# BRIEFING DOCUMENT FOR THE MEDICARE COVERAGE ADVISORY COMMITTEE ON TRANSMYOCARDIAL REVASCULARIZATION

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## I. INTRODUCTION

As manufacturers and distributors of the two FDA-approved medical devices for transmyocardial revascularization (TMR), PLC Medical Systems, Inc., Edwards Lifesciences Corporation, and CardioGenesis Corporation are pleased to provide the industry perspective on the evidence supporting this important therapy. Significant progress has been made in the treatment of coronary artery disease (CAD), through medical therapy, percutaneous coronary interventions (PCI), and coronary artery bypass graft (CABG) surgery[†]. However, there remains a subset of patients with medically refractory angina caused by diffuse, distal CAD that cannot be resolved with direct revascularization. It is for these patients that TMR was developed.

A substantial body of data regarding TMR has been produced in multiple randomized, clinical trials (RCTs) (primary evidence), in nonrandomized studies (secondary evidence), and in observational or retrospective studies (tertiary evidence). The cumulative results through one year, and more recently through five years, validates the safety, effectiveness, and substantially improved health outcomes for TMR in the treatment of selected patients with refractory angina due to diffuse disease, either when used alone or as an adjunct to CABG in patients who would be incompletely revascularized by CABG alone. The Centers for Medicare and Medicaid Services (CMS) has provided coverage for beneficiaries in need of TMR since 1999.

[†] PCI and CABG therapies are sometimes referred to as direct revascularization.

Critical analyses of the available data by several well-qualified technical assessment bodies and physician specialty societies have concluded that the weight of the evidence favorably supports TMR for certain patients and/or that TMR provides significant angina relief in certain patients. These assessments or practice guidelines, listed in reverse chronological order, are as follows:

1) The Agency for Healthcare Research and Quality (AHRQ) Technology Assessment of Percutaneous Myocardial Laser Revascularization and Transmyocardial Laser Revascularization 2004;
2) Society of Thoracic Surgeons (STS) Workforce on Evidence-Based Surgery 2004;
3) ECRI Technology Assessment Report on Transmyocardial Laser Revascularization (TMR)/ Percutaneous Myocardial Laser Revascularization (PMR) for Treatment of Refractory Angina 2004[†];
4) American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines 2002 (published 2003);
5) Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center Assessment on TMR as an Adjunct to CABG Surgery for the Treatment of Coronary Artery Disease 2001, reviewed in 2004.

Enclosed is a comprehensive briefing document containing a discussion of the clinical evidence supporting TMR. This document only discusses TMR. PMR is an unapproved and non-covered technology, has not been established as an alternative to TMR, and has no demonstrated relationship to TMR. Due to the absence of FDA

[†] CMS is not providing the MCAC panel with the ECRI technology assessment. We are including the ECRI technology assessment as an attachment.

approval for any percutaneous myocardial revascularization (PMR) system, CardioGenesis Corporation, the developer of a PMR system, has requested that PMR not be considered by the Medicare Coverage Advisory Committee (MCAC) at this time.

## II. EXECUTIVE SUMMARY

On May 28, 2004, CMS announced its intention to convene the Medicare Coverage Advisory Committee (MCAC) on July 14, 2004, to discuss and provide recommendations regarding the scientific evidence available for TMR and PMR as treatments for severe angina. [Federal Register Notice May 28, 2004]. As detailed in the Federal Register notice, CMS requires that all materials submitted for consideration contain responses to the specific questions intended for MCAC review.

This section of the briefing document provides summary responses to the questions posed by CMS. An innovative question format has been presented by CMS, and we respond to the questions in the format provided. Section II.A includes the responses for TMR as sole therapy and Section II.B includes the responses for TMR as adjunctive therapy in patients who would be incompletely revascularized by CABG alone. Following a background review in Section III, concise summaries and discussions of the scientific technology assessments of TMR are provided in Section IV. Section V includes concise summaries and discussions of the significant clinical trial data supporting the responses to the MCAC questions.

A. **TMR As Sole Therapy**

1. How well does the evidence address the effectiveness of TMR in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?

☐ ☐ ☐ ☐ ■

Limited Moderate Complete

| 2. | How confident are you in the validity of the scientific data for this outcome? (no confidence = 1; moderate confidence =3; high confidence = 5) | How likely is it that TMR will improve this outcome (compared to Usual Care)? (not likely = 1; reasonably likely = 3; very likely = 5) |
|---|---|---|
| Short-Term Mortality | 4 | 1 |
| Long-Term Survival | 3 | 3 |
| Morbidity | 4 | 5 |
| Quality of Life | 4 | 5 |

3. How confident are you that TMR will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?

☐ ☐ ☐ ☐ ■

No Confidence Moderate Confidence High Confidence

4. Based on the literature presented, how likely is it that the results of TMR in the treatment of chronic, medically refractory angina can be generalized to:

The Medicare population (aged 65+):

| ☐ | ☐ | ☐ | ☐ | ■ |
|---|---|---|---|---|
| Not likely | | Reasonably Likely | | Very Likely |

Providers (facilities/physicians) in community practice:

| ☐ | ☐ | ☐ | ☐ | ■ |
|---|---|---|---|---|
| Not likely | | Reasonably Likely | | Very Likely |

B. **TMR + CABG**

1. How well does the evidence address the effectiveness of TMR+CABG in the treatment of chronic, refractory angina in study patients?

| ☐ | ☐ | ☐ | ■ | ☐ |
|---|---|---|---|---|
| Limited | | Moderate | | Complete |

| 2. | How confident are you in the validity of the scientific data for this outcome? (no confidence = 1; moderate confidence =3; high confidence = 5) | How likely is it that TMR + CABG will improve this outcome (compared to Usual Care)? (not likely = 1; reasonably likely = 3; very likely = 5) |
|---|---|---|
| Short-Term Mortality | 4 | 3 |
| Long-Term Survival | 3 | 2 |
| Morbidity | 4 | 3 |
| Quality of Life | 3 | 4 |

3. How confident are you that TMR + CABG will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?

| ☐ | ☐ | ☐ | ■ | ☐ |
|---|---|---|---|---|
| No Confidence | | Moderate Confidence | | High Confidence |

4. Based on the literature presented, how likely is it that the results of TMR + CABG in the treatment of chronic, medically refractory angina can be generalized to:

The Medicare population (aged 65+):

| ☐ | ☐ | ☐ | ☐ | ■ |
|---|---|---|---|---|
| Not likely | | Reasonably Likely | | Very Likely |

Providers (facilities/physicians) in community practice:

| ☐ | ☐ | ☐ | ☐ | ■ |
|---|---|---|---|---|
| Not likely | | Reasonably Likely | | Very Likely |

In addition to carefully evaluating the evidence, it is important for the MCAC panel to acknowledge that its responses to the questions will influence Medicare coverage of TMR. Given the effect that MCAC recommendations have on coverage decisions, we urge the panel to consider the implications of providing CMS with a basis for potentially reversing an existing coverage policy in the absence of compelling new, valid, scientific evidence that either a significant error was made in the original coverage decision or that TMR is unsafe or ineffective.

The issues raised by TMR's detractors (*e.g.*, lack of consensus regarding the mechanism of action, difficulty in precisely quantifying the incremental benefit of TMR when TMR is done as an adjunct to CABG) were debated when the initial coverage decision was made, at a time when results from multiple RCTs with one-year follow-up were available. The positive evidence for TMR and CABG + TMR has increased in the interim with supportive, positive, long-term follow-up data from multiple RCTs. Moreover, there is no compelling new evidence suggesting that CABG + TMR does not provide an incremental benefit over CABG alone to those suffering from angina caused by diffuse CAD, and there is no valid evidence that CABG + TMR is less safe than CABG alone.

Careful evaluation of the evidence supports the conclusion that TMR is safe and beneficial. Again, we urge the panel to answer the questions posed in a manner consistent with the evidence, which we believe supports continuing existing Medicare coverage for TMR as both a sole therapy and when performed in combination with CABG.

## III. BACKGROUND

### A. The Underlying Disease

The American Heart Association (AHA) estimates that 6,600,000 people in the United States suffer from angina pectoris (manifested as chest pain), which typically occurs when CAD causes the heart's oxygen demand to exceed the supply provided by the diseased coronary arteries. [AHA 2003 update]. Most patients who experience angina pectoris due to CAD are optimally treated with medical management, percutaneous coronary interventions (PCI), or coronary artery bypass grafting (CABG). Unfortunately, CAD is a debilitating, progressive disease that in its later stages sometimes cannot be managed with medications, PCI, or CABG. It has been reported that up to 12% of patients with CAD have medically refractory angina and are ineligible for PCI or CABG due to the presence of diffuse CAD and consequently suffer significant morbidity and mortality. [Muhkerjee 1999, 2001].

Aside from the patients who are ineligible for either PCI or CABG, some patients undergoing CABG are incompletely revascularized (*i.e.*, not all areas of ischemic myocardium are adequately grafted). It has been reported that incomplete revascularization following CABG procedures, caused by diffuse CAD, occurs at an incidence rate of up to 25%. [Weintraub 1994]. Moreover, it has been documented that diffuse CAD, appropriately quantified, is a significant and independent predictor of operative mortality, [Graham 1999] particularly in the elderly [Osswald 2001], and of perioperative adverse events. [Weintraub 1994, Graham 1999, Osswald 2001]. Additional studies have documented that diseased but non-grafted arteries have a significant negative influence on patient long-term, event-free survival (*i.e.*, absence of

death, recurrent angina, myocardial infarction, or the need for repeat CABG). [Bell 1992, Lawrie 1982, Schaff 1983].

### B. **Development of TMR**

The clinical problem of medically refractory, severe angina due to the presence of diffuse CAD, along with the inability to achieve a complete revascularization in a subset of CABG patients, prompted the search for successful therapies. Sen and other pioneers suggested therapies that mimicked the blood flow in the reptilian heart (*i.e.*, flow directly from the ventricle into the adjacent myocardium), and first described transmyocardial revascularization using hollow needles. [Sen 1965]. The next step in the development of modern techniques for TMR was the investigation of laser energy for transmyocardial channel creation. [Mirhoseini 1981, 1983]. Ultimately, carbon dioxide ($CO_2$) and holmium:yttrium-aluminum-garnet (Ho:YAG) laser systems were developed to perform TMR for the relief of refractory angina in patients having diffuse CAD in areas of the myocardium that are unsuitable for PCI or CABG. These systems represent the current state of the art in TMR delivery systems.

### C. **Patient Selection and TMR Surgical Technique**

Patients who undergo TMR have severe angina not controlled by optimal medical therapy and caused by an area of the heart that is not amenable to direct coronary revascularization. They generally have a poor quality of life, have had prior direct coronary revascularization, prior myocardial infarctions, and are more likely to have diabetes and multiple risk factors for CAD. TMR is performed under general anesthesia. Exposure of the heart for laser application in sole therapy is through a limited left anterior thoracotomy. Most TMR patients have had previous CABG procedures and therefore have thick scar tissue. The cardiothoracic surgeon must take care not to injure the left

phrenic nerve, left ventricle, epicardial vessels, as well as any grafts. Laser energy is applied to the free wall of the left ventricle. The $CO_2$ system uses a single energy pulse to create 1-mm diameter, transmurally-ablated channels in ischemic myocardium. The Ho:YAG system utilizes a fiber optic to deliver multiple pulses of laser energy to create 1-mm diameter, transmurally-ablated channels in ischemic myocardium. Laser channels are placed approximately every square centimeter in the distal two-thirds of the left ventricle, avoiding obviously scarred areas. After the laser channels are created, blood travels through the channels until a clot is formed on the epicardial surface.

### D. **Physiologic Mechanism of Action of TMR**

The underlying mechanism of clinical improvement from TMR is the source of ongoing scientific inquiry. Four mechanisms of action have been postulated: blood flow through patent channels, denervation (nerve disruption or remodeling), angiogenesis (the formation of new vessels from pre-existing vessels via cellular outgrowth), and the placebo effect. The patent channel theory is currently de-emphasised, and the consistent results in multiple, one-year RCTs, augmented by recently available five-year RCT results, render the placebo effect a less likely explanation of the persistent, long-term benefits of TMR. Furthermore, the placebo effect cannot explain the experimental [Horvath 1998, 2001] or clinical [Donovan 1997] improvement in function of chronically ischemic myocardium after TMR.

Overall, the scientific evidence suggests that denervation possibly plays a role in the immediate post-treatment phase, and that the most likely mechanism responsible for clinical improvement following TMR is angiogenesis. Below is a discussion of denervation and angiogenesis.

### 1. Denervation of Myocardium

Denervation refers to the loss or remodeling of myocardial neurons potentially resulting in decreased pain sensation. Kwong et al. first provided evidence of regional myocardial denervation two weeks following Ho:YAG TMR in a nonischemic canine model. [Kwong 1997]. But others, including Hirsch et al, were unable to demonstrate an acute effect of TMR on the increased neuronal activity elicited by the epicardial application of bradykinin or veratridine. [Hirsch 1999]. Minisi and colleagues demonstrated that left ventricular receptors with sympathetic afferent fibers remain intact after TMR and are capable of continuous transmission, thereby making denervation unlikely as the primary mechanism for the sustained clinical effect of TMR. [Minisi 2001]. In recent work in a chronic ischemic porcine model, TMR-treated myocardium had regional sympathetic denervation three days post-operatively, with reinnervation by six months. This study suggests that denervation may occur acutely, but that long-term clinical outcomes are probably not due to denervation. [Hughes 2004].

One hypothesis has suggested that if TMR produces regional denervation, clinically silent ischemia could be expected in the postoperative period. Hughes et al. studied 21 patients who underwent TMR. Forty-eight hours postoperatively they observed ischemic ECG changes that were clinically silent in more than half of the patients. [Hughes 1999]. But in a blinded core lab analysis of 182 symptom-limited exercise tests at baseline and one year following randomization to TMR or continued medical management, Myers and associates reported that TMR did not induce significant silent ischemia, and concluded that denervation may not be a significant factor contributing to long-term angina relief following TMR. [Myers 2002]. Therefore, these clinical observations confirm experimental observations that denervation appears to occur

acutely and mechanisms other than denervation appear to account for long-term clinical outcomes.

2. Angiogenesis

Angiogenesis is currently the leading mechanism of action theory for TMR's persistent benefits. Angiogenesis resulting from laser revascularization has been reported in both acute and chronic ischemic canine models. Yamamoto and colleagues correlated increased vascular growth resulting from laser tissue treatment to a significant increase in blood flow capacity. [Yamamoto 1997]. Using both $CO_2$ and Ho:YAG systems, one study identified evidence of new vascular growth in the vicinity of laser channel remnants two to three weeks following treatment in normal canine myocardium, manifested by a high proliferation of smooth muscle cells. [Kohmoto 1998].

Investigators at Duke University examined the neovascular response six months post-TMR using both $CO_2$ and Ho:YAG systems in a porcine model of hibernating myocardium, and reported significant increases in new vessels in lased regions. [Hughes 1998]. In an evaluation of their cumulative studies and findings, Hughes and Lowe indicate that TMR clearly induces neovascularization in lased regions, likely due to an upregulation of the angiogenic cascade secondary to an inflammatory response after laser treatment [Hughes 2002].

In an ischemic porcine model, TMR has also been shown to upregulate vascular endothelial growth factor (VEGF) messenger RNA and increase expression of other growth factors after TMR. [Horvath 1999]. Horvath et al. also showed improved resting function (as measured by dobutamine stress echo) after TMR in a chronic ischemic porcine model. [Horvath 1998]. These results were reinforced by a 2001 Horvath et al. study, which demonstrated that TMR provided significant recovery of ischemic

myocardial function (as measured by ventricular wall thickening at rest and with dobutamine stress echo) in an ischemic porcine model. Functional improvement suggests less myocardial ischemia, which is consistent with an increased blood supply to the myocardium from new vessels created through laser induced angiogenesis. These findings are consistent with the histologic examination of an explanted TMR-treated human heart in which multiple vessels within the channel remnant and adjacent to the channel were observed, with red blood cells present in the lumen. [Domkowski 2001].

Objective evidence of improved perfusion following TMR has been demonstrated in several but not all studies, and this evidence supports the angiogenesis mechanistic theory. Employing technitium sestamibi/thallium scans to determine the areas of scar (fixed defects) and ischemia (reversible defects) at one year, Schofield et al. noted no increase in the number of fixed defects in TMR patients, but a doubling of the number of fixed defects in the medically managed group over the same time frame, indicating that TMR resulted in a restoration of myocardial perfusion. [Schofield 1999]. Frazier et al. reported a 20% improvement in perfusion of previously ischemic areas in the TMR group and a 27% worsening of perfusion in the ischemic areas of the medical management group at 12 months ($p=0.002$). [Frazier 1999]. Horvath et al. also demonstrated an improvement in perfusion using dual isotope scanning at one year after TMR. [Horvath 1997]. Additionally, after N-13 ammonia positron emission tomography (PET) assessment, subendocardial perfusion improved significantly compared to subpericardial perfusion after TMR treatment. [Frazier 1995].

E. **FDA Approval of TMR Devices**

The United States Food and Drug Administration classifies both the $CO_2$ and Ho:YAG TMR laser systems as Class III medical devices. A Class III medical device is one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. [21 U.S.C. § 360c(a)(1)(C)]. All Class III devices are subject to the premarket approval (PMA) process of scientific review to ensure safety and efficacy. [*Id.*]. Both TMR laser systems went through the PMA process, including randomized, controlled clinical trials with one-year follow-up, and were found to be safe and effective for the treatment of a defined subset of angina patients.

The $CO_2$ laser system was approved in 1998, and it is indicated: " . . . for the treatment of patients with stable angina (Canadian Cardiovascular Society Class 3 or 4[†]) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium not amenable to direct coronary revascularization." [The Heart Laser PMA Supplement, 1999].

The Ho:YAG laser system was approved in 1999, and it is indicated: " . . . for treatment of stable patients with angina (Canadian Cardiovascular Society Class 4) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium with reversible ischemia not

[†]Canadian Cardiovascular Society (CCS) Class 3 is defined as a marked limitation of physical activity. Walking one to two level blocks and climbing one flight of stairs under normal conditions at a normal pace. CCS Class 4 is defined as maximal angina sometimes at rest; patients unable to carry out any physical activity without discomfort – anginal syndrome may be present at rest.

amenable to direct coronary revascularization." [Summary of Safety and Effectiveness Data, The TMR2000 (formerly The Eclipse) Holmium Laser System 1999].

F. **Medicare Coverage of TMR**

CMS issued a national coverage policy on TMR in July 1999, shortly after the FDA approvals. The national coverage policy appears in section 35-94 of the Coverage Issues Manual ("TRANSMYOCARDIAL REVASCULARIZATION (TMR) FOR TREATMENT OF SEVERE ANGINA -- COVERED"), which provides in part that:

> Transmyocardial revascularization (TMR) is a surgical technique which uses a laser to bore holes through the myocardium of the heart in an attempt to restore perfusion to areas of the heart not being reached by diseased or clogged arteries. This technique is used as a late or last resort for relief of symptoms of severe angina in patients with ischemic heart disease not amenable to direct coronary revascularization interventions, such as angioplasty, stenting or open coronary bypass. The precise workings of this technique are not certain . . . However, research at several facilities indicates that, despite this uncertainty, the technique does offer relief of angina symptoms for a period of time in patients for whom no other medical treatment offering relief is available. Studies indicate that both reduction in pain and reduction in hospitalizations are significant for most patients treated. Consequently, we have concluded that, for patients with severe angina (Class III or IV, Canadian Cardiovascular Society, or similar classification system) for whom all other medical therapies have been tried or evaluated and found insufficient, such therapy offers sufficient evidence of its medical effectiveness to treat the symptomatology. It is important to note that this technique does not provide for increased life expectancy, nor is it proven to affect the underlying cause of the angina. However, it appears effective in treating the symptoms of angina, and reducing hospitalizations and allowing patients to resume some of their normal activities of daily living. [Medicare Coverage Issues Manual Section 35-94].

Shortly after issuing the original coverage decision, which limits TMR coverage to FDA-approved indications for the lasers, CMS issued an addendum explaining that

TMR is covered in circumstances specified in the policy when used as an adjunct to CABG. The addendum, issued in an October 1999, provides as follows:

> In response to questions from practicing physicians, the Coverage and Analysis Group is posting this addendum to make it clear that, in cases where transmyocardial revascularization (TMR) is used as an adjunct to coronary artery bypass grafting (CABG), such use constitutes a covered use of TMR under the terms of our current manual instruction (CIM section 35-94). As outlined in that instruction, coverage is provided when TMR is used as a late or last resort for patients with severe angina caused by areas of the heart not amenable to surgical therapies, such as CABG. In cases where patients are scheduled for a CABG but are found, often during the procedure, to have areas of viable myocardium that cannot be bypassed because of diffuse or distal disease Medicare will cover adjunctive TMR in those areas refractory to the scheduled therapy. The areas of the myocardium involved are not amenable to CABG, and the laser is being used in accordance with its FDA approval for use in treating severe angina. This is consistent with other Medicare coverages of multiple surgical procedures in those cases where they are medically reasonable and necessary for the patient being treated. (emphasis added) [Addendum to TMR Coverage Decision Memorandum].

This addendum to the TMR coverage policy indicates that CMS recognized in 1999, based primarily on the data presented for FDA approval, that it was reasonable and necessary to cover TMR applied to areas of viable but diffusely-diseased, non-bypassable myocardium, even though other sections of the patient's myocardium could be served with a graft. As described below, more scientific evidence is available or emerging, confirming the benefit of TMR, and further supporting CMS' original decision to cover TMR as sole therapy and as an adjunct to CABG in selected patients.

## IV. SCIENTIFIC TECHNOLOGY ASSESSMENTS OF TMR

### A. CMS' Evaluation of the Scientific Evidence on TMR: AHRQ Technology Assessment of Percutaneous Myocardial Laser Revascularization and Transmyocardial Laser Revascularization

CMS, through AHRQ, commissioned the Duke Center for Clinical Health Policy Research and Evidence-based Practice Center to prepare a technology assessment

(AHRQ assessment) of TMR and PMR in preparation for the upcoming MCAC meeting. The stated purpose of this technology assessment is to provide a summary and description of the technology, a review of the peer-reviewed clinical literature on the outcomes associated with the use of TMR as sole therapy, CABG + TMR, and PMR, and a description of the mechanism of action studies for each of the procedures reviewed. Only the TMR and CABG + TMR aspects of the AHRQ assessment will be discussed in this briefing document, with the emphasis on the clinical literature review and mechanism of action studies and the associated conclusions.

AHRQ searched the medical literature and included in their review RCTs that report efficacy of TMR in terms of angina and/or survival. Observational studies reporting surgical complications related to TMR (*i.e.*, mortality and other serious complications such as cardiac tamponade, re-operation, and infection) and studies describing the nature of utilization of TMR (*i.e.*, TMR alone, CABG + TMR, patient eligibility criteria) were also reviewed.

After summarizing the results of the 8 RCTs, 19 observational studies, and three follow-up studies that met the AHRQ inclusion criteria, they formulated the following conclusions regarding TMR and CABG + TMR:

> TMR [as sole therapy] has been evaluated in seven clinical trials; all seven studies report significant improvement in the frequency and/or severity of angina after TMR, with no net improvement in survival [at one year]. Two trials with prolonged follow up suggest that symptomatic improvement is persistent, although other studies demonstrate a trend towards diminished relief after the first 6 months following TMR. The only benefit in survival following TMR as sole therapy compared to medical treatment has been found in a 5-year follow up of a multicenter, randomized experience. In addition to symptomatic relief, TMR was associated with an increase in exercise tolerance and quality of life. There were no consistent trends regarding the impact of TMR on admission for unstable angina, reduction in antianginal medications, cardiac events, or

other complications (in particular congestive heart failure that might follow myocardial tissue damage due to therapy). Any symptomatic benefit of TMR appears to be out of proportion to demonstrable improvement in myocardial perfusion. Only one of three trials that examined myocardial perfusion demonstrated some improvement in perfusion after TMR. Only one trial assessed the benefit of TMR plus CABG; this suggested that the addition of TMR significantly reduced mortality without influencing anginal symptoms. Although both groups realized significant angina relief through 1 year, 5-year follow up indicated that CABG plus TMR provided superior angina relief compared to CABG alone. Regarding the 12-month survival benefit, it appeared to be explained entirely by the lower rate of 30-day mortality in TMR plus CABG vs. CABG alone patients (1.5 percent vs. 7.6 percent).

Both clinical trials and observational studies provide information on the adverse effects of TMR. In clinical trials, 30-day mortality was variable, up to five percent. In observational studies, 30-day mortality was up to 15 percent, with 12-month mortality ranging between 13 percent and 25 percent. Risks appear to be higher in those patients with recent acute cardiac events, unstable angina, and depressed ventricular function.

In addition, there are some data from observational studies regarding utilization of the procedure. Notably, TMR – a procedure intended as palliative therapy for advanced refractory coronary disease – is frequently used for less severe patients in community practice. Approximately 25 percent of patients have angina that is not severe enough to satisfy FDA labeling requirements or Medicare coverage criteria for use of TMR.

The available studies have notable limitations. These include:

<u>Lack of a clear definition of "maximal medical therapy" prior to inclusion in a study and in the control arm of clinical trials</u>. It appears that a significant proportion of patients initially referred for TMR with refractory angina can be stabilized medically.

<u>Frequent treatment crossovers</u>. In two major trials, Frazier and colleagues and Allen and colleagues allowed crossovers from the medical therapy group to the TMR group. In the Frazier trial, crossover was allowed as "an incentive for patients assigned to maximal therapy to remain in the study if medical therapy failed."

<u>Frequent lack of blinding in outcomes assessment</u>. This could lead to an apparent increased therapeutic effect of TMR/PMR. Though it is evidently difficult (though not impossible) to blind patients to their treatment, it is feasible to blind the individual responsible for assessing trial outcomes, as was done in blinded validations of two trials at 1 year and in the randomized long-term follow-up studies.

<u>Presence of a placebo effect</u>. This is likely to be a powerful factor in an intervention such as TMR or PMR, particularly in early follow up. (emphasis in original) [AHRQ 2004].

Careful review of the AHRQ assessment reveals several problems with the methodology, data interpretation, and the above quoted conclusions. The next section of this briefing document addresses these concerns.

## B. **Criticism of the AHRQ Assessment**

### 1. Methodology and Data Analysis Problems

The AHRQ assessment extracts clinical trial results and experimental data from review articles (e.g., Saririan 2003; Huikeshoven 2002), rather than from the original published studies. These review articles are opinion papers and are not substitutes for the original published studies. Furthermore, the AHRQ assessment fails to mention the published national practice guidelines by the American College of Cardiology (ACC/AHA) and the Society of Thoracic Surgery (STS), two respected physician specialty societies. Each of these physician groups analyzed the original TMR RCTs and published their recommendations. It is inexplicable that the authors of the AHRQ assessment would rely on the Saririan and Huikeshoven review articles and not include the assessments of the American College of Cardiology and the Society of Thoracic Surgery in their data analysis.

The AHRQ assessment describes and summarizes studies in a significantly variable and sometimes incomplete manner. For example, few study summaries have a clear identification of primary and secondary endpoints, patient populations studied, and key outcome results. Most of the study summaries make no mention of enrollment criteria or endpoints, and they generally provide terse descriptions of results. Furthermore, some important studies are omitted from the review, including the Horvath sole therapy observational long-term study from 2001, and the Frazier CABG + TMR

trial from 1999. This lack of completeness and precision is concerning because such reporting can bias an assessment.

It is accepted in the medical and scientific community and by CMS that the level of evidence afforded by a RCT is superior to that afforded by prospective observational studies, and that prospective observational studies are in turn superior to retrospective observational studies. [Decision Memo for Electrostimulation for Wounds]. Despite this accepted understanding of clinical trial evidence strength, this assessment seems to downgrade the published one-year RCTs and five-year follow-up studies relative to retrospective or prospective observational studies. It is legitimate to consider recent studies examining practice patterns, however, these non-randomized studies should not supersede the observations and conclusions from multiple RCTs.

Significance data (i.e., p-values) are frequently lacking in the AHRQ discussion of randomized trials, and some key results from the trials are omitted that are necessary for a complete and unbiased understanding of the results. In addition, the review of observational studies on TMR as sole therapy is confusing, in part due to significant differences in the year in which the studies were performed and to variations in the patient populations. Studies conducted prior to the RCTs should be identified as early feasibility studies, and studies involving high-risk patients should be clearly identified. Section V of this briefing document (clinical scientific data on TMR) provides a more complete description of the relevant studies.

There are also deficiencies in the summary of experimental data. Animal studies are helpful in determining the laser-tissue interactions and the mechanisms of action of TMR. But in the AHRQ assessment, the type of animal model for the experimental

studies is not described. Large animal models in which there is chronic ischemia treated by laser revascularization are considered more valid and more readily translated to humans than a nonischemic rodent model, which provides minimal insight into the human application of TMR.

2. Problems with the AHRQ Conclusions

Certain conclusions in the AHRQ assessment are inconsistent with the data. For example, AHRQ states that "[t]wo trials with prolonged follow up suggest that symptomatic improvement is persistent, although other studies demonstrate a trend towards diminished relief after the first 6 months following TMR." The two trials referred to with prolonged follow-up are RCTs, each with 100 or more patients. The trials that AHRQ say demonstrate a trend toward diminished relief are single-center nonrandomized studies, with less than 50 patients and poor follow-up. It is incorrect for AHRQ to suggest that these very different types of studies can be used in a comparable manner to arrive at the above conclusion. Furthermore, AHRQ completely excludes a long-term, multicenter, observational, follow-up report by Horvath and colleagues, which was consistent with the two randomized follow-up studies in identifying significant and sustained angina relief and quality of life improvement in TMR patients.

Another dubious conclusion is the statement by AHRQ that "[i]t appears that a significant proportion of patients initially referred for TMR with refractory angina can be stabilized medically." AHRQ provides no basis for this conclusion, and there is nothing in the AHRQ assessment that supports this apparent opinion-based remark.

AHRQ also asserts the following regarding the two RCTs that permitted crossovers: "In the Frazier trial, crossover was allowed as 'an incentive for patients assigned to maximal therapy to remain in the study if medical therapy failed.'" This

quote supplied by ARHQ on the Frazier RCT does not provide complete information regarding the crossover aspect of the two RCTs that permitted crossovers. AHRQ fails to state that both trials had *a priori* crossover criteria. Also, ARHQ does not specify that the analyses in these two RCTs accounted for crossovers and yielded highly significant findings. Furthermore, the continued long-term follow-up by Allen through five years specifically accounts for crossovers. This conclusion is an incomplete and inaccurate assessment of the design of the RCTs.

Another AHRQ criticism of the design of the RCTs that is overstated and potentially misleading regards the lack of blinding of some of the RCTs. AHRQ's conclusion regarding blinding of the RCTs is as follows:

> This [lack of blinding] could lead to an apparent increased therapeutic effect of TMR/PMR. Though it is evidently difficult (though not impossible) to blind patients to their treatment, it is feasible to blind the individual responsible for assessing trial outcomes, as was done in blinded validations of two trials at 1 year and in the randomized long-term follow-up studies. [AHRQ 2004].

AHRQ de-emphasizes the fact that the Allen and Frazier sole therapy RCTs included blinded angina assessment validations at one-year and that the Allen five-year angina class assessments were conducted by blind evaluators. The Burkhoff RCT also included blinded angina assessments throughout the trial and a blinded core lab evaluation of exercise, and Allen's CABG + TMR trial blinded the patients through one-year. Given this information about blinding in the RCTs, this AHRQ conclusion demonstrates a significant disconnect between this concluding remark and the actual trial data and results.

AHRQ also inflates the importance of the placebo effect. They conclude that the placebo effect "is likely to be a powerful factor in an intervention such as TMR or PMR,

particularly in early follow up." Although the placebo effect likely influences early outcomes in any clinical trial involving innovative technology, it diminishes over the long-term. The significant one-year angina improvement results from multiple RCTs and the reported persistent significant angina relief beyond three years [Aaberge 2002] and five years [Allen 2004, Horvath 2001] following TMR suggest that the placebo effect is not the primary mechanism responsible for the enduring clinical benefits of TMR.

As for objective measures of TMR's efficacy, AHRQ states that "any symptomatic benefit appears to be out of proportion to any demonstrable improvement in myocardial perfusion." This statement is misleading. Perfusion and other objective measurements of demonstrable improvement have been obtained in both RCTs and nonrandomized studies. Furthermore, seeking a direct correlation between symptoms and perfusion may be a fallacy, because surgeons frequently see patients who have a single branch artery with a critical stenosis that causes severe symptoms, while numerous other patients are asymptomatic and have severe three-vessel CAD.

Further, it is incorrect for AHRQ to state that "only one of three trials that examined myocardial perfusion demonstrated some improvement in follow-up." Admittedly, not all of the RCTs had perfusion as an end-point. AHRQ acknowledges a 20% improvement in perfusion to the ischemic myocardium in the TMR treated patients relative to a 27% worsening of perfusion in the medical management group in the Frazier RCT. [Frazier 1999]. But in addition to the Frazier study, Schofield reported a decrease in ischemic myocardium after TMR treatment [Schofield 1999]. A careful reading of the Schofield paper indicates that a significant number of ischemic segments in the TMR patients became normal over the year of follow-up. A similar decrease in the number of

ischemic segments in the medical management patients led to a doubling of the infarcted segments, without an increase in normal perfusion. These findings suggest a restoration of myocardial perfusion in the TMR group.

In addition, surrogates for increased perfusion, exercise tolerance and time to angina, were significantly improved in the Aaberge RCT. [Aaberge 2000]. Two hundred TMR patients from a nonrandomized multi-centered trial also demonstrated a significant improvement in perfusion at 3, 6, and 12 months postoperatively [Horvath 1997]. Additionally, Cooley, et al. demonstrated improved perfusion by positron emission tomography. [Cooley 1996]. Donovan et al. demonstrated with dobutamine stress echo an improved wall motion stroke index at rest and an even more marked improvement with stress without an increase in the infarcted areas, along with a significant decrease in the ischemic areas in patients treated with sole therapy TMR. [Donovan 1997]. Horvath et al. have further confirmed this improvement in regional contractility using contrast enhanced and CINE MRI. [Horvath 2000].

Finally, the overall strength of AHRQ's assertions and conclusions is limited, as it does not provide any value-added analytical assessment of the data beyond a literature survey. AHRQ's approach is contrasted with the recent technical assessment performed by ECRI (see below Section IV.C.2.), which includes meta-analyses on mortality and angina relief from the sole therapy RCTs, as well as confirmatory sensitivity analyses of the angina relief outcomes.

### C. Other Scientific Technology Assessments and Physician Specialty Society Practice Guidelines on TMR

To our knowledge, there are currently two additional technology assessments and two physician specialty society practice guidelines evaluating the scientific evidence on

TMR as sole therapy and/or TMR as an adjunct to CABG. These four published technology assessments or practice guidelines are as follows[†]:

- STS Workforce on Evidence-Based Surgery 2004;
- ECRI 2004;
- ACC/AHA Task Force on Practice Guidelines 2002 (published 2003);
- BCBSA TEC 2001, reviewed 2004.

These four assessments are publicly available and are discussed below.

1. STS Workforce on Evidence-Based Medicine 2004

The most recent and publicly available assessment was conducted by the STS Workforce on Evidence-based Medicine, published in the Annals of Thoracic Surgery. [Bridges 2004]. This national practice guideline includes a review of the published evidence on TMR as sole therapy and as an adjunct to CABG, and includes evidence-based recommendations for appropriate therapeutic applications of TMR. Adopting the same grading scheme as the ACC/AHA, STS recommends sole therapy TMR in patients with chronic, stable angina and classifies the treatment as Class I (evidence or general agreement that a given procedure or treatment is useful and effective), and assigns a level of evidence A (high, data derived from multiple randomized clinical trials with large numbers of patients).

For adjunctive TMR, STS classifies treating patients with chronic, stable angina as Class IIA (the weight of the evidence is in favor of usefulness/efficacy), and assigns a level of evidence B (data derived from a single randomized clinical trial or from several nonrandomized studies).

[†] The technology assessments and practice guidelines will both be referred to as "assessments."

The overall conclusion of the STS Workforce was as follows: "Transmyocardial laser revascularization may be an acceptable form of therapy for selected patients: as sole therapy for a subset of patients with refractory angina and as an adjunct to coronary artery bypass graft surgery for a subset of patients with angina who cannot be completely revascularized surgically." [Bridges 2004].

2. ECRI Technology Assessment 2004

ECRI is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization, and has been designated, like BCBSA, an Evidence-based Practice Center (EPC) by AHRQ. ECRI prepared a technology assessment for Tricare, titled: *Transmyocardial Laser Revascularization (TMR)/Percutaneous Myocardial Laser Revascularization (PMR) for Treatment of Refractory Angina*. [ECRI 2004]. The technology assessment was submitted to Tricare in October 2003 and was made available to the public in a slightly different format in January 2004. It is anticipated that Tricare will use this technology assessment to initiate a coverage policy revision on TMR.

The ECRI technology assessment includes a comprehensive analysis of the available data on TMR and TMR as an adjunct to CABG, and states that "[f]or patients with heart disease accompanied by refractory angina, reduction in angina symptoms is an important health outcome." [ECRI 2004]. ECRI poses a series of questions related to TMR, but the question asked that was most related to the MCAC evaluative questions is as follows: "Is TMR plus standard medical therapy more effective than standard medical therapy for treatment of refractory angina? ECRI's answer to this question is as follows: "TMR plus medical therapy is more effective than medical therapy alone for relief of angina symptoms in patients with refractory angina." [ECRI 2004]. Citing their random-

effects meta analysis of the five RCTs comparing TMR and medical therapy at one year, ECRI found "a large and statistically significant increase in the proportion of patients with a reduction of two or more angina classes in the TMR group compared to the standard-therapy group (odds ratio=9.30, 95% CI 4.62 to 18.54, $p<0.0000001$)." The ECRI assessment continued to state that "TMR [alone] does not improve one-year survival or overall hospitalization rates, but it does significantly reduce hospitalizations for unstable angina."

Regarding TMR + CABG, the ECRI assessment concluded that "[f]or patients who are eligible for TMR plus CABG, we conclude that this treatment appears to be more effective than CABG alone at improving one-year survival [and that] the strength of the evidence supporting this conclusion is moderate." The assessment continues to state that "present evidence does not suggest that TMR plus CABG reduces angina symptoms or increases exercise tolerance more than CABG alone. However, the possibility that a small proportion of patients may receive a benefit in reduced angina symptoms cannot be ruled out." [ECRI 2004]. Of note is that the ECRI assessment did not benefit from peer-reviewed, long-term follow-up reports of three randomized controlled trials (one sole therapy [Allen 2004], two adjunctive therapy [Frazier 2004[†], Allen 2004[‡]]) that were not published or available at the time that these four assessments were conducted. The Allen five-year CABG + TMR follow-up data is particularly significant in that CABG+TMR patients had a significantly lower mean angina score at five years compared to CABG

[†] This paper is scheduled for publication in the Texas Heart Institute Journal 2004, Vol. 31, No. 3 (September 2004).
[‡] This paper is scheduled for publication in the Annals of Thoracic Surgery 2004, Vol. 78, (August 2004).

alone patients and there were significantly fewer CABG + TMR patients with severe angina (class III/IV) at five years relative to the CABG alone group.

3. ACC/AHA Task Force on Practice Guidelines 2002

The ACC/AHA technology assessment of TMR, conducted by the ACC/AHA Task Force on Practice Guidelines, was published in *Circulation* in 2003. [Gibbons 2002]. The task force recommends TMR with a Grade IIA (the weight of the evidence is in favor of usefulness/efficacy), and a level of evidence A recommendation (high, data derived from multiple randomized clinical trials with large numbers of patients). The overall conclusion reached by the ACC/AHA was as follows:

> The surgical TMR technique has generally been associated with improvement in symptoms in patients with chronic stable angina. The mechanism for improvement in angina symptoms is still controversial. Possible mechanisms for this improvement include increased myocardial perfusion, denervation of the myocardium, stimulation of angiogenesis, or perhaps some other unknown mechanism.

Citing one randomized trial of adjunctive TMR, the ACC/AHA states that "one year survival was better in the combination therapy group", and "angina relief and exercise treadmill improvement were no different at 12 month follow-up."

4. BCBSA Technology Assessment 2001

The Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC) is an AHRQ Evidence-based Practice Center (EPC). It issued a technical assessment of adjunctive TMR in May 2001, entitled: *TMR as an Adjunct to CABG Surgery for the Treatment of Coronary Artery Disease.* [BCBSA 2001]. BCBSA has recently revisited its TMR + CABG policy and stated that it "intends to revisit its assessment of TMR + CABG in the future and hopes that the results of a confirmatory trial will be available within 3 to 5 years." [Letter from N. Aronson to K. Horvath]. In

the meantime, the most recent BCBSA TMR + CABG technology assessment is the 2001 assessment. The overall conclusion by BCBSA in their 2001 technology assessment regarding TMR + CABG was as follows:

> Current evidence supports TMR as an adjunct to CABG for patients with CABG as a standard of care but with one or more areas of reversible ischemia not amenable to bypass grafting, due to diffuse or distal disease. The major benefit is an absolute decrease in perioperative mortality by 6%, which continues to remain statistically significant at 1-year follow-up. There does not appear to be any increased morbidity associated with adding TMR to CABG. Unlike prior studies evaluating TMR as sole therapy for patients with intractable angina who were not candidates for CABG, there was no benefit seen in symptoms when comparing TMR plus CABG to CABG alone. However, both groups of patients did have decreased anginal class and increased cardiac perfusion and exercise tolerance. [BCBSA 2001].

It is important to reiterate that these four assessments did not benefit from three RCTs (one sole therapy [Allen 2004], two adjunctive therapy [Allen 2004 {in press}, Frazier 2004 {in press}]) that were not published at the time these four assessments were conducted. These important long-term follow-up studies are discussed in Section V (clinical scientific data) of this briefing document. Despite the fact that these assessments did not have the benefit of the long-term follow-up from these three RCTs, the assessments all indicate that the weight of the evidence favors the use of TMR as sole and/or adjunctive therapy in selected patients.

## V. CLINICAL SCIENTIFIC DATA ON TMR FOR SEVERE ANGINA AND RESPONSES TO THE MCAC EVALUATIVE QUESTIONS

### A. TMR as Sole Therapy for CAD

#### 1. Primary Evidence: Randomized, Controlled, Clinical Trials

Five prospective, controlled trials involving 937 randomized patients have evaluated sole therapy TMR plus optimal medical management in comparison to optimal medical management alone. [Frazier 1999, Allen 1999, Aaberge 2000, Burkhoff 1999,

Schofield 1999]. Patients were suffering from Class III or IV angina despite optimal medical treatment, and were not candidates for CABG or PCI because of distal, diffuse coronary artery disease. Inclusion and exclusion criteria were similar among the trials. Exclusion criteria common to all the trials were depressed left ventricular ejection fraction (<25% or <30%), absence of reversible ischemia on myocardial perfusion scan, overt or uncompensated heart failure, inability to undergo study tests, and conditions precluding thoracic surgery. Two trials (Allen and Burkhoff) also excluded patients with clinically significant ventricular arrhythmias, recent myocardial infarctions, or recent change in antianginal drugs or anginal pattern. Patients were randomly assigned 1:1 to one of two arms, and were followed through one year. Three of these trials (Frazier, Allen, and Aaberge) have long-term follow-up evaluations, with each demonstrating significant and sustained relief of angina in TMR patients. [Horvath 2001; Allen 2004; Aaberge 2002]. A discussion of these long-term outcomes is also provided below. Patient demographics are illustrated in Table 1 and key outcomes are summarized in Table 2.

**Table 1. Patient demographics in the five randomized, controlled trials of sole therapy TMR**

| | Frazier | Allen | Burkhoff | Aaberge | Schofield |
|---|---|---|---|---|---|
| BASELINE CHARACTERISTICS | | | | | |
| Number of centers | 12 | 18 | 16 | 1 | 1 |
| Patients (N) | 192 | 275 | 182 | 100 | 188 |
| Crossover allowed | Yes | Yes | No | No | No |
| Age (mean years) | 61 | 60 | 63 | 61 | 60 |
| Male gender | 81% | 74% | 89% | 92% | 88% |
| Ejection fraction (mean) | 0.50 | 0.47 | 0.50 | 0.49 | 0.48 |
| Class III/IV | 31%/69% | 0%/100% | 37%/63% | 66%/34% | 73%/27% |
| CHF | 34% | 17% | nr | nr | 9% |
| Diabetes | 40% | 46% | 36% | 22% | 19% |
| Hyperlipidemia | 57% | 79% | 77% | 76% | nr |
| Hypertension | 65% | 70% | 74% | 28% | nr |
| Prior myocardial infarction | 82% | 64% | 70% | 70% | 73% |
| Prior CABG | 92% | 86% | 90% | 80% | 95% |
| Prior PCI | 47% | 48% | 53% | 38% | 29% |
| OPERATIVE RESULTS | | | | | |
| No. of channels (median) | 36 | 39 | 18 | 48 | 30 |
| Operative mortality | 3.3% | 5.3% | 1.1% | 4.0% | 3.3% |

**Table 2. Published 12-Month Results in Randomized Clinical Trials of TMR as Sole Therapy Versus Medical Management Alone**

| RCT (Author) | Number of Patients | Crossover Allowed? | Laser | Symptomatic Improvement: % of Patients With a Decrease of ≥ 2 CCS Angina Classes: TMR vs. MM (p value) | Objective measures: Change in Exercise Time (s): TMR vs. MM (p value) or Change in Perfusion: TMR v. MM (p value) | Quality of Life: TMR vs. MM (p value) (Assessment) | Survival: TMR vs. MM (p value) |
|---|---|---|---|---|---|---|---|
| Frazier | 192 | Yes | $CO_2$ | 72 vs. 13 (p < 0.001) | Perfusion: +20% vs. -27% perfusion (p = 0.002) | 38% vs. 6% (p < 0.001) (SF-36) | 85% vs. 79% (p = NS) |
| Allen | 275 | Yes | Ho:YAG | 76 vs. 32 (p < 0.001) | Exercise capacity: 5.0 vs. 3.9 METS (p = 0.05) | 21% vs. 12% (p = 0.003) (Duke Activity Status Index) | 84% vs. 89% (p = NS) |
| Aaberge | 100 | No | $CO_2$ | 39 vs. 0 (p < 0.01) | Exercise time: + 8 vs. –10 (p = NS) Time to Chest Pain: (p <0.01) | NA | 88% vs. 92% (p = NS) |
| Burkoff | 182 | No | Ho:YAG | 61 vs. 11 (p < 0.0001) | Exercise time: + 65 vs. – 46 (p < 0.0001) | Better throughout study for TMR vs. MM (p < 0.001) (Seattle Angina Questionnaire) | 95% vs. 90% (p = NS) |
| Schofield | 188 | No | $CO_2$ | 25 vs. 4 (p < 0.001) | 40 s longer in TMR patients (p = 0.15) Test stopped for angina: 43% vs. 70% (p < 0.001) | NA | 89% vs. 96% (p = NS) |

a. Frazier et al. RCT

In a prospective, controlled trial conducted at 12 U.S. centers, Frazier et al. randomized 192 patients with Canadian Cardiovascular Society (CCS) class III or IV angina to either $CO_2$ TMR plus optimal medical management or to optimal medical management alone (MM). Angina was classified in a blinded manner by an independent evaluator. The majority of patients (>65%) were in CCS class IV at baseline. This trial permitted crossover from the MM arm to the TMR arm provided the *a priori* treatment

failure criteria were met (requiring intravenous anti-angina therapy and inability to be weaned from them for at least 48 hours). At one year, significantly more patients in the TMR group than in the MM group had a reduction in angina of two or more classes (72% vs. 13%, $p<0.0001$). Patients in the TMR group also had significantly improved quality of life according to the SF-36 questionnaire as compared to the MM group ($p<0.001$). Myocardial perfusion, as measured by thallium 201 single-photon emission computed tomographic imaging, improved by 20% in the TMR group and worsened by 27% in the MM group at 12 months ($p=0.002$). In the first year of follow-up, 2% of the patients assigned to undergo TMR were hospitalized because of unstable angina, compared with 69% of the MM patients ($p<0.001$). The perioperative mortality rate was 3%, and was significantly predicted by the occurrence of unstable angina. Although one-year survival rates were similar between TMR and MM groups (85% vs. 79%, $p=0.50$), investigators observed significantly increased event-free survival (freedom from death, acute myocardial infarction, unstable angina, or class IV angina) in TMR vs. MM patients (66% vs. 11%, $p<0.001$).

Horvath and colleagues followed 78 TMR patients from the original trial for an average of five years (and up to seven years). [Horvath 2001]. The average pre-TMR angina class for these patients was $3.7 \pm 0.4$. After a mean of five years angina class was significantly improved to a mean of 1.6 ($p<0.0001$). This was unchanged from the mean class at one year (1.5, p=ns). Also at this long term follow-up, there was a significant and sustained improvement in angina class distribution: 68% of patients had a decrease of at least two angina classes, 81% of patients were in class II or better, and 17% were angina-free. Seattle Angina Questionnaire (SAQ) scores improved by an average of 170% from

the baseline assessment. These long-term data confirm that the relief of angina is both significant and sustained in study patients.

b. Allen et al. RCT

In a prospective, controlled trial conducted at 18 U.S. centers, Allen et al. randomized 275 patients with Canadian Cardiovascular Society (CCS) class IV angina to either Ho:YAG TMR plus optimal medical management or to optimal medical management alone (MM). This trial permitted crossover from the MM arm to the TMR arm provided the *a priori* treatment failure criteria were met (requiring intravenous anti-angina therapy and inability to be weaned for at least 48 hours). At one year, significantly more patients in the TMR group than in the MM group had a reduction in angina of two or more classes (76% vs. 32%, $p<0.0001$). Patients in the TMR group also had significantly improved quality of life according to the Duke Activity Status Index (DASI) as compared to the MM group ($p<0.001$). An independent laboratory conducted a masked assessment of angina and quality of life at 12 months. Myocardial perfusion, as measured by thallium scanning, showed no differences between groups.

Exercise tolerance times were significantly higher in the TMR than in the MM group at one year ($p=0.05$). The overall perioperative mortality rate was 5%, and was reduced to 2% in the last 100 randomized patients due to refinement of surgical technique. Although one-year survival rates were similar between TMR and MM groups (84% vs. 89%, $p=0.23$), investigators observed significantly higher rates of survival free of cardiac events (54% vs. 31%, $p<0.001$), freedom from treatment failure (73% vs, 47%, $p<0.001$), and freedom from cardiac-related hospitalization (61% vs. 33%, $p<0.001$) in TMR vs. MM patients.

Allen and colleagues recently published their multicenter, five-year follow-up of this study, involving 212 randomized patients. [Allen 2004]. To eliminate the potential for assessment bias in this long-term follow-up, blinded independent assessors performed angina assessments across centers. Due to the fact that 26% of MM patients met the *a priori* treatment failure criteria and crossed over to receive TMR while unstable, analyses were conducted to retain the crossover patients within their original randomized arm (intention to treat) as well as to evaluate them as a separate group (three-group analysis). Consistent with the one-year follow-up results, intention to treat analyses determined that significantly more TMR than MM patients continued to experience at least a two-class angina improvement from baseline (88% vs. 44%, $p<0.001$) or were free from angina symptoms altogether (33% vs. 11%, $p=0.02$) at a mean of five years. In the three-group analysis, improvement in angina among randomized TMR patients was superior to that observed for MM patients excluding crossovers (88% vs. 37%, $p<0.001$). Five-year Kaplan-Meier survival was significantly increased for patients randomized to TMR compared to MM (65% vs. 52%, $p=0.05$), with a significantly lower annualized mortality rate for TMR compared to MM patients beyond one year (8% vs. 13%, $p=0.03$). Importantly, the investigators found that freedom from angina at one year and angina improvement at one year were significantly predictive of long-term freedom from angina and the survival benefit observed in randomized TMR patients, respectively. No differences between groups in antianginal medication usage were observed. These long-term data confirm that the relief of angina is both significant and sustained in patients randomized to TMR compared to medical therapy, and demonstrate a survival benefit to sicker, Class IV patients who are initially randomized to TMR.

c. Aaberge et al. RCT

In a prospective, controlled trial conducted at one Norwegian center, Aaberge et al. randomized 100 patients with New York Heart Association (NYHA) class III or IV angina to either $CO_2$ TMR plus optimal medical management or to optimal medical management alone (MM). The majority of patients (>70%) were in class III at baseline. At one year, significantly more patients in the TMR group than in the MM group had a reduction in angina of two or more classes (39% vs. 0%, $p<0.01$). Exercise tolerance times were similar at one year, however, time to chest pain was significantly higher in the TMR than in the MM group at one year ($p<0.01$), and angina was reported as an exercise-limiting factor in significantly fewer TMR than MM patients ($p<0.01$). The overall perioperative mortality rate was 4%. The one-year survival rates were similar between TMR and MM groups (88% vs. 92%, p=ns).

Aaberge and colleagues published their long-term follow-up of this study, involving 100 randomized patients. [Aaberge 2002]. Consistent with the one-year follow-up results, analyses at a mean follow-up time of 43 months determined that significantly more TMR than MM patients continued to experience at least a two-class angina improvement from baseline (24% vs. 3%, $p<0.001$), and significantly more TMR than MM patients were in class II or better (60% vs. 24%, $p<0.01$). Hospitalizations for unstable angina were significantly reduced in TMR versus MM patients ($p<0.05$). Long-term follow-up revealed similar mortality rates for the TMR (22%) and MM (24%) groups. These long-term data confirm that the relief of angina is both significant and sustained in patients randomized to TMR compared to medical therapy.

d. Burkhoff et al. RCT

In a prospective, controlled trial conducted at 16 U.S. centers, Burkhoff et al. randomized 182 patients with Canadian Cardiovascular Society (CCS) class III or IV angina to either Ho:YAG TMR plus optimal medical management or to optimal medical management alone (MM). Unique to this trial was the exclusion of patients who did not have least one area of protected myocardium. At one year, significantly more patients in the TMR group than in the MM group had a reduction in angina of two or more classes (61% vs. 11%, $p<0.0001$). Similarly, as assessed by a blinded, independent evaluator, improvement to CCS class II or better was reported in significantly more TMR than MM patients (48% vs. 14%, $p<0.001$). Patients in the TMR group also had significantly improved quality of life according to each component of the Seattle Angina Questionnaire (SAQ) as compared to the MM group at one year ($p<0.001$). Myocardial perfusion, as measured by thallium scanning, showed no differences between groups. As evaluated by a blinded core laboratory using a modified Bruce treadmill protocol, exercise time increased significantly in TMR compared to MM (65 sec vs. -46 sec, $p<0.0001$). The overall perioperative mortality rate was 1%. The one-year survival rates were similar between TMR and MM groups (95% vs. 90%, p=ns).

e. Schofield et al. RCT

In a prospective, controlled trial conducted at one UK center, Schofield et al. randomized 188 patients with CCS class III or IV angina to either $CO_2$ TMR plus optimal medical management or to optimal medical management alone (MM). The majority of patients (>70%) were in class III at baseline. At one year, significantly more patients in the TMR group than in the MM group had a reduction in angina of two or more classes (25% vs. 4%, $p<0.001$). Exercise times using a modified Bruce treadmill exercise test

and a 12-minute walk test were similar between groups at one year. However, the treadmill test was stopped more frequently for angina among MM than TMR patients ($p<0.001$), and nitrate usage and frequency of angina during or after the walk test were significantly lower in TMR than MM patients ($p \leq 0.04$). The overall perioperative mortality rate was 5%. The one-year survival rates were similar between TMR and MM groups (88% vs. 96%, p=ns).

Interestingly, Schofield reported a decrease in ischemic myocardium in the TMR group and the medical management group. A significant number of ischemic segments in the TMR patients became normal over the year of follow-up, but a similar decrease in the number of ischemic segments in the medical management patients led to a doubling of the infarcted segments, without an increase in normal perfusion. This finding suggests a restoration of myocardial perfusion in the TMR group.

2. Secondary Evidence: Nonrandomized Studies

a. Patients with Stable Angina

Several early feasibility and development studies were conducted prior to the randomized controlled trials. Additional small, single-center studies have been performed during or after the conduct of the randomized trials. Studies with fewer than 25 patients are not included in this review.

- Horvath reported results from 200 patients who underwent TMR at 8 sites in the U.S. [Horvath 1997]. Significant reductions in angina class, hospital admissions for angina, and number of perfusion defects in the treated left ventricular free wall were observed through one year. Operative mortality was 9%.
- Schneider reported results from 41 patients who underwent TMR at a single center in Germany. [Schneider 2001]. Of these 41 patients, 14 received TMR alone and 27

underwent adjunctive TMR. Only 50% of TMR alone (n=8) and 22% of adjunctive TMR patients (n=6) were available for follow-up at 36 months. Angina class was reduced from baseline (mean 3.5) following TMR alone at 18 months (mean 1.7) and 36 months (mean 2.4); and after adjunctive TMR at all time points (mean 1.7). Significant changes in thallium scintigraphy, ejection fraction, or exercise tolerance were not observed in patients who were available to undergo these assessments. The perioperative mortality was 0%, and the mortality at 36 months was 36% and 11% following TMR alone and adjunctive TMR, respectively.

- DeCarlo reported results from 34 patients who underwent TMR at a single site in Italy. [DeCarlo 2000]. Significant improvements in angina class, cycle ergometer exercise, and hospitalization rates were observed in 23 patients followed to one year. Actuarial survival was 76% at three years.

b. Patients with Unstable Angina

In addition to the Allen and Frazier RCTs, several early feasibility and development studies evaluated TMR in higher risk groups, including patients with unstable angina.

- Allen presented information on 42 patients with Class IV refractory angina who received TMR while stable (n =23) or unstable (n=19), unable to be weaned from intravenous nitroglycerin. [Allen 1998]. Mean length of stay was 5.5 days. Mean angina class significantly improved through six months in both groups to 1.1 ± 0.1 ($p<0.001$). Overall operative mortality was 12%, with no late deaths.
- Dowling reported outcomes of TMR performed at 14 centers in 85 Class IV patients with unstable angina. [Dowling 1998]. At one year, 75% of patients had class II angina

or better, and mean angina class improved significantly to 1.6 ± 1.3 ($p<0.001$). Operative and one-year mortality rates were 12% and 22%, respectively.

- Nagele reported outcomes following TMR performed in 60 patients with refractory angina (mean class 3.3). [Nagele 1998]. At three months (n=49) mean angina class improved to 1.8 ± 0.8; at three years, angina class was 2.6 ± 0.9, but only 19 patients (32%) were available for assessment. Positron emission tomography data showed no improvement in patients who underwent the assessment at six months. Operative and 3-year mortality rates were 12% and 30%, respectively.
- Burkhoff reported single-center outcomes following TMR performed in 132 patients with refractory angina. [Burkhoff 1999, J Am Coll Cardiol]. Approximately half of the patients enrolled had unstable angina. Each vascular territory was graded at baseline as either having (AMP=1) or not having (AMP=0) blood flow through an unobstructed major vessel in the territory. Overall 30 day mortality and one year mortality were 12% and 22%, respectively, both of which were significantly predicted by AMP=0 ($p \leq 0.002$).
- Hattler reported outcomes following TMR performed in 76 patients with refractory unstable angina, and compared their outcomes with 91 stable patients receiving TMR during the same period. [Hattler 1999]. Significant improvement in angina class (two or more classes from baseline) was observed in patients who received TMR while unstable at 3 months (69%), and at 6 and 12 months (82% and 82%), and was similar to stable patients who received TMR. Operative mortality in unstable and stable patients was 16% and 3%, respectively ($p=0.005$). However, mortality after 30 days and to one year was similar between groups (13% and 11%, respectively [$p=0.83$]).

### 3. Tertiary Evidence: Registries and Retrospective Studies

- Burns et al. presented results in 1999 from a non-U.S. registry based on data that was collected prior to the randomized trials conducted in the U.S. to support FDA approval. [Burns 1999]. The authors report data from 16 of 22 European and Asian centers on 932 patients (80% sole therapy) registered with the Transmyocardial Laser Revascularization International Registry. Substantial variability in the quality of reporting across centers was noted. Operative mortality was 9.7%. Of the patients surviving and evaluated at one year, 34% improved by $\geq$ 2 angina classes from baseline. Patients having treadmill exercise data showed an increase of 30% in total time at one year.
- Peterson identified a total of 3,717 patients receiving TMR using either the FDA-approved $CO_2$ or Ho:YAG laser system at 173 U.S. hospitals voluntarily participating in the Society of Thoracic Surgeons (STS) Adult Cardiac Database. [Peterson, 2003]. Of the 3,717 patients receiving TMR, 661 patients received TMR as sole therapy. The overall number of sites performing TMR increased from 33 (7% of total STS sites) in 1998 to 131 (36% of sites) in 2001, subsequent to the FDA approvals of the two systems in late 1998 and 1999 and the initiation of Medicare coverage in 1999 and 2000. The overall mortality rate following TMR in the 661 sole-therapy patients was 6.4%. Operative mortality was increased in 413 of those patients with recent myocardial infarction, unstable angina, or depressed ventricular function (7.9%), which is consistent with and somewhat improved compared to the operative mortality rates for unstable angina observed in clinical studies conducted prior to FDA approval (9% to 22%). [Dowling 1998, Allen 1999, Frazier 1999, Hattler 1999]. When evaluating 243 patients

without these risk factors, the operative mortality rate was reduced to 3.7%, similar to the operative mortality rate observed across the five RCTs (1% to 5%).

4. MCAC Evaluative Questions for TMR as Sole Therapy

The cumulative data from five prospective, randomized clinical trials with 937 patients comparing TMR as sole therapy to medical management represents a systematic gathering of clinical outcome data for a therapy applied in isolation against a control group. As discussed below, this evidence more than adequately addresses the evaluative questions posed to the MCAC. The first section on the list of MCAC -- TMR Evaluative Questions concerns TMR as sole therapy for refractory angina. The first question asks, "How well does the evidence address the effectiveness of TMR in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?" The five answer choices for this question are listed on a continuum from limited to moderate to complete.

Based on the five well-designed, prospective, RCTs evaluating TMR, the answer to this first question is that the evidence completely addresses the effectiveness of TMR in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated.

CMS applies certain generally accepted methodological principles when assessing clinical research studies. Accordingly, CMS has stated that:

> A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. (Emphasis added) [Decision memo for Electrostimulation for Wounds].

Based on sound scientific principles, CMS has designated the randomized, controlled trial as the type of study with the greatest strength. Given the availability of five well-designed RCTs, the available evidence fully addresses the effectiveness of TMR. Note that the five RCTs and all three associated long-term follow-up studies produced consistent results showing significant benefits of TMR. Therefore, there are no concerns about conflicting study results that would call for further investigations. Moreover, recent operative outcomes from physicians in community practice [Peterson 2003] confirm the results in the RCTs.

The second question concerning TMR as sole therapy is in two parts. The first part asks the panel members, "How confident are you in the validity of the scientific data" for four outcomes: (1) short-term mortality, (2) long-term mortality, (3) morbidity, and (4) quality of life? The answer choices for this question are listed on a continuum from no confidence to moderate confidence to high confidence. For the same four outcomes, part two of the question asks, "How likely is it that TMR will improve this outcome (compared to usual care)?" The answer choices for this question are listed on a continuum from not likely to reasonably likely to very likely.

Again, for the same reason that question one above was answered in the affirmative, the evidence provides high confidence of data validity for each of the outcomes. The five RCTs examined short-term mortality, long-term survival, morbidity (reflected in assessments of angina and event-free survival), and three of the five RCTs examined quality of life (measured by standardized assessment instruments). As mentioned above, RCTs are the type of clinical trial with the greatest validity, and having five separate RCTs examining the listed outcomes should lead to a high degree of

confidence regarding the validity of the data for each of the listed outcomes. Moreover, as discussed previously, results from the STS database highlighting TMR in community practice reaffirm these findings. [Peterson 2003].

The second part of question two asks about the effectiveness of TMR, *i.e.*, "how likely is it that TMR will improve the respective outcomes?" (*i.e.*, short-term mortality, long-term mortality, morbidity, and quality of life). The RCTs report operative mortality following TMR in the range of 1% to 5%. In the Frazier, Allen, and Burkhoff RCTs the 30-day mortality for patients randomized to MM was in the range of 0% to 5%. These rates are comparable to operative mortality rates of 3% for patients undergoing CABG alone. [Ferguson 2002, Shroyer 2003]. Each of the TMR RCTs demonstrated no statistically significant difference in survival at one year. Of the two studies that followed patients beyond one year, Allen reported increased Kaplan-Meier survival for sicker, Class IV patients randomized to TMR (65%) versus MM (52%), p=0.05. [Allen 2004]. Thus, sole therapy TMR does not appear to improve or reduce operative mortality risk, but it does suggest improvement in long-term survival in sicker, class IV patients.

Morbidity is defined as a diseased state or symptom. [Merriam Webster Medical Dictionary]. The primary symptom of CAD is angina, and therefore angina is a key measure of CAD associated morbidity. All five of the TMR sole therapy RCTs showed a statistically significant decrease of at least two angina classes relative to MM at one year, with sustained relief long-term in three follow-up studies. ECRI bolsters the RCT angina results in their technology assessment with a meta-analysis of the five RCTs. ECRI stated in their assessment, "Our meta-analysis indicates that TMR plus medical therapy leads to significantly greater angina reduction as measured by the proportion of patients

with angina reduction $\geq$ 2 classes at one year following treatment." Their final conclusion on efficacy of angina reduction is that "ECRI concludes that TMR plus medical therapy is more effective than medical therapy alone for relief of angina symptoms in patients with refractory angina."

Some have questioned the effect of the lack of blinding on the angina outcomes reported in the TMR studies. None of the TMR RCTs was blinded, and this aspect of the RCTs has led some to suggest that angina relief following TMR may have been the result of a placebo effect induced by the surgical incision. However, there is limited validation of a long-term placebo effect from a sham thoracotomy. [Allen 2000 letter]. Furthermore, the overwhelmingly positive one-year results from the five RCTs and the persistent, significant angina relief beyond three years [Aaberge 2002] and at five years [Horvath 2001, Allen 2004] following TMR argues against attributing the clinical benefits of TMR to a placebo effect. Finally, the observed survival benefit linked to angina improvement in sicker, Class IV patients also refutes the placebo effect as a plausible explanation for the long-term outcomes.

Reinforcing the angina results as measures of decreased morbidity in TMR patients is improved event-free survival. Two RCTs that had prospectively defined major adverse cardiac event (MACE) endpoints (Frazier & Allen) found significantly improved event-free survival ($p<0.001$) in TMR vs. MM patients at one year, and fewer major adverse cardiac events certainly indicate less morbidity from CAD after TMR.

Exercise tolerance is an objective measure of a patient's functional status, and is inversely proportional to a patient's morbidity from CAD. Four of the five TMR RCTs reported data on exercise times, and two of the RCTs (Allen and Burkhoff) reported

statistically significant increases in total exercise tolerance after TMR at one year. Although the two remaining trials (Aaberge and Schofield) did not find differences in total exercise times, significant differences in time to chest pain and/or nitrate usage favoring the TMR group were identified. These data provide additional objective evidence and further support the conclusion that TMR improves morbidity relative to medical therapy alone.

With such consistently positive results for reduced morbidity (*i.e.*, decreased angina, better event-free survival, improved exercise times) after TMR, it is, in the words of the MCAC questions, very likely that TMR would improve morbidity compared to usual care.

As for quality of life, the three RCTs that measured quality of life each demonstrated a statistically significant improvement in quality of life for TMR patients, which is consistent with the demonstrated improvement in angina. With consistently positive quality of life improvement among all three RCTs that measured quality of life, it is also very likely that TMR will improve quality of life.

The third question for TMR as sole therapy relates to the second question, and it asks the MCAC panel: "How confident are you that TMR will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?" CMS defines the term "net health benefit" as " the balance between risks and benefits" for TMR as sole therapy. Or, stated differently, for TMR a net health benefit exists if the benefits > risks. The five answer choices for this question are listed on a continuum from no confidence to moderate confidence to high confidence. Based on the five well-designed, prospective,

RCTs evaluating TMR, the answer to this third question is that panel members should express high confidence that TMR will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated.

According to CMS' definition of net health benefit, the extent to which the benefits of TMR outweigh the risks of TMR corresponds to the confidence level one has in a net health benefit for TMR. The benefits of TMR as sole therapy are summarized above in the answer to question two. All five of the sole therapy TMR RCTs showed a statistically significant decrease of at least two angina classes relative to MM at one year, with sustained long-term relief in three follow-up studies. This angina benefit was confirmed, as described above, by the ECRI meta-analysis that indicated that TMR plus medical therapy leads to significantly greater angina reduction than MM alone. Other outcomes described above in the response to question two that reflect a positive health benefit after TMR are better event-free survival, better exercise time, and improved quality of life. In summary, the sole therapy RCTs demonstrate the significant benefits of TMR.

The other factor that is weighed against the benefits of TMR in determining the net health benefit of TMR is the risks associated with performing TMR surgery. Risk in the context of surgical intervention refers to the operative mortality (death within 30 days of the procedure) and the operative major morbidity (within 30 days of the procedure). [Ferguson 2002, Peterson 2003]. There is some variability among studies as to what constitutes operative morbidity. Examples of such measures include arrhythmias, myocardial infarction, heart failure, stroke, and rehospitalization.

As discussed above in response to question two, operative mortality following TMR in the five RCTs was 1% to 5%, and the 30-day mortality in the Frazier, Allen, and Burkhoff RCTs for patients randomized to MM was in the range of 0% to 5%. These rates are comparable to the operative mortality rates of 3% for patients undergoing CABG alone. [Ferguson 2002, Shroyer 2003]. Therefore, operative or 30-day mortality for TMR as sole therapy is not significantly different than other relatively similar operative interventions (*i.e.* CABG) or no intervention (*i.e.* MM). ECRI concluded the same in their technology assessment by stating that "none [of the RCTs] found a statistically significant between-group difference [in 30-day mortality]" and "no excess mortality is evident" with TMR. [ECRI 2004].

Nonrandomized studies generally have reported higher 30-day mortality rates following TMR than the RCTs. [ECRI 2004]. However, these studies tend to have a higher percentage of patients with unstable angina and conditions such as global myocardial ischemia and diminished left ventricular function that are recognized risk factors for morbidity and mortality after TMR. In fact, four of the five sole therapy RCTs excluded patients with unstable angina. Therefore, nonrandomized TMR study results are a poor indicator of the 30-day TMR mortality and do not provide valid data for assessing the TMR 30-day mortality risk.

In addition to 30-day mortality risk, it is necessary to consider the risk of 30-day morbidity when determining if TMR is associated with a positive net health benefit. As stated above, 30-day morbidity can be measured by any of a number of major events resulting in significant morbidity. The Allen RCT was the only RCT that compared 30-day morbidity for the TMR and MM groups, and this data was part of the original PMA

application for the Ho:YAG laser and not the published study. The 30-day morbidity results from the Allen RCT were mixed. Rehospitalization for angina was significantly lower in the TMR group, but arrhythmias and hypotension were significantly greater for the TMR group. There was no difference between TMR and MM groups for other measures of 30-day morbidity. It is important to recall that patients eligible for TMR generally have very advanced CAD that is not amenable to direct revascularization, and therefore a certain level of perioperative morbidity, particularly cardiac-related morbidity, is not unexpected.

A net health benefit requires that the benefits of TMR outweigh the operative risks. The benefits of TMR are extensive, and include significant symptomatic relief, less morbidity, and an improved quality of life. Commenting on the overall risk of the TMR procedure, ECRI concluded in their technology assessment that "TMR may be reasonably safe in patients who are not candidates for conventional revascularization procedures." Therefore, given the dramatic benefits associated with TMR and the reasonable risk profile for a desperately ill patient population, one should have high confidence that TMR provides a net health benefit for patients who are not candidates for direct revascularization. FDA concluded the same after weighing the risks and benefits of TMR and approving the PMA for each laser.

The fourth and final question for TMR as sole therapy addresses whether the evidence on TMR can be generalized to the Medicare population and to physicians in community practice. TMR is for patients with end-stage CAD, who tend to be elderly.

The average age of the patients in the five randomized clinical trials was 61. The age range of patients varied but encompassed patients from the late forties to the late seventies. Therefore, based on the average age of study patients and the range of patients enrolled in the studies, the evidence from these studies can be generalized to Medicare patients.

As for generalizability of the TMR evidence to physicians in community practice, the only physicians using TMR technology are trained cardiothoracic surgeons, who traditionally have the longest post-graduate training of any medical subspecialty. Prior to offering TMR to his or her patients, a surgeon must complete a rigorous training program, including proctoring by an experienced TMR surgeon prior to performing cases unsupervised. Based on the exceptional level of training and skill of cardiothoracic surgeons in general and the required TMR training program prior to adopting the technique, the TMR technique is generalizable to thoracic surgeons in community practice.

### B. **Adjunctive TMR for CAD**

As previously discussed, incomplete revascularization after CABG due to diffuse coronary artery disease occurs in up to 25% of patients, and when appropriately quantified, is a powerful independent predictor of operative mortality and a significant risk for late cardiac events. [Weintraub 1994; Graham 1999; Osswald 2001]. Based on the demonstrated benefits following TMR as sole therapy for medically refractory CAD, it has been used in conjunction with CABG in patients afflicted by diffuse CAD who would be incompletely revascularized by CABG alone. Despite this logical application of the technology by physicians, combined therapy has not been studied as extensively as sole therapy TMR; consequently, the benefit of combined therapy is supported by a

smaller data set compared to that available for TMR as sole therapy. Nonetheless, two prospective RCTs have been conducted for combined CABG with TMR in appropriately selected patients, and patients from each of these trials have been followed long-term. These studies and certain nonrandomized studies are discussed below.

1. Primary Evidence: Randomized, Controlled Trials (RCTs)

Two prospective, controlled trials involving 312 randomized patients have evaluated adjunctive therapy TMR in comparison to CABG alone in patients with diffuse disease who would be incompletely revascularized by CABG alone. [Frazier 1999; Allen 2000]. Patients in the Frazier trial were considered high risk. Both of these trials have included long-term follow-up evaluations, with each demonstrating significant and sustained benefits in adjunctive TMR patients. [Frazier 2004 (in press), Allen 2004 (in press)]. A discussion of these long-term outcomes is also provided below.

a. Frazier et al. RCT

In a prospective, controlled trial conducted at five U.S. centers, Frazier et al. randomized 49 patients who would be incompletely revascularized by CABG alone due to severe, distal, diffuse coronary artery disease to adjunctive TMR (CABG + TMR, n=22) or CABG alone (n=27). Patients were at high operative risk due to depressed ejection fraction (<0.35 [19%]), unstable angina (16%), and prophylactic placement of an intraaortic balloon pump (18%). At a mean age of 63 years, patients had a mean ejection fraction of 0.46 ± 0.11; 59% of patients had a previous myocardial infarction, and 45% had undergone a prior CABG surgery. A strong trend in reduced operative mortality was observed in the CABG+TMR group compared to the CABG alone group (9% vs. 33%, p=0.09). At one year, the rate of treatment failure (*i.e.*, death, repeat revascularization, or failure to improve by two or more classes) was non-

significantly reduced in CABG+TMR versus CABG alone patients (37% vs. 66%, p=0.3).

Frazier followed 44 of the randomized patients from the original trial for an average of four years. [Frazier 2004 (in press)]. Both groups experienced significant improvement in angina class from baseline, and long-term mortality was similar between groups (35%, CABG + TMR; 42%, CABG alone). A significant reduction in percutaneous or surgical repeat revascularization was observed in CABG+TMR versus CABG alone patients, (0% vs. 24%, $p<0.05$), even though the numbers of bypass grafts placed (3.1±0.7 vs. 3.1±0.8) were similar between groups. The long-term freedom from treatment failure (freedom from death, repeat revascularization, and recurrent angina) showed a strong trend favoring CABG + TMR patients (39% vs. 14%, p=0.06).

b. Allen et al. RCT

In a prospective, controlled trial conducted at 24 U.S. centers, Allen et al. randomized 263 patients who would be incompletely revascularized by CABG alone due to one or more ischemic areas not amenable to bypass grafting to adjunctive TMR (CABG + TMR, n=132) or CABG alone (n=131). At a mean age of 64 years, patients had a mean ejection fraction of 0.51; 60% of patients had a previous myocardial infarction, and 26% had undergone a prior CABG surgery. Patients were blinded to treatment through one year. Significantly reduced operative mortality was observed following CABG + TMR compared to CABG alone (1.5% vs. 7.6%, p=0.02), although the Parsonnet-predicted mortality risk was comparable (6.3%, CABG + TMR vs. 6.6%, CABG alone, p=0.80). CABG + TMR required reduced postoperative inotropic support (30% vs. 55%, p=0.0001), and afforded increased 30-day freedom from major adverse cardiac events (97% vs. 91%, p=0.04). Improvements in angina and exercise treadmill

scores were similar between groups. Compared to CABG alone patients, CABG + TMR patients had significantly increased one-year survival (95% vs. 89%, p=0.05) and freedom from major adverse cardiac events defined as death or myocardial infarction (92% vs. 86%, p<0.05).

More recently, a five-year follow up of this work has been presented [Allen, 2004 (in press)]. Independent, blinded assessors conducted assessments. Whereas both randomized groups experienced significant improvement in CCS angina class from baseline during follow-up, CABG + TMR patients had a significantly lower mean angina score at five years compared to CABG alone patients (0.4 ± 0.7 vs. 0.7 ± 1.1, p=0.05). Also, there were significantly fewer patients with severe angina (class III/IV) at five years (0% vs. 10%, p=0.009), and the groups were well matched in this regard at baseline (68% vs. 74%, p=0.37).

In addition, there tended to be more CABG + TMR compared to CABG alone patients who were angina-free (78% vs. 63%, p=0.08). Significantly more diabetic patients who received CABG+TMR were free from angina at five years compared to diabetics who received CABG alone (93% vs. 63%, p=0.02). Although the operative characteristics were similar between groups, non-significant increases in grafting of the circumflex artery and overall number of grafts placed per patient were found in the CABG alone group (3.1±1.1 vs. 3.4±1.1, p=0.08). Despite this, CABG alone patients still had worse overall angina compared to CABG + TMR patients. In a multivariable analysis, predictors of long-term freedom from angina included diabetes (p=0.04), no prior CABG (p=0.002), and a strong trend favoring CABG + TMR treatment (p=0.06). Long-term (six year) survival was similar in patients randomized to CABG + TMR and

CABG alone (p=0.90). The presence of diabetes, prior dialysis, decreased ejection fraction, and increased age was found to be predictive of increased long-term mortality risk.

2. Secondary Evidence: Nonrandomized Studies

Several feasibility and nonrandomized studies have been performed prior to or after the conduct of the randomized trials. Studies with fewer than 25 patients are not included in this review.

- Trehan et al. reported on a series of 77 patients in India who underwent CABG + TMR for diffuse CAD not amenable to CABG alone. Their results showed that at 12 months 89% of the patients were angina-free. Twelve-month exercise stress tests showed an average increase from 5.2 at baseline to 9.7 minutes at 12 months. Thallium scanning done at 3, 6 and 12 months postoperatively showed that myocardial perfusion in grafted segments had an exponential trend of improvement, and perfusion in TMR segments showed a linear trend in the same period with a total gain of 28.4%. Early mortality was 1.2% in the CABG + TMR group.
- Schneider reported results from 27 patients who underwent CABG + TMR at a single center in Germany. [Schneider 2001]. Only 22% of patients (n=6) were available for follow-up at 36 months. Angina class was reduced from baseline (mean 3.5) through follow-up (mean 1.7). No significant changes in thallium scintigraphy, ejection fraction or exercise tolerance was observed in patients who were available for these assessments. Mortality at 36 months was 11%.
- Stamou et al. reported the single-center, one-year follow-up results after CABG + TMR in a consecutive series of 169 high-risk patients having refractory angina

and at least one myocardial ischemic area not amenable to CABG. [Stamou 2002]. One-year survival and event-free survival (freedom from death, stroke, myocardial infarction, and repeat revascularization) were 85% and 81%, respectively. The incidence of severe (class III/IV) angina was significantly reduced at one year compared to baseline (4% vs. 90%, $p<0.001$).

- Guleserian reported single-center outcomes following TMR performed in 81 high risk patients with refractory angina (ejection fraction<0.40 [n=37], unstable angina [n=30], or congestive heart failure [n=33]). [Guleserian 2003]. Of these 81 patients, 34 underwent sole therapy TMR and 47 underwent adjunctive TMR. Operative mortality was 9% and 4% following TMR alone or adjunctively with bypass, respectively. Operative mortality tended to be higher in patients with ejection fraction <0.40 (11%), compared with patients having unstable angina (10%) or CHF (9%). Quality of life evaluated at 18 months was lower in 24 sole therapy patients compared to 34 adjunctive TMR patients and 20 patients who received CABG only during the same time period, however, sole therapy patients had significantly increased cardiac interventions and myocardial infarctions, making this comparison unremarkable.

### 3. Tertiary Evidence: Registries and Retrospective Studies

Two retrospective, 30-day outcome studies have been reported.

- Wehberg and associates compared the results of 30-day clinical follow-up in a consecutive series of 36 patients with refractory angina who received CABG+TMR to the results of 219 patients not eligible for TMR who received CABG alone during the same period. [Wehberg 2003]. Groups were similar in terms of baseline angina class III/IV

(100% and 100%), age, and ejection fraction (49% and 52%). The number of bypass grafts placed and operative times were similar between groups. Intensive care unit times and time to discharge were significantly reduced in the CABG + TMR group (1.6 vs. 2.1 days [$p<0.001$] and 7.1 vs. 8.2 days [$p<0.001$]). The 30-day readmission rate was significantly lower in the CABG + TMR group (2.8% vs. 7.8%, $p<0.05$), as was the frequency of atrial fibrillation (16% vs. 37%, $p<0.03$). Operative mortality was 0% in CABG+TMR patients and 2.3% in concurrent CABG alone patients.

- Peterson, et al. retrospectively analyzed the STS registry 30-day reported data from 2,475 patients who received TMR combined with CABG. [Peterson 2003]. Overall operative mortality in this group was 4.2%. When considering patients without recent myocardial infarction, unstable angina, or depressed left ventricular ejection fraction, the operative mortality rate fell to 2.6%, which is lower than the operative mortality reported by the STS for patients receiving CABG alone. [Shroyer 2003]. Peterson et al. also compared 390 patients in the STS database who received CABG + TMR with a control group created from 39,000 CABG-only patients with triple-vessel disease who received <3 grafts. Operative mortality was similar between groups, and the authors conclude that they could not verify the mortality benefit observed in the RCTs. The appropriateness of this comparison is questionable because it assumes that incomplete revascularization in the control group occurred in an area of ischemic viable myocardium supplied by a diffusely diseased, ungraftable coronary artery and that all participating centers accurately and consistently defined three-vessel disease. It is not possible to verify this through a query of the STS database.

It is important to also note that surgeons are increasingly operating on patients with diffuse coronary artery disease, which has been shown to be a powerful independent predictor of operative mortality. [Weintraub 1994; Graham 1999; Osswald 2001]. Unfortunately, the presence of diffuse coronary artery disease is not factored into the STS database or any other national database source. Thus, such case-matched comparisons against CABG + TMR-treated patients with diffuse coronary artery disease are unreliable because control database sources fail to account for diffuse coronary artery disease and therefore underestimate predicted operative mortality in this select patient group. [Allen 2004 letter].

### 4. MCAC Evaluative Questions for TMR as Adjunctive Therapy to CABG

The evaluative MCAC questions are the same for TMR as adjunctive therapy to CABG as for TMR as sole therapy. The first question asks, "How well does the evidence address the effectiveness of TMR + CABG in the treatment of chronic, refractory angina in study patients?" Again, five answer choices for this question are provided on a continuum from limited to moderate to complete.

Two RCTs [Allen 2000, Frazier 1999] provide significant primary data on combined therapy in patients who would be incompletely revascularized by CABG alone. Both of these studies have long-term follow-up of randomized patients. [Allen 2004 (in press), Frazier 2004 (in press)].

As previously discussed, CMS considers RCTs to be the strongest form of clinical evidence, and therefore two RCTs are adequate to address the effectiveness of CABG + TMR inquiry. Notably, the BCBSA TEC agrees. [BCBSA 2001]. In commenting on the quality of the original Allen combined therapy study, BCBSA made

the following assessment in their May 2001 TEC Assessment of TMR as an adjunct to CABG:

> Overall, however, the results in the trial do permit evaluation on the benefits of TMR as an adjunct to CABG. This trial is well designed with appropriate randomization and allocation concealment. There are no differences between the control and experimental group's baseline patient demographic or operative characteristics, suggesting that there are no systemic biases that could be influencing results. More importantly, the trial is a multicenter trial. Outcomes were similar at all institutions. This is highly indicative that the results obtained by this one randomized, controlled trial would be reproducible.

In addition, the non-randomized trials summarized above provide further evidence for TMR + CABG.

The second MCAC panel question concerning TMR + CABG is in two parts. The first part asks the panel members, "How confident are you in the validity of the scientific data" for four outcomes, (1) short-term mortality, (2) long-term mortality, (3) morbidity, and (4) quality of life? For the same four outcomes, part two of the question asks, "How likely is it that TMR will improve this outcome compared to usual care?" For each outcome, the panel evaluation form provides a response scale from no confidence to moderate confidence up to high confidence.

As detailed above, the Allen CABG + TMR RCT demonstrates a significantly better short-term mortality for the combined patients versus the CABG alone patients, and Frazier's results in high-risk patients are consistent. [Allen 2000; Frazier 1999]. The Allen study also shows significantly better Kaplan-Meier survival at one year for the combined patients relative to the randomized control patients who were incompletely revascularized by CABG alone. Because this study was a well-designed RCT, the highest level of evidence in the CMS hierarchy, it suggests moderate to high confidence

in the data, as echoed by both BCBSA and more recently ECRI in their technology assessments of TMR. ECRI stated: "TMR appears to be effective at improving survival among candidates for TMR plus CABG hybrid procedures. The strength of evidence for this outcome is moderate." [ECRI Technology Assessment, 2004].

Therefore, based on the significantly better short-term survival, it is at least reasonably likely that TMR + CABG would improve this outcome. The aforementioned Peterson et al. retrospective study does not detract from this conclusion. Peterson stated that operative mortality was similar between CABG and CABG + TMR groups and concluded that the mortality benefit for adjunctive therapy observed in the RCTs could not be verified. However, as discussed above, the appropriateness of this comparison is questionable because it assumes that incomplete revascularization in the control group occurred in an area of ischemic viable myocardium supplied by a diffusely diseased, ungraftable coronary artery and that all participating centers accurately and consistently defined three-vessel disease. It is not possible to verify this through a query of the STS database, and therefore Peterson's conclusion is suspect. Peterson acknowledges this limitation in his response to the Allen and colleagues letter to the editor [Allen 2004 letter]: "We agree with Dr. Allen and colleagues that observational treatment comparisons, even when risk-adjusted, may still be challenged by unmeasured patient selection biases." Improvement in long-term survival after CABG + TMR is less certain because, although a significant benefit was seen at one year in the Allen study, no difference between groups was observed at six years. [Allen 2004].

As for morbidity and quality of life, significant improvements were observed in both RCTs at one year. Allen reported increased freedom from major adverse cardiac

events (death or myocardial infarction) in CABG + TMR patients versus CABG alone (92% vs. 86%, $p<0.05$). Frazier reported a trend toward increased freedom from treatment failure (death, repeat revascularization, or failure to improve by two or more classes) in CABG + TMR patients versus CABG alone (37% vs. 66%, $p=0.3$). The Allen five-year follow-up data for CABG + TMR show that, while both groups improved significantly over baseline, the CABG + TMR group had a lower mean angina score ($0.4 \pm 0.7$) than the CABG only control group ($0.7 \pm 1.1$), $p=0.05$. The CABG + TMR group also had a significantly lower number of patients with severe angina (class III/IV) versus CABG only patients (0% vs. 10%), $p=0.009$. Notably, baseline CCS angina class distribution was similar between groups ($2.9 \pm 1.3$, CABG + TMR; 2.8, CABG alone, $p=0.50$).

The significant, long-term difference in angina scores for the CABG + TMR patients, the improved one-year event-free survival, and the trend toward improved freedom from treatment failure indicate less morbidity and an improved quality of life for CABG + TMR patients. Therefore, it is at least reasonably likely that combined therapy will improve morbidity and between reasonably likely and very likely that combined therapy will improve quality of life.

The third question for CABG + TMR relates to the second question, and it asks the MCAC panel: “How confident are you that TMR + CABG will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?” CMS defines the term “net health benefit” as “ the balance between risks and benefits” for TMR + CABG. In other words, for TMR + CABG, net health benefit exists if the benefits >

risks. The five answer choices for this question are listed on a continuum from no confidence to moderate confidence to high confidence. Based primarily on the Allen and Frazier combined therapy RCTs, the answer to this third question is that panel members should express between moderate to high confidence that TMR + CABG will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated.

BCBSA asked a similar question in their 2001 technology assessment on CABG + TMR. Criterion number three of the five TEC criteria that BCBSA uses to assess whether a technology improves health outcomes requires that "[t]he technology must improve net health outcome." The BCBSA assessment for this criterion is as follows:

> In the one published randomized, controlled trial, perioperative mortality was decreased from 7.5% to 1.5% (p=0.02) with the addition of TMR to CABG. This benefit persisted at one year with survival rates of 95% and 89% (p=0.05) in patients treated with CABG plus TMR compared to CABG alone. No differences were seen in anginal class or exercise treadmill scores. Adverse events were similar in both treatment groups. There did not appear to be any complications associated with adding TMR to standard CABG, aside from the risk of complications for which patients undergoing CABG are already at risk.
> One smaller randomized, controlled trial, published only in abstract form, found a non-significant trend to support this result. Comparing TMR and CABG to CABG, the perioperative mortality was 9% vs. 33% (p=0.09). It was not reported if there were any benefits with TMR plus CABG in anginal class, perfusion, or exercise tolerance compared to CABG alone. These results are the inverse of prior findings evaluating TMR as sole therapy, where anginal class was improved without any effect on mortality or cardiac perfusion. However, studies of TMR as an adjunct to CABG differ in that both experimental and control groups undergo surgery. Thus both groups experience operative risks as well as benefits of surgical revascularization.
> An additional concern with both trials is that the perioperative mortality of patients treated with CABG alone is much higher than the perioperative mortality seen in other studies. However, the populations within both these studies are higher risk by definition, as many patients with coronary artery disease not amenable to complete revascularization have more severe disease. The perioperative mortality calculated using Parsonnet

> risk modeling is 6.6%, which compares to the 7.5% mortality found in the study (p=0.5).
> A final limitation with these results is that the surgeons who later managed patients postoperatively and assessed health outcomes were not blinded. The major outcome affected by TMR, mortality, is objective and should not be influenced by surgeon bias during the evaluation process. It is conceivable that surgeons may have managed patients differently during surgery or postoperatively based on which treatment each patient received. However, surgical and postoperative characteristics were similar in each treatment group.

BCBSA summarizes the short-term mortality benefit from the one-year Allen combined therapy trial, and properly emphasizes that there are no complications associated with adding TMR to the CABG procedure, aside from the risk of complications for which patients undergoing CABG are already at risk. On the safety of the combined procedure, ECRI also concluded: "TMR plus CABG may be safer than CABG alone for selected patients who are candidates for combined TMR and CABG procedures." ECRI also concluded that "[e]arly and overall morbidity did not differ significantly between patients receiving TMR plus CABG plus medical therapy and patients receiving CABG plus medical therapy.

Additional benefits of TMR + CABG described by data that were not available at the time the BCBSA and ECRI technology assessments were prepared include the angina benefit from the five-year Allen follow-up. Recall that in the Allen five-year follow-up, CABG + TMR patients had a significantly lower mean angina score at five years compared to CABG alone patients (0.4 ± 0.7 vs. 0.7 ± 1.1, p=0.05). Also, there were significantly fewer patients with severe angina (class III/IV) at five years (0% vs. 10%, p=0.009), and the groups were well matched in this regard at baseline (68% vs. 74%, p=0.37). These data add further support to the BCBSA conclusion that for CABG +

TMR, the benefits outweigh the risks and therefore combined therapy provides a net health benefit.

The fourth and final question for TMR + CABG addresses whether the evidence on combined therapy can be generalized to the Medicare population and to physicians in community practice. TMR + CABG is intended for patients with end-stage CAD, who tend to be elderly, as reflected in the mean age of 64 years reported in the Allen RCT and the mean age of 65 reported by Peterson for CABG + TMR.

For the same reasons as described for sole therapy, TMR + CABG is applicable to physicians in community practice who treat patients with the problem of diffuse CAD leading to incomplete revascularization. Moreover, BCBSA asked a similar question in their technology assessment in that one of their evaluation criteria was that "[t]he improvement [from TMR] must be attainable outside the investigational settings." In referring to the original Allen combined therapy study, BCBSA made the following observation:

> The main published randomized, controlled trial evaluating TMR as an adjunct to CABG was a multicenter study. Twenty-four investigational sites enrolled from 1 to 39 patients. Within this study, perioperative deaths were randomly distributed. Sites performing fewer procedures had similar perioperative mortality rates. Furthermore, TMR as an adjunct to CABG has been used safely at additional sites in the collection of cohort studies evaluating safety and effectiveness. The major complications of TMR as sole therapy were a result of cardiopulmonary bypass and sternotomy, both of which are standard procedures during a CABG. Overall, the modifications required to add TMR to standard CABG are relatively minor. Therefore, based on the above, TMR as an adjunct to CABG for patients who would otherwise be undergoing CABG but who have documented areas of ischemic myocardium that is not amenable to bypass grafting due to distal or diffuse vascular disease meets the TEC criteria [of attainable improvement outside of the investigational settings]. [BCBSA 2001].

Based on Blue Cross Blue Shield's careful observation and well reasoned conclusion and the previously mentioned rigorous training that new TMR surgeons must complete prior to offering TMR to their patients, TMR as an adjunct to CABG is generalizable to cardiothoracic surgeons in community practice.

## VI. CONCLUSION

Based on the above-described results of multiple, well-designed RCTs, we have demonstrated by responding to CMS' questions to the MCAC that TMR is safe and effective in the long-term relief of angina compared to MM alone. We have also shown that CABG + TMR is safe and effective in improving short-term mortality and five-year angina relief relative to CABG alone. Subsequent to the FDA approvals for the technology and the original CMS coverage decisions, four independent technology assessments have concluded that the weight of the evidence supports TMR for the treatment of patients with refractory angina, when used as sole therapy or as adjunctive therapy in selected patients.

In addition to the formal data analyses, it is important to re-emphasize that TMR and TMR + CABG are used to treat a very small subset of severely ill angina patients for whom other treatments (CABG or PCI) are unsuitable or inadequate. The operative risks of TMR and TMR + CABG must be evaluated in light of the demonstrated benefits, both late and long-term, in this group of patients having diffuse, distal coronary artery disease. The data demonstrate no increased risk in appropriate randomized, controlled comparisons, robust evidence of benefits for sole therapy, and significant evidence of benefits for combined therapy in selected patients. More recent retrospective evaluations of observational data in community practice confirm the operative outcomes in sole

therapy patients, and suggest improvement in outcomes in sicker patients. Therefore, TMR as sole therapy and combined with CABG for medically refractory angina in selected patients with diffuse CAD should remain covered by CMS as currently defined.

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