Weekly	At least 2– 3 times per week until optivolemic	At least 2 – 3 times per week until pressure stabilizes
Opti-volemic	X		
Hyper-volemic		X	
Hypo-volemic		X	
Medication modifications			X
Significant deviations in trend data			X

CHAMPION Newsletter


(866) 376-5611

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[Message From Your National PIs](#)

[From Your Clinical Project Manager](#)

[Depression and HF](#)

[Important Points to Remember](#)

[CHAMPION Case Study](#)

[Study Coordinator Conference Call](#)

[Important Patient Screening Reminders](#)

[Patient Enrollment by Site](#)

CHAMPION
Team
Contact
Information

Bradley Jeffries,
M.D., M.S.
VP, Clinical
Operations
(678) 651-2339
(404) 432-6882 Cell
(877) 293-3816 Fax

Susan Neville, R.N.
Clinical Project
Manager
(678) 651-2326
(404) 393-0737 Fax

Pam Cowart, R.N.
Clinical Nurse
Specialist
(678) 651-2384

MESSAGE FROM YOUR NATIONAL PIs – Sleep Apnea in Patients with Heart Failure

Sleep disordered breathing (SDB) is a highly prevalent disease that is estimated to affect approximately one in five American adults or 43 million people. Eighty-five percent of patients with SDB may not be diagnosed. Sleep apnea, a subset of SDB, affects approximately 19 million American adults, and is associated with numerous co-morbidities including cardiovascular disease, hypertension, stroke, type II diabetes, and obesity.

A large percentage of patients with cardiovascular disease have sleep apnea, with an estimated prevalence of approximately 50% in patients with hypertension, 40% in patients with systolic heart failure (HF), and over 50% in patients with diastolic HF. There is evidence to support prevalence rates as high as 75% in subsets of HF patients with increased disease severity.

A recent expert consensus document, “Sleep Apnea and Cardiovascular Disease”, published July 28, 2008 in JACC summarizes the evidence that treating HF with continuous positive airway pressure (CPAP) can improve HF symptoms and surrogate cardiovascular endpoints such as left ventricular ejection fraction. An increased interaction between cardiovascular specialists and sleep medicine physicians can potentially improve patient care and provide an individualized approach to the management of patients with co-morbid HF and sleep apnea.

Phillips-Respironics is willing to spend time with your staff educating them on sleep apnea. We encourage you to consider this opportunity to raise the importance of sleep apnea to all of your patients. A representative from Phillips-Respironics will be contacting you shortly to discuss your willingness to have them present an awareness program at your site.

William Abraham, MD
Philip Adamson, MD

FROM YOUR CLINICAL PROJECT MANAGER

Thank you for your continued interest and enthusiasm in the CHAMPION trial.

Congratulations on the recent first enrollments by:

- Dr. Marc Silver and his coordinator Laretta Ichniowski (Advocate Christ, Chicago, IL) – October 23rd, 2008

DEPRESSION AND HEART FAILURE

Depression rates can be much higher among patients with more advanced HF. 21.5 % of HF patients have depression with 11% in NYHA FC I vs. 42% in NYHA FC IV.¹ When compared with non-depressed patients, the odds are 3 times greater that depressed patients will be non-compliant with medical treatment recommendations.²

When screening potential subjects, please consider the patient's history of both depression and compliance. Experience suggests that enrolling a non-compliant patient in a clinical trial does not necessarily improve their compliance especially if depression is present.

Gofredo, M.D.
 Clinical Project
 Manager
 (678) 651-2445

Amina Mirza
 Senior Clinical
 Research Associate
 (678) 651-2329

Bill Thornton
 Senior Clinical
 Research Associate
 (678) 651-2446

Renee Gaitor
 Clinical Research
 Associate
 (678) 651-2328

Ashley Vaughn
 Clinical Research
 Associate
 (678) 651-2325

John Henderson
 Clinical Database
 Monitor
 (678) 651-2365

Maha Khalaji
 Clinical Database
 Monitor
 (678) 651-2342

Jordan Bauman
 Clinical Database
 Monitor
 (678) 651-2364

Angela Graham
 Clinical Operations
 Coordinator
 (678) 651-2327

Angie Crockett
 Clinical Research
 Assistant
 (678) 651-2443

Chris Bess
 Drug Safety Nurse
 (678) 651-2338

Jill Calkins
 HF Nurse
 (678) 651-2345

Andrena Lawrence
 Clinical Data
 Manager
 (678) 651-2391

1. (Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects and associations with clinical outcomes. J Am Coll Cardiol, 2006 Oct 17;48(8): 1527-37.)
2. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000 Jul 24; 160(14):2101-7.

IMPORTANT POINTS TO REMEMBER

- Please inform CardioMEMS within 24 hours of learning about any serious adverse events (fax in the SAE form to 1-877-293-3816).
- If a treatment or control patient is hospitalized and needs hemodynamic assessment the CM sensor reading **MAY NOT** be used to manage the patient acutely. A RHC or Swan must be used. Please inform CardioMEMS if a RHC or Swan procedure is scheduled so that comparative measurements may be obtained.
- In the event of a death, please make every effort to obtain a device interrogation (if applicable) and request an autopsy.
- Please enter data into eCaseLink within 5 days of the visit.
- Once version 1.7 of the protocol is approved at your site, please work with your billing department to submit all applicable CHAMPION patient bills.

CHAMPION CASE STUDY

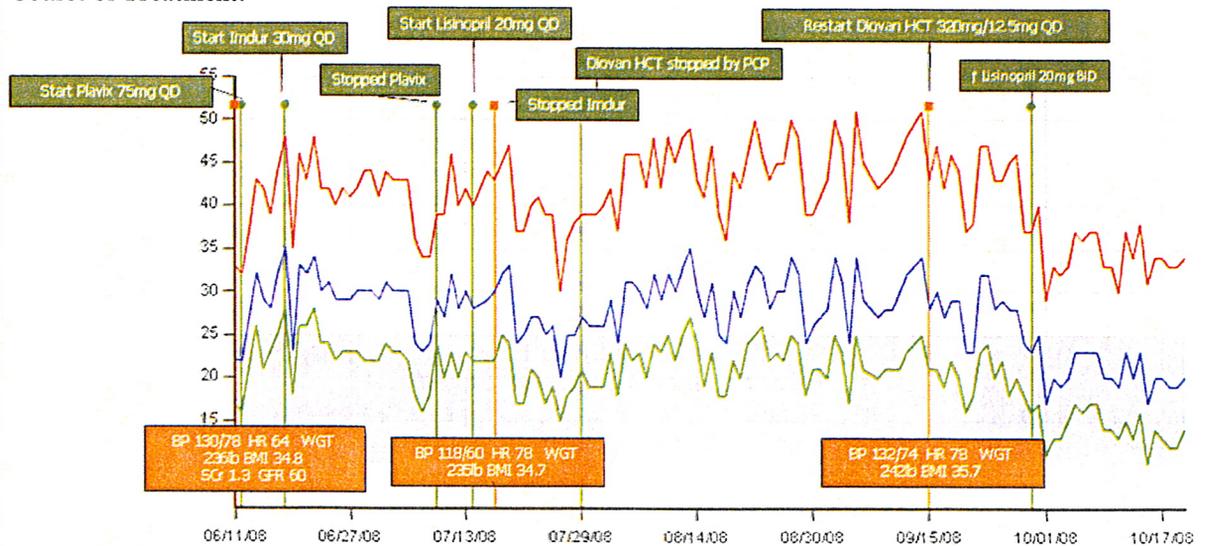
Site: Kennestone Hospital, Rajnish Prasad, MD

Patient Vitals: 58 yo white male, CM implant 6/11/2008
 Swan hemodynamics at implant: PA 38/9(20), PCWP 13, CO 7.9, PVR 0.89

PMHx: diastolic heart failure- LVH with EF 60%, diabetes- insulin dependent, obesity, CAD, hyperlipidemia, HTN, pulmonary edema

Initial Meds: Diovan HCT 320mg/25mg QD, Omega-3 QD, Labetolol 400mg QD, Insulin as directed, Vytarin 10mg QD, Glucosamine QD, Aspirin 81mg QD, multivitamin QD, Plavix 75mg QD

Course of Treatment:



STUDY COORDINATOR CONFERENCE CALL

Thank you for your participation in the weekly study coordinator conference calls. The next call is Monday, October 27th, at 3pm EDT.

Dial-in number: (877) 746-4263

Participant Code: 0257808#

Monday, 3:00pm EST

We have now added a WebEx feature to allow you to follow along with the slides online while you are on the conference call. To view the WebEx, follow the instructions below:

1. Just before the start of the call, go to the link provided in your e-mail invitation.
2. If prompted, enter the meeting password: atlbaby1.
3. Click "Join Now".
4. Follow the instructions that appear on your screen to join the teleconference.

IMPORTANT PATIENT SCREENING REMINDERS

During the screening process please remember:

- Patients must be Class III without inotropic support.
- Class IV patients are excluded.
- NYHA classification is intended to be a historical assessment documented at the screening visit.
- The stable medication criteria apply only to beta-blockers, ACE-I or ARB; the "stable" criteria do not apply to diuretics and other medications associated with HF.
- These medications apply only to those patients with reduced LVEF.
- Patients are frequently intolerant to these medications or they may not be indicated (i.e., ACE cough, COPD).
- Please do not load patients with Plavix prior to the implant procedure. The post-procedure protocol requirement of Plavix for 30 days and ASA for life is sufficient
- Patients with diastolic heart failure are not excluded from participation in the study.
- It is important to remember that subjects in the TREATMENT arm of the clinical trial should be receiving standard of care HF management plus HF management based upon hemodynamic information obtained from the HF Pressure Measurement System. This additional information should be used to treat patients above the usual standard of care.
- It is important to think creatively and utilize all the resources at your institution in order to offer treatments such as IV diuretics in an outpatient setting as an alternative to hospital admission strictly for IV diuretic therapy. If administering IV diuretics in an outpatient setting is not feasible at your institution, consider providing this therapy in settings such as the Emergency Department, physician office or research clinic. It is also important to remember that many Home Health Care providers are trained and permitted to administer IV diuretics.



PLEASE call your CRA, Susan Neville, or Dr. Brad Jeffries if you have any questions regarding inclusion/exclusion criteria!



CHAMPION Clinical Research Coordinators Weekly Conference Call

January 12, 2009



Low Sodium Diet

Eating less sodium and restricting fluid intake is an important part of heart failure treatment. Cutting back on sodium makes less work for the heart. Sodium is a mineral found in table salt and many prepared foods. It may not be easy to eat less sodium, but it is well worth the effort.

♥ How much sodium should you eat?

Shake the salt habit! Most people with heart failure are advised to limit sodium to about **2,000 milligrams (mg) per day**. That is about equal to the sodium in 1 teaspoon of table salt. This will help to balance the water content in the body and decrease the chance of retaining fluid.

♥ How does sodium affect heart failure?

When the heart cannot pump blood normally, less blood reaches the body's major organs. The kidneys respond by retaining sodium and water. The extra fluid collects in the lungs and other parts of the body. Eating foods that are high in sodium makes the body retain even more fluid, which also raises blood pressure. This means the heart has to work much harder.

♥ What are the hidden sources of sodium?

Canned soups, deli meats, bacon, ham, potato chips and fast foods are especially high in sodium. It may surprise you to learn that sodium is also "hidden" in club soda, tomato juice, baking soda, store-bought breads, cakes, cereals and dairy products. Even bottled waters can contain large amounts of sodium.

Tips on Limiting Sodium



Hide the salt shaker

Removing the salt shaker from your table is a good start. Season foods with herbs and spices instead. Lemon juice, vinegar, fresh garlic, basil, oregano, curry and ginger are a few seasonings that can be used. Do Not Add Salt during cooking. Also, avoid using garlic salt, onion salt, baking soda, soy sauce, and teriyaki sauce



Read food labels carefully

Look at the Nutrition Facts Panel on a food label to figure out how much sodium is contained in a single serving of food. Look at the serving size and the amount of milligrams of sodium. Decide if this is a high or low sodium food. Keep track of the milligrams you take in throughout the day.

HIGH sodium = more than 400 mg sodium per serving **LOW** sodium = less than 140 mg sodium per serving
VERY LOW sodium = less than 35mg sodium per serving



Choose fresh instead of prepared foods

Switching to fresh or frozen vegetables, fruits, fish, meat and poultry can greatly reduce the amount of sodium in your diet. When you must buy prepared or packaged foods look for foods labeled “low-sodium” or “sodium-free”.



Give your taste buds time to adjust

Low-sodium foods may taste bland at first especially if you are used to eating salty foods. In just a few weeks your taste buds will adjust. Soon your craving for salty foods will decline and you will enjoy the natural flavor of foods.

Reading Food Labels

Learn how to read labels to make good low sodium choices. Ingredients are listed by weight, in order from highest to lowest. Food additives high in sodium include salt, baking powder, brine, or any additive that says the word "sodium". Look for the words "monosodium glutamate" or "di-sodium phosphate" on the label.

Follow these steps when reading the nutrition information on the Food label:

1. Check the serving size.
Nutrient values are expressed per serving. Compare your serving size to the serving size listed.
2. Check the milligrams of sodium per serving
3. Check the ingredient list.

Look for the following sodium-containing ingredients: salt, sodium brine, baking soda, baking powder, soy sauce.

Nutrition Facts				
Serving Size 1/2 cup (114g)				
Servings Per Container 4				
Amount Per Serving				
Calories 90	Calories From Fat 30			
		% Daily Value*		
Total Fat 3g		5%		
Saturated Fat 0g		0%		
Trans Fat 0g				
Cholesterol 0mg		0%		
Sodium 300mg		10%		
Total Carbohydrate 13g		4%		
Dietary Fiber 3g		12%		
Sugars 0g				
Protein 3g				
Vitamin A 18%	●	Vitamin C 2%		
Calcium 4%	●	Iron 4%		
* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.				
	Calories	2,000	2,500	
Total Fat	Less than	65g	80g	
Sat Fat	Less than	20g	25g	
Cholesterol	Less than	300mg	300mg	
Sodium	Less than	2,400mg	2,400mg	
Total Carbohydrate		300g	375g	
Fiber		25g	30g	
Calories per gram:				
Fat 9	●	Carbohydrate 4	●	Protein 4



Fluid Restriction

How much fluid can you drink? 2 Liters a Day

Any food or beverage that is liquid at room temperature is treated as a fluid in the diet. This includes:

- Water (including that taken with pills)
- Soda pop
- Coffee
- Tea
- Juice
- Ice cubes (size may vary; let 3 ice cubes melt in an 8-ounce measuring cup to determine the fluid content)
- Popsicle (1 double=1/3 cup fluid=3 ounces)
- Alcohol
- Soups
- Milk
- Mineral Water
- Gelatin
- Ice Cream or Sherbet
- Kool-Aid

2 quarts or liters	= 8 cups	= 64 ounces	= 2000 cc
1 quart or liter	= 4 cups	= 32 ounces	= 960 cc
1 pint	= 2 cups	= 16 ounces	= 480 cc
	1 cup	= 8 ounces	= 240 cc
	½ cup	= 4 ounces	= 120 cc
	1/3 cup	= 3 ounces	= 90 cc
	¼ cup	= 2 ounces	= 60 cc
2 Tbs	= 1/8 cup	= 1 ounces	= 30 cc
1 Tbs		= 1/2 ounces	= 15 cc

Tips for Fluid Control

1. Drink to quench thirst only. If you avoid high sodium foods, you will have less thirst.
2. Try having allowed fruits and vegetables ice cold between meals. Frozen grapes and strawberries are examples.
3. Use sour candies and chewing gum to moisten mouth.
4. Take the pills you can with your meal time liquids
5. Keep a bottle of mouthwash in the refrigerator. Rinse your mouth out with it when you are thirsty. Do not swallow it.
6. Drink from small cups and glasses. Four ounces of juice will look like more in a six ounce glass than it does in a twelve ounce glass.
7. Freeze some of your fruit juice or lemonade in an ice cube tray and use it as part of your fluid. It will be softer and easier to chew than regular ice cubes.
8. Do not drink from habit or to be social
9. Check the package of ice cream bars and popsicles to see how many ounces they contain. Do the same for soft drinks, beer etc.
10. Keep lips moist with lip balm or lipstick.

Salt Substitutes

Consult your physician before using any of the following substitutes.

- No Salt -- 1/4 tsp.: 650 mg Potassium/0 mg Sodium
- Morton's Lite Salt -- 1/4 tsp.: 350 mg Potassium/290 mg Sodium
- Morton's Salt Substitute -- 1/4 tsp.: 610 mg Potassium/0 mg Sodium
- Cardia Salt Alternative -- 1/4 tsp.: 180 mg Potassium/270 mg Sodium
- AlsoSalt-- 1/4 tsp.: 356 mg. Potassium/0mg Sodium
- NuSalt -- 1/6 tsp.: 530mg Potassium/0mg Sodium
- Mr. Dash-- ¼ tsp.: 0mg Potassium/0mg Sodium



	Study CM-06-04 CHAMPION	Subject Initials: <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Subject ID: <input type="checkbox"/> <input type="checkbox"/> - <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Site Subject
HF REFERENCE MATERIAL - WORKSHEETS			

Medications Used in Heart Failure Management

Beta Blockers

Coreg (Carvedilol)
 Inderal (Propranolol)
 Lopressor (Metoprolol)
 Toprol XL (Metoprolol)
 Tenormin (Atenolol)
 Betapace (Sotalol)
 Cartrol (Carteolol)
 Corgard (Nadolol)
 Blocadren (Timolol)
 Levatol (Penbutolol)
 Kerlone (Betaxolol)
 Sectral (Acebutolol)
 Visken (Pindolol)
 Zebeta (Bisoprolol)
 Ziac (Bisoprolol HCTZ)
 Monocal
 Nadolol

Possible Contraindications:

COPD
 Peripheral Vascular Disease
 Heart Block/ Bradycardia/ sick Sinus Syndrome
 Severe Diabetes Mellitus

Angiotensin Converting Enzyme (ACE) Inhibitors **(And Angiotensin II Receptor Blockers-ARB)**

Accupril (Quinapril)
 Altace (Ramipril)
 Capoten (Captopril)
 Lotensin (Benazapril)
 Monopril (Fosinopril)
 Prinivil (Lisinopril)
 Vasotec (Enalapril)
 Zestril (Lisinopril)
 Zestoretic (Lisinopril HCTZ)
 Cozaar (Losartan)
 Diovan (Valsartan)
 Hyzaar (Losartan HCTZ)
 Avapro (Irbesartan)
 Atacand (Candesartan)

Possible Contraindications:

Hypersensitivity/ACE Cough
 Renal Impairment
 LV outflow tract (Aortic Stenosis)
 Pregnancy

Aldosterone Antagonist

Aldactone (Spirolactone)

Version 1.7/ 30JUN08

Aldactizide (Spirolactone HCTZ)

Possible Contraindications:

Hyperkalemia
 Severe Renal Impairment
 Pregnancy/Breast Feeding
 Addison's disease

Loop Diuretics

Lasix (Furosemide)
 Bumex (Bumetanide)
 Demedex (Torsemide)
 Torem (Torsemide)

Possible Contraindications:

Hyponatremia
 Hypokalemia
 Hypotension

Thiazide Diuretics

Diuril (Chlorothiazide)
 Microzide (Hydrochlorothiazide)
 Naqua (Trichlormethiazide)
 Lozol (Indapamide)
 Zaroxolyn (Metolazone)
 Naturetin (Bendroflumethiazide)
 Diucardin (Hydroflumethiazide)
 Aquatensen (methyclothiazide)
 Renese (polythiazide)
 Hydromel (Quinethazone)

Possible Contraindications:

Diabetes
 Lupus
 Renal Disease
 Liver Disease
 High triglyceride levels or cholesterol
 Pancreatitis

Nitrates

Isordil

Nitrong SR
 Nitrodur
 Nitropaste/Transderm Nitro/Minitran (topical applications)

Possible Contraindications:

Headache
 Extreme lightheadedness

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Page | 69



Study CM-06-04
CHAMPION

Subject Initials:

Subject ID:

Site Subject

HF REFERENCE MATERIAL – WORKSHEET

Drugs That May Exacerbate Heart Failure

Drugs	Mechanism	Onset	Recommendation
α - blockers for HTN Doxazosin (Cardura®) Prazosin (Minipress®)	<ul style="list-style-type: none"> ↑ risk of HF 	Months	<ul style="list-style-type: none"> Other antihypertensives preferred in HF May be acceptable if used to treat BPH
Amphetamines Dextroamphetamine (Dexodrine®) Dexmethylphenidate (Focalin®) Methylphenidate (Ritalin®)	<ul style="list-style-type: none"> Activation of sympathetic nervous system Proarrhythmic 	Unknown	<ul style="list-style-type: none"> Avoid use in HF
Endothelin Receptor Antagonist Bosentan (Tracleer®)	<ul style="list-style-type: none"> Fluid retention, risk of HF exacerbation 	Days to weeks	<ul style="list-style-type: none"> Monitor patients closely
Ca Channel Blockers Diltiazem (Cardizem®, Cartia®) Verapamil (Calan®, Isoptin®)	<ul style="list-style-type: none"> Negative inotropic activity Possible activation of RAAS 	Days to months	<ul style="list-style-type: none"> Amlodipine, felodipine preferred CCBs in HF Beta Blockers or Digoxin preferred for rate control in HF patients with atrial fibrillation
Ca Channel Blockers Amlodipine (Norvasc®) Felodipine (Plendil®) Nifedipine (Procardia®)	Dose-dependant peripheral edema	Days to weeks	<ul style="list-style-type: none"> Amlodipine, felodipine preferred CCBs in HF Use only if CCB needed to treat HTN in HF patients Reduce dose or change to alternative therapy if edema not responsive to HF therapy
Anti-Convulsant Carbamazepine (Tegretol®)	<ul style="list-style-type: none"> Negative inotrope and chronotrope 	Unknown	<ul style="list-style-type: none"> Avoid use in HF if possible
Phosphodiesterase inhibitor Cilostazol (Pletal®)	<ul style="list-style-type: none"> May increase mortality in patient with HF Peripheral edema 	Unknown	<ul style="list-style-type: none"> Contraindicated in patients with CHF of any severity
Corticosteroids Prednisone Prednisolone Dexamethasone (Decadron®) Methylprednisolone (Medrol®)	<ul style="list-style-type: none"> Sodium and fluid retention 	Days to weeks	<ul style="list-style-type: none"> Monitor for new or increased HF Conservative use with lowest doses needed for efficacy Convert to agent with low mineralocorticoid activity when possible (ie., dexamethasone, triamcinolone, methylprednisolone, betamathasone)



Study CM-06-04
CHAMPION

Subject Initials:

Subject ID:

Site Subject

HF REFERENCE MATERIAL – WORKSHEET

Anti-Fungal Traconazole (Sporanox®)	<ul style="list-style-type: none"> Negative inotrope 	Days to weeks	<ul style="list-style-type: none"> Monitor for worsening HF symptoms
NSAIDs Ibuprofen (Advil®, Motrin®) Naproxen (Aleve®, Anaprox®) Celecoxib (Celebrex®) Diclofenac (Voltaren®)	<ul style="list-style-type: none"> Sodium and fluid retention Blunted diuretic response ↑SVR 	Days to 1 month	<ul style="list-style-type: none"> Avoid use if possible, especially if concurrent renal insufficiency Recommend use of acetaminophen for pain relief if possible
Biguanide- Anti-diabetic Metformin (Glucophage®)	<ul style="list-style-type: none"> Potential for elevated lactate levels due to hypoxia or renal insufficiency 	Anytime during therapy	<ul style="list-style-type: none"> Contraindicated if concurrent renal disease (Scr ≥ 1.5 mg/dl) Not recommended for patients with acute CHF due to decreased perfusion and hypoxia
Anti-Hypertensive Minoxidil (Loniten®)	<ul style="list-style-type: none"> Fluid retention Stimulation of RAAS 	2 – 4 wks	<ul style="list-style-type: none"> Avoid use in HF if possible
Thiazolidinedione- Anti-diabetic Rosiglitazone (Avandia®) Pioglitazone (Actos®)	<ul style="list-style-type: none"> Fluid retention, edema Cause or exacerbate HF 	Days to months	<ul style="list-style-type: none"> Contraindicated for use in Class III or IV HF Not recommended for use in symptomatic HF
Tricyclic Antidepressants Amitriptyline (Elavil®) Nortriptyline (Pamelor®) Doxepin (Sinequan®)]	<ul style="list-style-type: none"> Negative inotrope Proarrhythmic 	Weeks to years	<ul style="list-style-type: none"> Avoid use in HF patients if possible, especially if depression treatment level doses used
Tumor Necrosis Factor Antagonists Infliximab (Remicade®) Etanercept (Enbrel®)]	<ul style="list-style-type: none"> Increased risk of new-onset HF or HF exacerbation 	Days to months	<ul style="list-style-type: none"> Remicade at doses > 5mg/kg is contraindicated in moderate to severe HF Discourage use of both agents in patients with Class III or IV HF

References:

- Mabile CM, Spencer AP. Keeping your patient with heart failure safe. Arch Intern Med 2004; 164: 709-718.
- Slordal L, Spigset O. Heart failure induced by non-cardiac drugs. Drug Safety 2006; 29(7): 567-586.



Study CM-06-04
CHAMPION

Subject Initials:

Subject ID:

Site Subject

HF REFERENCE MATERIAL – WORKSHEET

Heart Failure Medications				
Generic (Trade) Drug	Initial Dose (mg)	Titration Steps	Target /Maximum Dose (mg)	Adverse Effects
Beta-blockers				
Carvedilol (Coreg®)	3.125mg BID	3.125, 6.25, 12.5 mg BID Uptitrate every 2 – 4 weeks	25mg BID (<85 kg) 50mg BID (>85kg) (6.25mg BID-minimal effective dose)	1. Hypotension/Dizziness 2. Fatigue 3. Fluid retention and worsening heart failure 4. Bradycardia 5. 2 nd or 3 rd degree heart block without pacemaker
Carvedilol Phosphate Extended Release(Coreg CR®)	10mg Daily	20mg, 40mg, 80mg Daily Uptitrate every 2 – 4 weeks	80mg Daily	
Metoprolol succinate (Toprol-XL®)	12-25mg Daily	25, 50, 100, 150mg Daily Uptitrate every 2 – 4 weeks	200mg Daily (maximum 200 Daily)	
Bisoprolol (Zebeta®)	1.25mg BID		5mg Daily(<85 kg) 10mg Daily(>85kg) (maximum dose 20 Daily)	
Metoprolol tartrate (Lopressor®)	12-25mg BID		50mg BID (maximum 100mg BID)	
Ace Inhibitors- Angiotensin-converting enzyme inhibitors				
Captopril (Capoten®)	6.25-12.5mg TID	12.5, 25mg TID Uptitrate every 1 -2 wks	50 TID (maximum 100 TID)	1. Hypotension/ Dizziness 2. Decreased Renal Function 3. Hyperkalemia 4. Cough 5. Angioedema
Enalapril (Vasotec®)	2.5mg BID	5mg BID Uptitrate every 1 -2 wks	10 BID (maximum 20 BID)	
Fosinopril (Monopril®)	5 -10mg Daily	5, 10, 20mg Uptitrate every 1-2 wks	40 Daily (maximum)	
Lisinopril (Prinivil®, Zestril®)	5mg Daily	10mg Daily Uptitrate every 1 -2 wks	20 Daily (maximum 40mg Daily)	
Quinapril (Accupril®)	5mg BID	10mg BID Uptitrate every 1-2 wks	20 BID (maximum)	
Ramipril (Altace®)	1.25mg BID 1.25-2.5 Daily	5 mg Uptitrate weekly	5mg BID , 10mg Daily	



Study CM-06-04
CHAMPION

Subject Initials:

Subject ID:

Site Subject

HF REFERENCE MATERIAL – WORKSHEET

Heart Failure Medications

Generic (Trade) Drug	Initial Dose (mg)	Titration Steps	Target /Maximum Dose (mg)	Adverse Effects	
ARB- Angiotensin Receptor Blockers					
Candesartan (Atacand®)	4-8mg Daily	4, 8, 16mg	32mg Daily (maximum)	1. Hypotension/ Dizziness 2. Decreased Renal Function 3. Hyperkalemia 4. Cough (lower incidence than with ACEI) 5. Angioedema	
Losartan (Cozaar®)	12.5 – 25mg Daily	12.5, 25, 50mg	50 Daily (maximum 100 Daily)		
Valsartan (Diovan®)	40mg BID	40, 80, 160mg	160 BID (maximum 320 Daily)		
Diuretics					
IV Diuretics					
Lasix • Other IV diuretics may be considered	40-80 mg IV If on oral home Lasix: Give same Daily dose IV (max 180mg) If not on oral home Lasix: Give 40mg IVP if SCr less than 2 Give 80 mg IVP if SCr greater than or equal to 2		Lasix Administration Guidelines: • 200mg or less given undiluted • 40mg or fraction thereof given over 2 min. • Flush with NS prior to and after dose	1. Hypotension, Fatigue, Dizziness (from over diuresis) 2. Hypokalemia 3. Hypomagnesaemia 4. Acute Renal Failure 5. Rash 6. Diuretic resistance 7. Hyperuricemia 8. Hypocalcemia	
PO diuretics					
Furosemide (Lasix®)	20-40 mg Daily or BID	Titrate to dry weight	Maximum 240mg BID		
Bumetanide (Bumex®)	0.5 – 1mg Daily or BID	Titrate to dry weight	Maximum 10mg Daily		
Torsemide (Demadex®)	10 mg Daily or BID	Titrate to dry weight	Maximum 200mg Daily		
Thiazide Diuretics					
Chlorthalidone (Hygroton®)	25 mg Daily	As needed	Maximum 50 mg Daily	1. Hypotension, Fatigue, Dizziness (from over diuresis) 2. Hypokalemia 3. Acute Renal Failure 4. Rash 5. Hyperuricemia	
Hydrochlorothiazide (HydroDIURIL®)	25 mg Daily	As needed	Maximum 50 mg Daily		
Metolazone (Zaroxolyn®)	2.5 mg Daily	As needed	Maximum 10mg Daily		
Aldosterone Antagonist					
Eplerenone (Inspra®)	25mg Daily	Titrate to 50mg Daily	Maximum 50mg Daily	1. Hyperkalemia 2. Sex-hormone mediated effects - Gynecomastia - Impotence - Menstrual irregularities	
Spirolactone (Aldactone®)	25mg Daily		Maximum 50mg Daily (maximum 100mg BID as diuretic)		



Study CM-06-04
CHAMPION

Subject Initials:

Subject ID:

Site Subject

HF REFERENCE MATERIAL – WORKSHEET

Heart Failure Medications

Generic (Trade) Drug	Initial Dose (mg)	Titration Steps	Target /Maximum Dose (mg)	Adverse Effects
Digoxin				
Digoxin (Lanoxin®, Digitek®)	0.25mg Daily for CrCl greater than 80 ml/min 0.125mg Daily for CrCl between 60 – 79 ml/min 0.0625mg Daily or 0.125 QOD for CrCl between 30 – 59 ml/min D/C if CrCl less than 30 ml/min		0.25mg Daily	1. Cardiac arrhythmias 2. Heart block 3. GI symptoms (anorexia, nausea, vomiting) 4. Visual disturbances 5. Disorientation, Confusion
Vasodilators				
Hydralazine (Apresoline®)	10 – 25mg TID		50- 100mg TID	Hydralazine & Nitrates 1. Headache 2. Hypotension 3. Dizziness 4. Nausea, vomiting, diarrhea 5. Reflex Tachycardia (minimized with concurrent B-Blocker) Hydralazine 1. Fluid retention 2. Lupus-like Syndrome Nitrates 1. Flushing 2. Tachyphylaxis
Isosorbide dinitrate (Isordil®)	10 - 20mg TID		20 - 80mg TID	
Isosorbide mononitrate (Imdur®)	30mg Daily		60 - 120mg Daily	
Isosorbide dinitrate 20mg and Hydralazine 37.5mg (BiDil®)	20mg/37.5mg TID		40mg/75mg TID	

Attachment E

Sponsor Recommendations and Conformance to Appendix E and ACC/AHA Guidelines

CardioMEMS Emails	Appendix E and 2005 ACC/AHA Guidelines
<p>On 5-7-2008, a CardioMEMS nurse wrote recommendations that include “PAD > 20: Consider increasing the loop diuretic. If patient responding to current Lasix dose, increase to 40 BID; if not currently responding to Lasix dose, increase to 80mg QD. IF no response consider adding PRN thiazide or switching to Demadex if bioavailability a concern.”</p>	<p>Increase Diuretics, Change Diuretics- Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p>
<p>On 6-6-2008, a CardioMEMS nurse wrote recommendations that include “Titrating loop diuretic as needed for elevated PA pressures. Recent upward trend in PA pressures suggest a need for more diuretic. Screen for sleep apnea and refer for sleep study if positive. Patient at high risk due to large size. (Sleep Apnea Screening tool attached.) Confirm patient is not using NSAIDS. Encourage a STRICT 2gm sodium, 2000ml Fluid restricted diet.</p>	<p>Increase Diuretics – Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p> <p>Sleep Apnea- Appendix E- pg. 1:</p> <p><i>If the pressures are outside the reference range after</i></p>

CardioMEMS Emails	Appendix E and 2005 ACC/AHA Guidelines
	<p><i>vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated.</i></p> <p>Appendix E- pg. 2: 2005 ACC/AHA Guidelines</p> <p><i>In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.</i></p> <p>2005 ACC/AHA Guidelines- pg. e162 - Sleep Apnea Screening:</p> <p><i>Screening for sleep apnea is a Class IIa recommendation.</i></p> <p>– <i>"Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (Level of Evidence: C)"</i></p> <p>Discontinuation of NSAIDs – Appendix E- pg. 1:</p> <p><i>"If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated."</i></p> <p>Appendix E- pg. 2: ACC/AHA Guidelines:</p> <p><i>"In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult."</i></p> <p>ACC/AHA Guidelines 2005- pg. e173:</p> <p><i>"Discontinuation of contraindicated medications is a Class I recommendation.</i></p> <p><i>"Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and</i></p>

CardioMEMS Emails	Appendix E and 2005 ACC/AHA Guidelines
	<p><i>reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs. (Level of Evidence: B)"</i></p> <p>Dietary Counseling- Appendix E- pg. 3:</p> <p><i>“Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <ol style="list-style-type: none"> <i>a. Increase or add loop diuretic</i> <i>b. Change to another loop diuretic</i> <i>c. Add thiazide diuretic (with caution)</i> <i>d. IV doses of loop diuretic</i> <i>e. Serum electrolyte evaluation with change in baseline medication</i> <i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i> <ul style="list-style-type: none"> • <i>Add or increase nitrates</i> • <i>Start or re-educate in salt intake and fluid restriction “</i> <p>2005 ACC//AHA Guidelines- pg. e175:</p> <p><i>“Of the general measures that should be used in patients with HF, possibly the most effective yet least utilized is close attention and follow-up. Nonadherence with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family, can reduce the likelihood of nonadherence and lead to the detection of changes in body weight or clinical status early</i></p>

CardioMEMS Emails	Appendix E and 2005 ACC/AHA Guidelines
	<i>enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration.”</i>
<p>On 10-30-2008, a CardioMEMS nurse wrote recommendations that include “PCWP 14 suggests increased volume- Consider increasing Lasix to 40mg BID or switching to Demadex if bioavailability a concern with Lasix. Consider using PRN Thiazide to facilitate diuresis. Up-titrate Diovan to optimal dose as tolerated (160mg BID). Add Hydralazine and Nitrates to current regimen uptitrating as tolerated. Evaluate patient's current compliance with treatment of his Obstructive Sleep Apnea. Consider re-evaluation of patient's Sleep Breathing Disorder diagnosis (OSA vs Central Sleep Apnea) and options for treatment.”</p>	<p>Increase Diuretics, Change Diuretics, Add Thiazide Diuretic- Appendix E- pg. 3:</p> <p><i>“Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic “</i></p> <p>Increase or add Vasodilators- Appendix E- pg. 1 and pg. 2:</p> <p><i>“If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed.”</i></p> <p><i>“Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in</i></p>

CardioMEMS Emails	Appendix E and 2005 ACC/AHA Guidelines
	<p><i>baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p> <ul style="list-style-type: none"> • Add or increase nitrates • <i>Start or re-educate in salt intake and fluid restriction”</i> <p>Sleep Apnea- Appendix E- pg. 1:</p> <p><i>“If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated.”</i></p> <p>Appendix E- Pg. 2: 2005 ACC/AHA Guidelines</p> <p><i>In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.</i></p> <p>2005 ACC/AHA Guidelines- pg. e162 - Sleep Apnea Screening:</p> <p><i>“Screening for sleep apnea is a Class IIa recommendation.”</i></p> <p><i>"Screening for hemochromatosis, sleep-disturbed breathing, or human immunodeficiency virus is reasonable in selected patients who present with HF. (Level of Evidence: C)"</i></p>
<p>On 12-12-2008, a CardioMEMS nurse wrote “What is your plan for management of [specific subject]? Implant hemodynamics (PA 68/41(52) PCWP 30 CO 1.5 PVR 14.67) suggested increased volume with a PCWP 30 in addition to PAH with a PVR 14.67. Addition of Ismo 40mg QD on 10/2/08 appears to have helped with a decrease in PAM from 43 to 31. She is on maximum medical therapy (ARB, BB, Nitrate, Aldactone, Digoxin, Diuretic) at this point.</p>	<p>Sildenafil- Appendix E- pg. 1:</p> <p><i>If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated.</i></p> <p>Appendix E- pg. 2: ACC/AHA Guidelines</p> <p><i>“In addition to these specific guidelines, the</i></p>

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<p>Would you consider challenging her with Sildenafil in addition to adjusting her diuretic regimen by switching to Demadex or possibly using outpatient IV diuretics?"</p>	<p><i>investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult."</i></p> <p>ACC/AHA Guidelines- pg. e200:</p> <p><i>Evidence supporting the use of sildenafil for the treatment of HF patients is described.</i></p> <p><i>"Recent studies suggest that sildenafil may produce hemodynamic benefits in patients with coronary artery disease and may act to improve some of the peripheral vascular abnormalities that characterize patients with HF."</i></p> <p>Change Diuretics or IV Diuretics- Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p>
<p>On 12-26-2008, a CardioMEMS nurse wrote "I wanted to alert you that [specific subject]'s mean pressure went from 27 on 12/24 to 53 on 12/26. Do you think this warrents her to take an extra dose of diuretics today? It is the holidays and we expect pressures to increase, but we still want to prevent her from going to the hospital."</p>	<p>Increase Diuretics- Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p>

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	<p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p>
<p>On 12-29-2008, a CardioMEMS nurse wrote “I wanted to alert you of an increasing trend in the mean of [specific subject]. Although his mean pressure trend remains relatively flat, his pressures have an upward trend. We are seeing several patients in the trial experience post-holiday rise in pressures most likely due to dietary indiscretion and medication noncompliance. Do you think this patient would benefit from a few days of increase diuretic until his pressures return to baseline? I also noticed that this patient is on Metformin in the face of renal insufficiency (SCr 1.4) which may be contributing to difficulty in managing his volume status.”</p>	<p>Increase Diuretics- Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p> <p>Dietary Counseling- Appendix E- pg. 3:</p> <p><i>“Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in</i></p>

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	<p><i>baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p> <ul style="list-style-type: none"> • <i>Add or increase nitrates</i> • <i>Start or re-educate in salt intake and fluid restriction “</i> <p>2005 ACC//AHA Guidelines- pg. e175:</p> <p><i>“Of the general measures that should be used in patients with HF, possibly the most effective yet least utilized is close attention and follow-up. Nonadherence with diet and medications can rapidly and profoundly affect the clinical status of patients, and increases in body weight and minor changes in symptoms commonly precede by several days the occurrence of major clinical episodes that require emergency care or hospitalization. Patient education and close supervision, which includes surveillance by the patient and his or her family, can reduce the likelihood of nonadherence and lead to the detection of changes in body weight or clinical status early enough to allow the patient or a healthcare provider an opportunity to institute treatments that can prevent clinical deterioration.”</i></p> <p>Discontinuation of TZDs – Appendix E- pg. 1:</p> <p><i>“If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated.”</i></p> <p>Appendix E- pg. 2: ACC/AHA Guidelines:</p> <p><i>“In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.”</i></p>

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	<p>ACC/AHA Guidelines 2005 pg. e202:</p> <p><i>“Evidence suggesting the negative of effects of thiazolidinediones in NYHA Class III patients is described.</i></p> <p><i>“Thiazolidinediones have been associated with increased peripheral edema and symptomatic HF in patients with underlying risk factors or known cardiovascular disease. The risk of developing edema with thiazolidinediones is dose related and is higher in diabetic patients who are taking concomitant insulin therapy... Initiation of these drugs is not recommended in patients with NYHA functional class III to IV symptoms of HF.”</i></p>
<p>On 8-21-2009, a CardioMEMS nurse wrote “I wanted to alert you to [specific subject]’s increase in pressures over the past week with a mean of 42 today. She responded nicely to extra Lasix back in May. Would you consider this again?” A response the same day from the physician, directed to the site nurse but including the CardioMEMS nurse, states “agree give extra dose for 3 days and check if anything different in terms of diet, activity, etc.”</p>	<p>Knowledge of subjects prior response to therapy- Appendix E – pg. 1:</p> <p><i>“Diuretics and vasodilators should be adjusted based on the subject’s baseline diuretic requirement, knowledge of the subject’s prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline.”</i></p> <p>Increase Diuretics- Appendix E- pg. 3:</p> <p><i>Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <p><i>a. Increase or add loop diuretic</i></p> <p><i>b. Change to another loop diuretic</i></p> <p><i>c. Add thiazide diuretic (with caution)</i></p> <p><i>d. IV doses of loop diuretic</i></p> <p><i>e. Serum electrolyte evaluation with change in baseline medication</i></p> <p><i>f. Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i></p>

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<p>On 11-16-2007, one of the national PIs sent the following email to CardioMEMS after talking with the principal investigator at a specific site. “I spoke with [the site principle investigator] this morning. We had a very collegial and productive discussion about hemodynamic monitoring, in general, and his patients, in particular. It sounds like patient #2 is very ill and will likely be made DNR. Patient #3 has had persistent elevation in her PA pressures, despite escalation of diuretic dose. Following [CardioMEMS employee]’s conversation with [the site principle investigator] yesterday, he increased the furosemide dose from 80 mg bid to 120 mg bid (the patient was previously [prior to 10/25] on 40 mg bid). The patient does not have any clinical signs of extra-cellular fluid volume excess. The patient does, in fact, have substantial mitral regurgitation. I suggested that he consider starting a long acting nitrate and letting me know what happens; we may need to back off of the diuretic, if the nitrate works. I also thanked him for his great and ongoing contribution to the study.”</p>	<p>Consultation with National Principle Investigators- Appendix E- pg. 1:</p> <p><i>“Consultation with the national PI’s is encouraged to optimize the success of medical management of PA pressures.”</i></p> <p>Add Vasodilator- Appendix E- pg. 1 and pg. 2:</p> <p><i>“If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed.”</i></p> <p><i>“Hyper-volemic Treatment Recommendations</i></p> <ul style="list-style-type: none"> • <i>Add or increase diuretic (and appropriate electrolyte replacement)</i> <ol style="list-style-type: none"> a. <i>Increase or add loop diuretic</i> b. <i>Change to another loop diuretic</i> c. <i>Add thiazide diuretic (with caution)</i> d. <i>IV doses of loop diuretic</i> e. <i>Serum electrolyte evaluation with change in baseline medication</i> f. <i>Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic</i> <ul style="list-style-type: none"> • <i>Add or increase nitrates</i> • <i>Start or re-educate in salt intake and fluid restriction”</i>
<p>On 5-7-2008 a CardioMEMS nurse wrote “There are a few of your patients whose PA pressures are trending upward or are borderline elevated. I have reviewed the following cases and would like to review with you the plan for medical management. I know my information may not be current/accurate so please update as</p>	<p>Consultation with National Principle Investigators- Appendix E- pg. 1:</p> <p><i>“Consultation with the national PI’s is encouraged to optimize the success of medical management of PA pressures.”</i> .”</p>

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appropriate. If you or [the site principle investigator] would like further consultation with one of the national PI's or member of the steering committee I would be glad to arrange that.”	