CAMBRIDGE HEART

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May 9, 2005
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Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: Request for National Coverage Determination on
Microvolt T-Wave Alternans (MTWA) Testing

Dear Dr. Phurrough:

I am writing to formally request a National Coverage Determination (NCD) for the expanded use of Microvolt T-wave Altemans (MTWA) for Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) type patient populations.

MTWA is a noninvasive diagnostic test for the prediction of sudden cardiac death (SCD). As set out below, an NCD on MTWA for these populations would reflect the recently available published peer reviewed literature that supports expanded coverage for Medicare beneficiaries. In addition, the NCD would insure uniform availability of testing, coverage and payment for MTWA as part of the pending follow-on implantable cardioverter defibrillator (ICD) registry that includes MADIT II and SCD-HeFT type patients.

A uniform national coverage policy for MTWA in these patient populations would make MTWA available to all Medicare beneficiaries who meet the criteria for ICD coverage and would likely prevent some beneficiaries from receiving unnecessary ICD therapy.

Summary of Key Points

- The MTWA testing system, utilizing the Analytic Spectral Method, is FDA cleared for the prediction of sudden cardiac death and has a unique CPT Code (93025). Local Medicare coverage for MTWA testing does not reflect recent clinical evidence and is not in alignment with new ICD patient eligibility criteria, compromising the ability of providers to utilize MTWA as a risk stratifier in these new ICD indicated patient populations.

- Published clinical studies demonstrate that one third of this new ICD eligible primary prevention patient population will likely test MTWA Normal (negative), be at very low risk for SCD, and not likely to benefit from ICD therapy. In comparison, two

thirds of the primary prevention patient population will likely test MTWA Abnormal (positive or indeterminate), confirming their perceived high risk for SCD and therefore likelihood of benefiting from ICD therapy.

- The initial Medicare Local Medical Review Policies (LMRPs) for MTWA testing (CPT code 93025) were similar to conventional arrhythmia diagnosis codes used for original ICD indications. Current LCDs for MTWA are inadequate for evaluating SCD or ventricular arrhythmic risk in Medicare eligible MADIT II and SCD-HeFT ICD type patients.

- An NCD for MTWA will result in uniform coverage policies and make MTWA risk stratification available to patients in the MADIT II and SCD-HeFT ICD eligible populations. Incorporating clinically proven risk stratification methodologies into the diagnosis algorithm for Medicare patients is critical to delivering the most appropriate care.

Background on Microvolt T-Wave Alternans (MTWA)

MTWA testing is a noninvasive diagnostic risk stratifier with a 98%+ negative predictive value (NPV) based on peer-reviewed, published scientific evidence. Appendices one and two contain a summary of published clinical data. T-Wave alternans refers to a beat-to-beat variability in the amplitude of the T-wave. MTWA is a provocative, noninvasive test that necessitates gradual elevation of the heart rate to approximately 110 beats per minute to capture the key alternans data. Results are reported as normal (negative) or abnormal (positive or indeterminate).

In June 2000, and November, 2001, the U.S. Food and Drug Administration (FDA) 510K clearances of the Heartwave® system (appendix 3) included indications that support testing a wide spectrum of patients at risk of ventricular tachyarrhythmias (VTs). The Heartwave® system measures the beat to beat variability in the amplitude of the T-wave during exercise, pharmacological stress or cardiac pacing. Utilizing the analytic spectral method, the Heartwave system measures the fluctuations of T-wave morphology, interprets the data and generates a formal interpretation and report of test results. Proprietary and disposable Micro-V sensors reduce noise and artifact while enabling measurement to the microvolt level.

SCD is one of the most common causes of death after a myocardial infarction or in heart failure patients with non-ischemic cardiomyopathy. Because of this, there is intense interest in risk stratification of these individuals to target the most appropriate therapy. Clinical studies have shown that MTWA normal patients are at very low risk of SCD even if they are characterized as MADIT II or SCD-HeFT type patients. While a routine EKG cannot detect these small fluctuations, MTWA utilizing specialty multi-segment sensors can detect minute fluctuations, allowing the computer algorithm to evaluate the results.

MTWA can be successfully used to risk stratify patients with known low left ventricular ejection fraction (LVEF) and identify those patients who should be referred on for ICD therapy as well as patients who are at low risk for SCD and therefore may be medically managed. Patients can be segmented into primary and secondary (prior life-threatening

arrhythmia) prevention. Patients in the secondary prevention group are already defined as high risk.

Clinical Benefits of MTWA in MADIT II and SCD-HeFT Type Patients

As noted, sudden cardiac death (SCD) is a major public health problem in the United States, with an estimated 400,000 deaths annually. Although coronary heart disease accounts for the majority of affected patients, non-ischemic heart disease (cardiomyopathy) can also lead to SCD.

The results of MADIT II and SCD-HeFT, the landmark randomized controlled clinical trials of implantable cardioverter defibrillators, have recently become available. The results of SCD-HeFT were published in the New England Journal of Medicine in January, 2005. SCD-HeFT, sponsored by National Institutes of Health, was designed to study whether amiodarone or an implantable cardioverter defibrillator reduces all-cause mortality compared to placebo in ischemic and nonischemic patients on conventional medical therapy with NYHA class II/III and an ejection fraction = 35%. The SCD-HeFT trial randomized 2521 patients from 148 clinical centers in the United States, Canada, and New Zealand. MADIT II was designed to determine if prophylactic implantable cardioverter defibrillator (ICD) therapy in moderately high-risk coronary patients – in addition to conventional therapy - would significantly reduce death compared with patients treated with conventional therapy alone.

As a result of these two large, well-designed studies, CMS has substantially increased the potential number of Medicare patients eligible to receive ICDs for primary prevention to over 500,000 patients. The results of these clinical trials also highlight the clinical benefits of risk stratifiers such as MTWA. The clinical trial results showed modest absolute survival benefits in patients with both ischemic and non-ischemic heart disease with left ventricular dysfunction treated with implantable cardioverter defibrillators as compared to optimal medical therapy. As a result, many of those Medicare patients truly at risk will not receive appropriate therapy. Additionally, even those patients who never receive therapy from their ICD will face both the short and long term morbidity associated with the original implant. The psychological effect of living with an ICD is now being studied.

The MADIT II study demonstrated that implantation of an ICD reduced mortality from 19.8% to 14.2% or a 5.6% reduction in absolute mortality during 20 months of follow-up in patients with a prior myocardial infarction and left ventricular ejection fraction =30%. The reduction in absolute mortality seen in the SCD HeFT trial was similarly low to MADIT II at 1.6% per year after 60 months. In addition, ICD complication rates of 5% at the time of implantation and 9% later in the course of the trial were reported. In both studies, only 1 in 5 patients received appropriate therapy from their ICD. This has led to the recognition that low ejection fraction patients would benefit from effective risk stratification to direct ICD therapy to only those patients at significant risk especially when we consider the invasiveness and expense of the therapy.

Concerns have been raised both about the cost and potential morbidity of implanting ICDs in a large group of patients when only a small fraction of the patients would be expected to benefit from the treatment. This concern has given rise to the need for an effective means of risk stratifying the MADIT II and SCD HeFT populations so that ICD therapy can be

directed to only those patients who are at significant risk and thus likely to benefit from treatment for primary prevention of SCD.

Data from prospective clinical studies demonstrate that patients with a variety of cardiac disorders who test negative for MTWA are at extremely low risk for SCD and ventricular tachyarrhythmias. In particular, MADIT II and SCD-HeFT type patients who test MTWA negative have an extraordinarily low rate of ventricular tachyarrhythmic (VT) events. The data also suggests that MTWA negative patients can safely be treated and followed clinically without ICD implantation.

The following two tables are excerpted from a confidential preprint paper entitled "Can Microvolt T-Wave Alternans Testing Reduce Unnecessary Defibrillator Implantation" that is co-authored by Richard Cohen MD, PhD of the Massachusetts Institute of Technology. The event rate for MTWA negative patients is very low based on the clinical papers summarized in table 1. The all cause mortality rate for MTWA negative patients MADIT II and SCD-HeFT type patients is lower than the rate for those who received ICDs. The entire paper is included in appendix 4.

Table I. Annual Spontaneous Ventricular Tachyarrhvthmic Event Rates[1]

Study	Population	N	Follow-Up (months)	MTWA+	MTWA-	HR
Klingenheben[10], 2000	CHF (Prior MI and DCM)	107	18	16%	0%	oo
Hohnloser[11], 2003	DCM	137	18	17%	4%	4
Kitamura[12], 2002	DCM	83	21	16%	2%	9
Adachi[13], 2001	DCM	82	40	11%	1%	12
Grimm[14], 2003	DCM LVEF < = 0.45	263	72	3%	2%	1.5
Ikeda[15], 2000	Prior MI	102	13	30%	2%	16
Ikeda[16], 2002	Prior MI	834	24	4%*	0.5%*	8
Hohnloser et al [17], 2003	Prior MI LVEF < = 0.30	129	24	9%* 19%	0%* 3%	oo 6
Chow[18], 2003	Prior MI LVEF < = 0.30	203	18	8%	1%	6
All	All	1,811		8.4%	1.2%	7

The average VT event rate for MTWA negative patients in MADIT II and SCD-HeFT type patient populations from the studies summarized below is only 1.2% per year. These rates were observed in prospective natural history MTWA studies in patients similar to patients in MADIT-II and SCD-HeFT.

As the pool of potentially eligible patients for ICDs continues to expand as a result of the recent national coverage decision on ICDs and their role in the primary prevention of SCD, it will be clinically desirable to increase utilization of MTWA, which has been demonstrated to

be an effective risk stratifying tool for identifying those patients in the MADIT II and SCD-HeFT populations at substantially lower risk for SCD who will not likely benefit from ICD therapy.

Table II compares the efficacy of ICD therapy in the MADIT II and SCD-HeFT studies to the efficacy of MTWA in similar populations. The upper portion of table reviews the annualized mortality data from the MADIT II and SCD-HeFT prospective ICD studies. (Note that the mortality rates vary slightly from the original published papers to account for the variable follow-up periods of each trial). The lower part of table reports results from prospective MTWA studies in non-ICD patients with mortality endpoint analyses. Comparison is made between mortality rates among the control patients in SCD-HeFT and MADIT II and the entire populations in the MTWA natural history studies, and between the ICD treated patients in SCD-HeFT and MADIT II and the MTWA Negative patients in the MTWA studies.

The average annual all cause mortality rate in these two landmark studies for patients with ICDs is 7.4% vs. only 2% for MTWA negative patients in similar patient populations.

Patients who test MTWA negative have a lower all cause mortality rate than MADIT II and SCD-HeFT patients treated with ICDs.

Table II. **Annual All Cause Mortality Rates[2]**

Study	Population	N	Follow-Up (months)	No ICD	ICD
MADIT II[2], 2002	Prior MI LVEF < = 0.30	1,232	20	13.2%	9.2%
SCDHeFT[3], 2004	CHF LVEF < = 0.35	2,521	60	9.0%	6.5%
All		3753		10.4%	7.4%
Bloomfield[9], 2003	Prior MI LVEF < = 0.30	177	24	7%	2%
Hohnloser et al[17], 2003	Prior MI LVEF < = 0.30	129	24	10%	7%
Costantini et al, 2004	DCM LVEF < = 0.40	282	24	3%	0%
Grimm et al[14], 2003	DCM LVEF < = 0.45	263	72	4% 2%	2%
All		851		5.3%	2.0%

All MTWA data presented in these tables were measured using the spectral analytic method and noise reducing multi-contact electrodes during exercise or pharmacologic stress or during cardiac pacing.

Medicare ICD Coverage with Evidence Development Registry

On January 27, 2005, as discussed *supra*, CMS issued a new ICD coverage decision (CAG-00157R3) that greatly expanded the covered indications for ICDs to include use for primary prevention of sudden cardiac death. As an integral part of the new coverage decision, CMS established a data collection registry requirement linked to payment for the ICD because of concerns including:

- the very modest absolute mortality benefit demonstrated in
    - o MADIT II - 5.6% at 20 months
    - o SCD-HeFT -1.6% at 60 months;
- the need to implant 14-18 ICDs to save one life
- the fact that only 20% of patients in both large studies receiving ICDs received appropriate therapy from the device
- the lack of available risk stratification methods that could identify which are the most appropriate patients that will benefit from use of an ICD when used for primary prevention of SCD

CMS reviewed physician input and the clinical literature associated with MTWA as part of the ICD coverage decision. CMS included a review of clinical literature for MTWA in the final decision memorandum in relation to the ICD registry. CMS stated in part:

> ***We do strongly encourage the inclusion of MTWA in subsequent clinical trials, registries and other data collection protocols in order to further evaluate this promising risk stratification technology and will work with stakeholders involved in the subsequent data collection systems to include this information.***

Therefore, it is likely that MTWA will become a required data element to be collected when the follow-on registry is complete and ready for implementation. The expanding, evidence-based indications for ICDs in various cardiac patient populations has lead to an increasing need for both providers and health plans to use risk stratification tools for determining which patients are at low risk for SCD and could therefore be managed conservatively on medical therapy.

Local Coverage Policies Do Not Reflect Latest Clinical Data

The current Medicare coverage for MTWA testing does not reflect the latest available clinical data and would not provide coverage that would allow testing of the expanded ICD eligible patient populations, inappropriately limiting the availability of this important risk stratification tool for MADIT II and SCD-HeFT type patients. It is critical that coverage of risk stratification with MTWA utilizing the Analytic Spectral Method is consistent for these new and large populations if Medicare patients are to receive the most appropriate care.

Local Medicare coverage policies for MTWA exist in 40 states, and in some of the remaining states, MTWA is reimbursed without a published policy. While many carriers have recently revised their LMRPs into LCDs and a few have also modified their coverage indications for MTWA testing, all of these changes preceded the January 2005 ICD national coverage decision.

The original indications/lCD-9 codes for MTWA testing mirrored the arrhythmia diagnosis codes associated with the then existing ICD coverage. The current, independently developed LMRPs for MTWA testing were created to narrowly identify patients at only the highest risk for SCD. Coverage indications for MTWA in LMRPs often included:

> *Documented arrhythmias, non-sustained ventricular tachycardia, inducible sustained Ventricular tachycardia and syncope and collapse.*

Prior to the January 2005 ICD national coverage decision, the ICD-9 codes used to support coverage for MTWA testing were very limited. With the expanded Medicare patient populations now eligible for ICD therapy and with the clinical data suggesting that negative MTWA patients are not likely to benefit from ICD therapy, the patient criteria and associate ICD-9 codes for MTWA should mirror the patient criteria and ICD -9 codes for ICDs. The current patient criteria and supporting ICD-9 codes for MTWA testing varies from state to state (appendix 5).

Despite data from prospective clinical studies demonstrating that patients with a variety of cardiac disorders who test negative for MTWA are at extremely low risk for SCD and ventricular arrhythmias, none of the current MTWA testing LCD/LMRPs are in alignment with the expanded January 2005 ICD national coverage decision that provides for primary prevention use of ICDs in the MADIT II and SCD HeFT populations. Nor have existing MTWA LCD/LMRPs kept pace with CMS' ICD primary prevention expansion of indications, thereby limiting Medicare patient access to a risk stratification tool that can aid in their physicians' judgment whether or not they will benefit from ICD therapy.

MADIT II and SCD-HeFT type patients who test MTWA negative have an extraordinarily low rate of ventricular tachyarrhythmic events and the data suggests that they can safely be treated and followed clinically without ICD implantation. A National Coverage Decision specific to MTWA testing using the Analytic Spectral Method must be developed to include testing of these Primary Prevention groups of patients as well. It is critical that MTWA testing be covered by Medicare to include these patient populations:

> 1. MADIT II patients who have a survived a previous myocardial infarction and have impairment of the left ventricle but no prior history of arrhythmia. To properly communicate indications for MADIT II patients, it is important to reflect heart failure or previous MI as the principal diagnosis rather than an arrhythmia.
> 2. SCD-HeFT patients with either ischemic or non-ischemic cardiomyopathy with NYHA Class II and III CHF and EF of less than or equal to 35%. To fully communicate the indication for SCD HeFT patients, it is important to reflect a principal diagnosis that is not related to an arrhythmia, but rather heart failure or cardiomyopathy.

Analysis of existing policies finds that some local carriers use only stand alone coding for MTWA testing, while others employ the primary and secondary pairing approach. Physicians/providers do not see the current coding as supportive to using MTWA as a risk stratifier in the most appropriate Medicare patients. With the expanded Medicare patient populations eligible for ICDs, the MTWA coding is now even more restrictive.

In its draft Coverage Guidance released on March 9, 2005, CMS outline factors to consider when requesting a NCD, including:

Local coverage policies are inconsistent or conflict with each other to the detriment of Medicare beneficiaries. For instance, the noted variation is not related to local differences in the capabilities of health care providers to use the technology effectively which can be resolved over time, but rather is causing significant disparities in the care available to Medicare beneficiaries that are unlikely to be addressed effectively through provider training and education or through the local coverage process;

Inconsistencies of ICD-9 coding to cover MTWA testing include:

- Only 2 states allow coverage for Heart Failure 428 series (CT, FL) as stand alone codes
    - 8 states allow Heart Failure as Secondary Diagnosis which must be paired with primary diagnosis codes that providers do not believe allows for use of MTWA
- Only 3 states allow coverage for Cardiomegaly 429.3 (NY, OH, WV)
- Family History V19.8 is allowed by 8 carriers but only with Secondary Diagnosis codes that providers do not believe allows for use of MTWA
- Old Myocardial Infarction 412 is not a covered indication in 38 of the states

Further inconsistency is seen even among states administered by the same Medicare Part B Carrier. For example:

- Cahaba GBA provides limited LCD coverage of MTWA for Georgia; Cahaba GBA states Alabama and Mississippi do not have LCD based coverage for MTWA;

- National Heritage Ins. Co. which administers Part B coverage for California as well as four New England States had originally established an LMRP that provided identical coverage in California and the New England states. In 2004 NHIC converted their MTWA LMRPs to LCDs, however, while NHIC California expanded coverage of MTWA in their LCD to include heart failure and cardiomyopathy codes NHIC for MA, NH, VT, & ME did not expand indications; and

- Arkansas BCBS has LCD coverage for 5 of the 6 states it administers yet has no LCD coverage for Rhode Island.

Recommendations for National Coverage Decision on Microvolt Twave Alternans

The recommended language for a national coverage policy on MTWA testing would be as follows:

Microvolt T-Wave Alternans testing is indicated for the risk stratification of patients meeting the CMS clinical guidelines for coverage of Implantable Cardioverter Defibrillator for primary and for secondary prevention of Sudden Cardiac Death (SCD). Microvolt T-wave alternans must be measured using the spectral analytic method and noise reducing multi-contact electrodes during exercise or pharmacologic stress or during cardiac pacing. Coverage is expanded to include but not limited to the following patient populations:

Secondary Prevention Group

Documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to transient or reversible cause,

Documented sustained ventricular tachyarrhythmia (VT), either spontaneous or induced by an EP study, not associated with an acute myocardial infarction (MI) and not due to a transient or reversible cause,

Primary Prevention Group

Documented familial or inherited conditions with a high risk of life - threatening VT, such as long QT syndrome or hypertrophic cardiomyopathy,

Coronary artery disease with a documented prior MI, a measured left ventricular ejection fraction (LVEF) =35%, *and inducible, sustained VT or VF at EP study.*

Documented prior MI and a measured LVEF =30%. (MADIT II group)

Patients with ischemic dilated cardiomyopathy (IDCM), documented prior MI, NYHA Class II and III heart failure, and measured LVEF = 35% (SCD HeFT type)

Patients with non-ischemic dilated cardiomyopathy (NIDCM) >9 months, NYHA Class II or III heart failure, and measured LVEF = 35% *(SCD HeFT type)*

Patients with non-ischemic dilated cardiomyopathy (NIDCM) > 3 *months,Class II or III heartfailure, and measured L VEF* = 35%. *(SCD HeFT type)*

Since all ICD eligible patients could be risk stratified with MTWA testing, the most appropriate ICD-9 codes for MTWA should mirror those recommendations issued by the Heart Rhythm Society on January 28, 2005 entitled "Diagnosis Codes for ICD Patients" (appendix 6).

Recommended Physician Supervision Level

Medicare LCD/LMRPs currently in existence have assigned MTWA testing as a Level 2 physician supervised diagnostic test. We recommend that an NCD continue to designate MTWA as Level 2, Direct Supervision:

Direct Supervision in the office setting means the physician must be present in the office suite and immediately available to furnish assistance and direction throughout the performance of the procedure. It does not mean that the physician must be present in the room when the procedure is performed.

Conclusion

In closing, I appreciate your review of this letter, and its accompanying documentation, and respectfully request a national coverage policy on MTWA. Please contact me at 781-271-1200 ext 277.

Sincerely yours,

David Chazanovitz

cc: Louis Jacques, MD
Director, Division of Items and Devices

[1] SCD and Cardiac Arrest endpoints only. Non-asterisked entries include SCD, Cardiac Arrest and Sustained Ventricular Tachycardia endpoints (including appropriate ICD discharge). SCD, sudden cardiac death; CHF, congestive heart failure; MI, myocardial infarction; LVEF, left ventricular ejection fraction; HR, Hazard Ratio.

The annual event rate, A, is used here to compare trials with different durations of follow-up. Ais derived from the data in the reported trials by setting the actuarial Event-Free Survival, S(T), at the end of the specified follow-up period, T, to the following formula: S(T) =exp(-AT). The Hazard Ratio (HR) is computed here as the ratio of the values of Afor MTWA+ versus MTWAgroups.
The values in the **All** row of the Table were computed as follows. N is the sum of all patients in the reported trials. The annual event rates represent averages of the annual event rates in each of the trials weighted by the number of patients in each trial. The Hazard ratio is the ratio of the average event rates. The Hohnloser[17] study in MADIT II type patients is excluded from the composite analysis because the patients from this study were all drawn from Klingenheben [10] and Ikeda [15, 16].

[2] Note - All quantities are computed as in Table I, except here the endpoint is all cause mortality rather than ventricular tachyarrhythmic events.