Testimony to the FDA's Circulatory System Devices Panel on the Premarket Approval (PMA) Application P100045 for the CardioMEMS Champion HF Monitoring System

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My name is Dr. Michael Carome, Deputy Director of the Health Research Group at Public Citizen. I am testifying on behalf of myself and Dr. Sidney Wolfe, Director of the Public Citizen Health Research Group. We have no financial conflicts of interest.

We oppose the Food and Drug Administration's (FDA) approval of the CardioMEMS Champion HF Monitoring System (the CardioMEMS System) for wirelessly measuring and monitoring pulmonary artery (PA pressure) and heart rate in patients with New York Heart Association (NYHA) class III heart failure who have been hospitalized for heart failure in the previous year because:

(1) The design and conduct of the single pivotal clinical trial evaluating the CardioMEMS System had multiple features that all created readily apparent bias with respect to the effectiveness endpoints in favor of the experimental group;
(2) The device has known short-term risks of serious harm related to the implantation procedure, as well as likely unforeseen long-term risks; and
(3) As a result of (1) and (2), there is insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh its risks.

Effectiveness Assessment — Study Design and Conduct Factors Created Readily Apparent Bias

The sponsor, CardioMEMS, Inc., conducted a single pivotal trial to evaluate the CardioMEMS System that was prospective, multicentered, randomized, controlled, and single-blinded (subjects only). The subjects had symptomatic NYHA class III heart failure and at least one hospitalization for heart failure within 12 months of enrollment. All subjects (N=550) received the investigational sensor device and after device insertion were randomized to the treatment arm (physician access to sensor pressure data to help guide medical therapy) or the control arm (no physician access to the sensor pressure data, standard medical therapy for congestive heart failure).[1]

The primary effectiveness endpoint was the rate of heart failure-related hospitalizations through six months.[2] Secondary effectiveness endpoints included the following:[3]

(1) Change from baseline in PA mean pressures
(2) Proportion of subjects hospitalized for heart failure
(3) Days alive outside of the hospital
(4) Total quality of life score on the Minnesota Living with Heart Failure Questionnaire (MLHFQ)

While statistically significant differences were seen in each of the pre-specified primary and secondary effectiveness endpoints, as well as many other supplementary endpoints (see the Table below), the absolute differences between the treatment and control groups for most endpoints were relatively small.

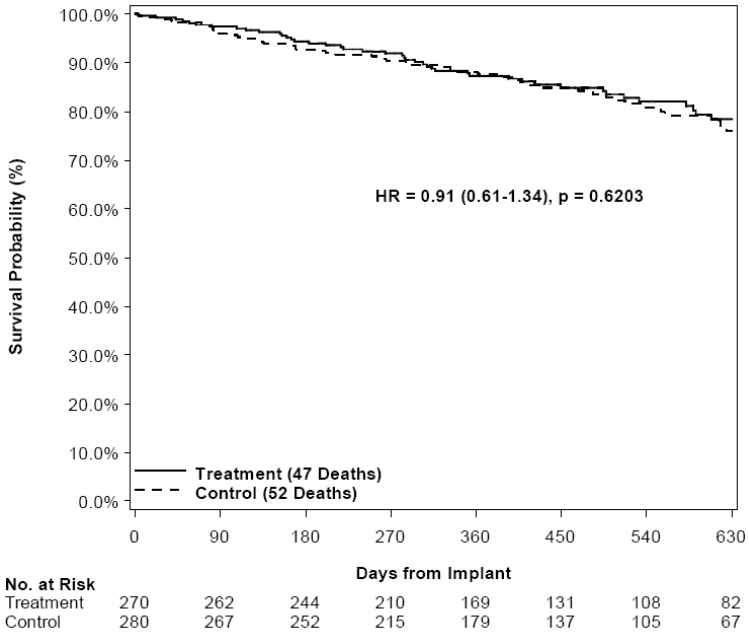
Table: Effectiveness Endpoint Results[4]

Endpoint	Treatment Group (N=270)	Control Group (N=280)	Absolute Difference	p-value
Rate of heart failure-related hospitalizations (events/patient/6 months)	0.32	0.44	0.12	0.0002
Mean change in PA mean pressure from baseline (AUC, mmHg days)	-156±1088	33±952	189	0.0077
Proportion of subjects hospitalized for heart failure at 6 months	55 (20.4%)	80 (28.6%)	8.2%	0.0292
Days alive outside hospital without heart failure hospitalization up to 6 months	174±31	172±38	2.3	0.0280
Days hospitalized for heart failure up to 6 months	2.2±6.8	3.8±11.1	1.6	0.0194
MLHFQ scores at 6 months	45.2±26.4	50.6±24.8	5.4	0.0236
MLHFQ change from baseline at 6 months	-10.6±24.9	-7.4±24.9	3.2	0.0373

Assuming these results were due to actual benefits of the device, the benefits of widespread clinical use of the CardioMEMS System in a real-world setting would certainly be less than was seen in the clinical study.

Also, there was no difference in mortality outcomes between groups over the duration of the study (see Figure below), and no statistically significant difference in all-cause hospitalization rates at six months (0.88 events/subject/6 months in the treatment group and 0.96 events/subject/6 months in the control group; $p = 0.4065$[5]).

Figure: Kaplan-Meier Survival Plot Over the Study Duration[6]



Several features of the design and conduct of the study created a readily apparent bias in favor of the treatment group. Thus, it is highly conceivable that the differences seen in the effectiveness endpoints were due in large part or even entirely to bias. These features include the following:

(1) Single-blinded study design: This is one feature of the study design contributing to study bias that was unavoidable. Nevertheless, clinical investigator awareness of each subject's study group assignment may have influenced decisions regarding both medical therapy and whether to hospitalize a subject, both of which would directly affect the primary and secondary effectiveness endpoints. For example, investigators, hoping to show that the CardioMEMS System was beneficial, may have been more likely to admit a control group subject than a treatment group subject despite being faced with similar clinical presentations. The study design did include use of a blinded, independent clinical endpoints committee that reviewed abstracted clinical data and determined when heart failure hospitalization endpoints were met.[7] However, this blinded review did not mitigate the apparent bias that resulted from clinical decisions being made by the unblinded clinical investigators managing the subjects.

(2) Consultation with the national principal investigators (PIs) regarding medical management of treatment group subjects only: The protocol under the FDA-approved investigational device exemption (IDE) included a provision in which clinical investigators at each of the study sites were encouraged to consult with the national PIs — who likely were nationally recognized experts in the management of congestive heart failure — "to optimize the success of medical management of PA pressures."[8] Apparently, no such encouragement for consultation was provided with respect to the medical management of control subjects, whose care might have been enhanced had the site clinical investigators consulted with the national PIs with the same frequency as for treatment group subjects. Such unbalanced consultations with the national PIs introduced a bias into the study design that favored the treatment group.

(3) Unbalanced content and frequency of telephone contacts between investigators and treatment group subjects versus control group subjects: The protocol under the FDA-approved IDE included scripts for telephone contact with subjects in both study groups. The scripts were identical except for subject-specific medication adjustments that occurred

in the treatment group in response to PA data.[9] The protocol also include a provision under which the sponsor, which had real-time access to all the PA data for subjects, sent email alerts to local site clinical investigators when PA readings for a treatment group subject were elevated.[10] Whenever a telephone contact occurred with a treatment group subject, a control group subject was randomly selected to receive a matching phone contact.[11] These were not comparable study interventions. Treatment subjects received telephone contacts that were based on contemporaneous subject-specific clinical information (i.e., PA pressure information) and included medication changes. Control subjects, on the other hand, received random, generically scripted calls unrelated to any pertinent contemporaneous contextual clinical information that may have warranted medication changes. Furthermore, the mean number of telephone contacts per treatment group subject was slightly higher than the mean number per control group subject (3.0 ± 2.3 versus 2.5 ± 1.8). Such imbalances in the content and frequency of the telephone contacts between study groups introduced bias that again favored the treatment group.

(4) Subject-specific treatment recommendations provided to individual site clinical investigators by nurses employed by the sponsor for treatment group subjects only: The most egregious source of bias was identified during an inspection of the CardioMEMS System pivotal trial by the FDA's Division of Bioresearch Monitoring (BIMO). The inspection revealed that "**nurses working for the sponsor** made medical recommendations for heart failure management for specific subjects during the course of the trial … **limited to Treatment (i.e., investigational) group subjects only** … the sponsor contacted investigational sites during the trial regarding recommendations for Treatment group subjects with respect to starting, stopping and/or titrating specific heart failure medications, including doses, intervals and duration" [emphasis added].[12] Such communications between the site investigators and the sponsor-employed nurses occurred via a known number of email contacts (1.5 follow-up email alerts per patient for first six months[13]) and an unknown number of telephone contacts. The FDA specifically noted the following based on a review of the email communications:[14]

- The sponsor made recommendations based on prior subject-specific responses.
- The sponsor made recommendations regarding the discontinuation of medications that the sponsor thought were disadvantageous.
- Recommendations for changes in medications that were beyond the scope of Appendix E were made based on PA pressure readings (for example, sildenafil).
- The sponsor suggested the use of outpatient IV diuretics; please note that the primary effectiveness endpoint was limited to inpatient hospitalization events.

Such contacts between sponsor employees, who were highly motivated to affect the outcome of the study in a direction that favored use of the CardioMEMS System, and individual site investigators regarding management of treatment group subjects only is highly unusual and, in combination with the lack of investigator blinding, created a high degree of bias in favor of the treatment group. Similar contacts and treatment recommendations by independent study nurses for control subjects based on monitoring of clinical parameters (such as weight, symptoms, and degree of edema) almost certainly would have improved effectiveness endpoint outcomes in such subjects.

In responding to the BIMO inspection findings, the sponsor argued that the contacts fell within the scope of the protocol as submitted to the FDA under the IDE. This argument is irrelevant. Such procedures created bias regardless of whether they were pre-specified in the protocol.

In responding to FDA's concerns about study bias, the sponsor stated the following:

> However, the FDA has not provided to date any evidence from the study to support a finding that … [these contacts] resulted in bias being introduced into the study results obtained.[15]

The sponsor fails to recognize the insidious nature of bias, which can influence investigator actions and judgments in subtle and not-so-subtle ways, and the paramount importance of ensuring, before a study begins, that the study is designed and conducted in a way that eliminates or minimizes bias to the greatest extent possible. Once a study is completed, it is impossible to prove how much of a difference between study group outcomes resulted from bias and how much was from an actual difference between the interventions being tested. In this case, most epidemiologists would conclude that the multiple features of the study design and conduct described above created readily apparent bias and prevent any valid conclusions from being drawn about the effectiveness of the CardioMEMS System.

Finally, consultations with national PIs, alerts from the device manufacturer, and treatment guidance from nurses employed by the manufacturer are all artificial, non-real world interventions that would not carry over to routine clinical practice if this device were approved for marketing.

Risk Assessment

The procedure for implantation of the CardioMEMS System sensor has many known risks of serious harm, including the following:[16]

- Infections
- Arrhythmias
- Bleeding, including hemoptysis
- Hematomas
- Thromboembolism
- Death

Furthermore, given the limited testing of this device in animals and human subjects, there is insufficient data regarding the long-term risks associated with this permanently implanted device.

Recommendation

In summary, Public Citizen strongly recommends that the FDA, in order to protect public health, not approve the PMA application for the CardioMEMS System because:

(1) The design and conduct of the single pivotal clinical trial evaluating the CardioMEMS System had multiple features that all created readily apparent bias with respect to the effectiveness endpoints in favor of the experimental group, thus preventing any valid conclusions from being drawn regarding the effectiveness of the device;
(2) The device has known short-term risks of serious harm related to the implantation procedure, as well as likely unforeseen long-term risks; and
(3) As a result of (1) and (2), there is insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh its risks.

[1] Food and Drug Administration. FDA executive summary: CardioMEMS Champion HF Monitoring System, prepared for the December 8, 2011 meeting of the Circulatory System Devices Panel. Webpage 11. Available at

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