

**Comments of Edwards Lifesciences LLC
on the Proposed Decision Memorandum
for Transcatheter Aortic Valve Replacement (TAVR)
(CAG-00430N)**

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I. Evidence Supports Coverage for Labeled Indications

A. Evidence Overview

Edwards Lifesciences (Edwards) believes that for appropriately selected Medicare beneficiaries, the evidence is more than adequate for the Centers for Medicare & Medicaid Services (CMS) to conclude that Transcatheter Aortic Valve Replacement (TAVR) improves health outcomes and should be considered reasonable and necessary under the Medicare statute if provided by multi-disciplinary heart teams in appropriate facilities, with outcomes data reported through a qualified registry. In the following section, we review The Placement of AoRTic TraNscathetER Valve Trial (PARTNER Trial) and other relevant data important to CMS' analysis, as well as more recent results from additional PARTNER data analysis, including two-year outcomes, quality of life (QOL), and non-randomized continued access. In addition, we address the principle concerns raised in the proposed decision memo.

1. The PARTNER Trial

The PARTNER Trial (NCT00530894), initiated in 2007, was a randomized clinical study designed in consultation with the Food and Drug Administration (FDA) to investigate the safety and effectiveness of TAVR in two discrete indications, studied in two separately powered protocols under one overarching trial design and trial management structure. More than 1,000 symptomatic severe aortic stenosis (AS) patients were assigned to one of two independently powered arms: a “non-surgical” arm (Cohort B), in which patients who were determined to be inoperable were randomized to either treatment with the Edwards SAPIEN Transcatheter Heart Valve (THV) (delivered transfemorally) or standard therapy, and a “surgical” arm (Cohort A), in which high-risk operable patients were randomized to either treatment with the Edwards SAPIEN THV (delivered transfemorally or transapically) or surgical aortic valve replacement (AVR). The primary endpoint was a superiority analysis of all-cause mortality over the duration of the trial for the inoperable cohort and a noninferiority analysis of all cause mortality at one year in the high-risk surgical cohort. Patients in both cohorts are consented to be followed for five years from randomization.

i. Cohort B

Cohort B included patients who were inoperable because they were deemed “too sick” (i.e., elderly, frail, or significant comorbidities) after an assessment by the heart team and two cardiac surgeons, or because of anatomic considerations, or both. TAVR improved survival by 20 percentage points at one year compared to standard therapy. On this basis, the “number needed to treat” (NNT) to save one life was approximately five,¹ The NNT is useful in understanding and comparing treatment benefits and Table 1 provides a comparison of TAVR and various other therapies in this regard. The NNT of 5 in TAVR and absolute difference in mortality is far superior to any of these therapies.

Table 1: Number Needed to Treat for TAVR and Various Therapies

Therapy	NNT	Benefit
Beta blockers for mild hypertension ²	332	To prevent 1 death over 5 years
Thiazide diuretics for mild hypertension ²	213	To prevent 1 death over 5 years
Implantable cardioverter defibrillators (ICD) with prior myocardial infarction (MI) and left ventricular (LV) dysfunction ³	133	To prevent 1 death over 1 year
Pravastatin for mild hypertension ²	126	To prevent 1 death over 4 years
Oral anticoagulants in non-valvular atrial fibrillation for primary stroke prevention ⁴	42	To prevent 1 death over 1.5 years
TAVR for inoperable symptomatic severe AS ¹	5	To prevent 1 death over 1 year

Moreover, TAVR demonstrated superior valve performance, with echocardiographic findings at 30 days showing:

- Increased valve area from 0.6 to 1.5 cm², p<0.001
- Decreased valve gradient from 45 to 11.1 mmHg, p<0.001

In this population, and in an environment of early operator experience and first-generation delivery systems, TAVR resulted in more frequent complications at 30 days compared to standard therapy, including:

- Major vascular complications, 16.2% vs. 1.1%, p<0.0001
- Major bleeding episodes, 16.8% vs. 3.9%, p<0.0001
- All stroke or transient ischemic attack (TIA), 6.7% vs. 1.7%, p=0.03
- Major strokes, 5.0% vs. 1.1, p=0.06

Importantly, clinically relevant and statistically significant changes in QOL were observed as early as one month post-procedure with a 13.3-point improvement (p< 0.001) in overall Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores compared with the standard therapy group. Even larger, clinically relevant changes in QOL were observable in the TAVR group at 6 months (mean difference 20.8 points, p<0.001) and 12 months (mean difference 26 points, p<0.001). At one year, these benefits approximate a two-level improvement in New York Heart Association (NYHA) functional class.⁵⁻⁶ In the KCCQ subscales, large clinically relevant differences were observed in the Symptom, Physical, QOL, and Social Limitations scores. It is important to note that every subgroup of the TAVR treatment group had a large, clinically relevant, and superior QOL benefit. Additionally, when QOL was considered with survival, the NNT to obtain an excellent outcome (i.e., one-year survival with ≥20-point improvement in KCCQ) was approximately 3.5. The other generic utility instruments showed equally significant improvements for TAVR patients. Gains in the SF-12 physical component were equivalent to a ten-year reduction in effective age.^{5,7}

ii. Cohort A

For high-risk surgical patients, TAVR provides a less invasive treatment alternative that avoids sternotomy and cardiopulmonary bypass. This promotes shorter procedural times, shorter hospital length of stays, and faster recovery.⁸⁻¹⁰ Thirty-day mortality trended lower in the TAVR group as compared to AVR (3.4% vs. 6.5%, $p = 0.07$). At one year, mortality rates were noninferior between groups, 24.2% and 26.8% for TAVR and AVR, respectively ($p=0.001$). Both TAVR and AVR provided consistent valve performance, with TAVR demonstrating slightly better results at one year with respect to:

- Mean aortic-valve gradient (10.2 vs. 11.5 mmHg, $p=0.008$)
- Aortic-valve area (1.59 vs. 1.44 cm², $p=0.002$)

Both TAVR and AVR were associated with important, but different, peri-procedural hazards. The occurrence of major bleeding events (19.5% vs. 9.3%, $p<0.001$) and new onset atrial fibrillation (16% vs. 8.6%, $p=0.006$) were higher in the AVR group, while TAVR resulted in more frequent adverse neurological events (5.5% vs. 2.4%, $p=0.04$), major vascular complications (11.0% vs. 3.2%, $p<0.001$), and moderate or severe paravalvular regurgitation (12.2% vs. 0.9%, $p<0.001$).

At 30-days, symptom improvement favored TAVR with more patients in the transcatheter group experiencing a reduction in cardiac symptoms to NYHA class II or lower ($p<0.001$). Similarly, among patients who participated in the six-minute walk test, TAVR patients were able to ambulate farther (median distance [m] 128 vs. 75 for TAVR and AVR, respectively; $p=0.002$). At one year, both treatment groups noted improvement in cardiac symptoms and functional capacity, with no significant differences between the groups.¹⁰

iii. New Evidence on Long-Term Benefits

In November 2011, two-year outcomes for Cohort B were presented at Transcatheter Cardiovascular Therapeutics (TCT) in San Francisco. At two years, survival benefits for patients treated with TAVR persisted, with survival curves diverging further – 56.7% versus 32.4%, for TAVR and standard therapy, respectively.¹¹ Also presented at TCT were QOL results for Cohort A. Both TAVR and AVR resulted in substantial improvement in disease-specific and generic QOL over one year of follow-up. For both TAVR and AVR, the KCCQ summary scores improved by approximately 25-30 points (MCID=5), and the SF-12 Physical and Mental scores improved by approximately 6 and 5 points, respectively (MCID=2).¹²

In January 2012, data were reported at the Society of Thoracic Surgeons (STS) annual meeting on additional transapical (TA) TAVR experience through The PARTNER Trial Non-Randomized Continued Access (NRCA) period. The study reviewed the 822 TA patients enrolled in the NRCA period and compared their results to the 104 TA patients and 103 surgical patients randomized in PARTNER Cohort A. During continued access, mortality was 8.2% at 30 days and, 23.6% at 1 year. Table 2 provides the more complete results.

Table 2: Clinical Outcomes (As Treated)*

Outcome	30 Days			1 Year		
	NRCA-TA	PARTNER AVR	PARTNER TA	NRCA-TA	PARTNER AVR	PARTNER TA
All-Cause Mortality	8.2%	7.6%	8.7%	23.6%	25.3%	29.1%
Stroke	2.0%	5.5%	7.0%	3.7%	7.0%	10.8%
Death or Stroke	9.9%	12.0%	15.5%	25.7%	29.7%	34.8%

In addition, NYHA functional class was significantly improved in the NRCA TA cohort at 30 days when compared to PARTNER AVR (p=0.0004) and PARTNER TA (p=0.0001).¹³ For NYHA, class I is defined as asymptomatic heart disease; class II is comfortable at rest, with symptoms during normal activity; class III is comfortable at rest, with symptoms during a less than normal level of activity; class IV is symptomatic at rest. Table 3 provides the more complete results.

Table 3: NYHA Class (As Treated – Survivors)

Outcome	30 Days			1 Year		
	NRCA-TA	PARTNER AVR	PARTNER TA	NRCA-TA	PARTNER AVR	PARTNER TA
NYHA class I or II	76.6%	61.0%	64.4%	88.7%	87.5%	82.9%

In summary, in the larger group of patients treated with TA valve replacement (NRCA TA), there was a trend toward patients feeling better faster and having improved outcomes.

2. New Developments

i. New Health Technology Assessment Available

In addition to the 2011 Belgian Health Technology Assessment (HTA) and the 2011 NICE review referenced by CMS, The California Technology Assessment Forum (CTAF) recently completed an evidence-based assessment of TAVR focusing extensively on The PARTNER Trial. During their February 8, 2012 meeting, the CTAF panel members voted unanimously (11-0), to conclude that “use of the SAPIEN transcatheter aortic valve meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes when used for the treatment of severe, symptomatic AS in patients determined to be inoperable by a cardiac surgeon, who can be treated using the transfemoral approach.”[†] The panel is comprised of experts representing a range of disciplines including medical ethics, outcomes research, consumer advocacy, practicing clinicians, methodologists, and technology assessment experts. The formal written recommendations of the panel will be available shortly.

* Note: All percents are Kaplan-Meier estimates. Comparisons of NRCA TA and randomized cohorts are limited, as the continued access group was not randomized. P-values between NRCA TA vs. PARTNER TA and NRCA TA vs. PARTNER AVR for clinical outcomes are all not significant.

[†] http://www.ctaf.org/UserFiles/File/2012%20Feb/TAVI_draft2%20pdf.pdf

ii. Evidence-Based Practice Guidelines Are Now Available

In the proposed decision memo, CMS noted that there currently are no evidence-based guidelines for this procedure.

Shortly after CMS released the proposed decision memo for public comment, the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement was accepted for publication in the Journal of the American College of Cardiology.¹⁴ Table 15 lists current treatment recommendations for patients with AS. In the inoperable population, TAVR is recommended in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival >12 months, and who have a prohibitive surgical risk as defined as an estimated 50% or greater risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease. TAVR also is considered a reasonable alternative to surgical AVR in patients at high surgical risk (STS \geq 8%).¹⁴

B. Response to Evidence Concerns Raised in the Proposed Decision Memo

The following sections address the principle concerns raised in the proposed decision memo related to The PARTNER Trial methodology and results.

1. Baseline Imbalances in Cohort B Do Not Impact the Primary Findings

In describing Cohort B of The PARTNER Trial, CMS notes that baseline characteristics were not balanced and included several between-group differences that were statistically significant, including a higher Logistic EuroSCORE (30.4% vs. 26.4%, p=0.04), more frequent chronic obstructive pulmonary disease (COPD) (52.5% vs. 41.3%, p=0.04) and more frequent atrial fibrillation (48.8% vs. 32.9%, p=0.04) in the standard therapy group. By contrast, TAVR patients had more extensively calcified aorta (19.2% vs. 11.2%, p=0.05).

While such baseline disparities sometimes occur despite randomization, multiple analyses accounting for potential imbalances were performed. The baseline imbalances noted by CMS were apparent to the investigators and were transparently discussed in the New England Journal of Medicine (NEJM) article.¹ Multiple adjusted analyses were performed prior to manuscript submission to account for these imbalances and even the most rigorous, fully adjusted analysis did not indicate any important differences in the one-year mortality outcomes. Finally, in preparation for the FDA panel meeting regarding approval of TAVR for inoperable patients in July, 2011, Edwards performed several additional analyses to address baseline imbalances. In the propensity analysis the endpoint p-values were still highly significant, again attesting to the robustness of the difference in mortality outcomes between the control and test patients.

In conclusion, the differences in baseline characteristics between the two study groups were a matter of chance, but not of importance or impact on the outcome of the primary endpoint of the

trial. Notably, a recent assessment[‡] by CTAF reached a similar conclusion, commenting that while the trial was not methodologically perfect, “none of these issues are of sufficient magnitude to explain the large one-year mortality difference between the two groups.”

2. Methodological Concerns are Misplaced

The proposed decision memo references a 2011 Belgian HTA¹⁵ suggesting the treatment effect of TAVR may be overestimated in The PARTNER Trial because of methodological concerns and the potential impact of conflicts of interest. We are troubled by CMS’ extensive reference to the Belgian assessment as the sole basis for many of the conclusions in the proposed decision memo. We address each of CMS’ concerns below but also mention that the Belgian HTA is the single European HTA that rejected outright the effectiveness of TAVR. Since TAVR was introduced in Europe, the Belgian Health Care Knowledge Center (KCE) has repeatedly taken a negative approach to TAVR; several other HTAs have taken a more balanced position.

We believe the trial was rigorously designed and executed. It included clearly objective primary endpoints that were adjudicated by an independent clinical events committee of expert physicians administered by the Duke Cardiovascular Research Institute (DCRI) who were not study investigators or otherwise involved in the design or conduct of the trial. The echocardiological endpoints were assessed by an independent echo core lab. All endpoints were prospectively designed and the adjudications were based upon source document verification from the patient’s medical record or other sources.

To address potential enrollment bias, none of the centers were permitted to enroll more than 15% of the total patients in the trial, thereby limiting the impact any individual center could have on the overall trial results. Lastly, all of the rigorous conflicts of interest and disclosure requirements specified by the FDA and the professional societies were proactively and rigorously adhered to in the trial.

3. TAVR Improves Survival in Both Anatomical and Medical Prohibitive Patients

The Belgian HTA, referenced by CMS, also notes that patients with prohibitive anatomical conditions were unevenly represented in Cohort B. Specifically, the total number of anatomically inoperable patients was approximately 30% in the TAVR group and 21% in the standard therapy group.

This assertion is unfounded. The anatomically inoperable subgroup of patients was never contemplated or powered for independent analysis in The PARTNER Trial. Nonetheless, upon request of the Belgian authorities, Edwards provided a post hoc analysis separating characteristics considered to be anatomically versus medically inoperable for Cohort B. This analysis showed a consistent reduction of the mortality in TAVR versus standard therapy in both subgroups of inoperable patients, which also is consistent with the risk reduction observed in the total population. Although patients who are anatomically inoperable may have fewer comorbidities, they have a similarly poor prognosis if they only receive conventional therapy.

[‡] http://www.ctaf.org/UserFiles/File/2012%20Feb/TAVI_draft2%20pdf.pdf

Severe symptomatic AS carries a dismal prognosis across a broad range of patients with various additional risk factors. In patients deemed inoperable due to either anatomical reasons or predicted high mortality risk related to comorbidities, TAVR has been proven to significantly reduce mortality versus standard therapy. The overall results were not driven by one or the other subgroups compared in this analysis.

4. BAV Can Be an Important Component of Standard Therapy in Inoperable Patients

In the proposed decision memo, CMS referenced the Belgian HTA questioning whether the control group actually received “standard therapy” when 84% of the control group received balloon aortic valvuloplasty (BAV).

In patients with inoperable AS, BAV is entirely appropriate as an important component of standard therapy.¹⁶ According to the 2008 Focused Update to the ACC/AHA Guidelines for the Management of Valvular Heart Disease,¹⁷ BAV is given a class IIb endorsement, and “may be considered” for palliation in patients with AS in whom AVR cannot be performed because of serious comorbid conditions. In Cohort B, BAV was found to be safe on an acute basis. Among 150 patients, only one death (0.7%) and 2 strokes (1.3%) occurred within seven days after the procedure.¹⁶ Moreover, Dr. Raj Makkar, in his presentation at TCT 2011, entitled “2 Year Outcomes from PARTNER Cohort B,” reported that the Kaplan-Meier all-cause mortality at one year for patients receiving standard therapy with BAV was not significantly different from patients receiving medical management alone.¹¹ Hence, BAV, as it was applied in Cohort B, was found to be a safe adjunctive procedure with no adverse impact on the overall results of the trial.

5. Continued Access Patients

In describing the Cohort B results from The PARTNER Trial, the proposed decision memo states that while one year mortality was an absolute 20% lower for patients who underwent TAVR as compared to standard therapy, one year mortality was in fact an absolute 12.7% higher for 90 patients who underwent TAVR compared to standard therapy in The PARTNER Trial’s continued access study.

We offer the following to consider these findings in the proper context. The primary cohort of 358 patients was randomized from all eligible patients in all of the qualified PARTNER sites. Once the primary cohort was enrolled, the FDA approved continued randomization in inoperable patients, with a very strict quota on the number of implants. Importantly, there was never any intention to analyze the outcomes from this small randomized cohort of inoperable patients, either as an independent study or in a pooled analysis with the primary cohort, as per an agreement between Edwards and the FDA. Nonetheless, a pooled analysis of the primary cohort and the continued access randomized patient cohort was performed at the suggestion of an FDA advisory committee member (July 20, 2011) to simulate a worse-case scenario tipping point analysis. All-cause mortality differences between TAVR and standard therapy at one year were still highly significant ($p=0.002$).

With regard to the survival benefit of TAVR more generally, Figulla et al. performed a systematic review of current literature in 2010 to “provide objective evidence on the efficacy and safety of [TAVR] at one-year follow-up and to assess whether [TAVR] confers a survival benefit compared with medical therapy.”¹⁸ The review was conducted in accordance with the toolkit of the German Scientific Working Group Technology Assessment for Health Care (GSWG) and major bibliographic databases were queried to identify all relevant publications. The investigators concluded that, based on the best available data, TAVR demonstrates improved one-year survival in patients with symptomatic severe AS compared with medical management. The survival benefit was 16.8%, which corresponds with and corroborates the 20% survival benefit reported in Cohort B. Notably, the baseline health status of medically managed patients in the review was dramatically better than for TAVR patients (logistic EuroSCORE 13.5% vs. 27.8%). Therefore, if TAVR were compared against medically managed patients with comparably poor health status, the benefit likely would have been even higher.¹⁸

6. Stroke Risk

As noted in the proposed decision memo, strokes were a concern in The PARTNER Trial.

In Cohort B, stroke or TIA occurred more frequently in TAVR patients than those receiving standard therapy at 30 days (6.7% vs. 1.7%, $p=0.03$) and one year (10.6% vs. 4.5%, $p=0.04$). However, the composite endpoint of major stroke or death from any cause was still significantly lower in the transcatheter group than in the standard therapy group at one year (33% vs. 50.3%, $p<0.001$).¹ In addition, despite the elevated risk of adverse neurological events, TAVR patients overall (including those who experienced neurological events) saw a marked improvement in QOL compared to standard therapy with a between-group difference in KCCQ summary scores of 13.3 points (MCID = 5) at 30 days and 26.0 points at one year.⁵ This is notable, since QOL instruments assess the impact of both the benefits and harms of an intervention and thus, provide useful information regarding net effects.

In Cohort A, stroke or TIA also occurred more frequently in high-risk TAVR patients than those receiving AVR at 30 days (5.5% vs. 2.4%, $p=0.04$) and one year (8.3 vs. 4.3%, $p=0.04$). However, the composite endpoint of major stroke or death from any cause was comparable for both groups at 30 days (6.9% vs. 8.2%, $p=0.52$) and one year (26.5% vs. 28.0%, $p=0.68$).

i. New Data

Encouragingly, the stroke rates in the recently presented NRCA TA patient cohort appeared to be trending lower compared to the original PARTNER TA group at 30 days, 2.0% vs. 7.0%, respectively, and 1 year, 3.7% vs. 10.8%, respectively.¹³ These results suggest a trend toward improved outcomes in the more recent group of patients treated.

7. PARTNER Results Are Generalizable

With respect to the generalizability of The PARTNER Trial results, the proposed decision memo cites a higher 30-day mortality rate from European post-market registry (SOURCE) data as compared to the intention-to-treat PARTNER Trial results.

We consider this comparison inappropriate due to the different procedural and patient characteristics in these groups. The SOURCE Registry¹⁹⁻²⁰ includes a significantly higher percentage of TA procedures—an approach widely accepted for patients with more severe cardiovascular disease burden—than observed in The PARTNER Trial (55% vs. 19%). The SOURCE Registry also uses different patient inclusion and exclusion criteria.

A comparison of approach-specific outcomes in patients who actually received TAVR (as-treated) reveals that The PARTNER Trial results are, in fact, comparable to those of the SOURCE Registry. Among transfemoral patients in Cohorts A (high-risk operable) and B (inoperable) of The PARTNER Trial, 30-day mortality rates were 3.7% and 6.4%, respectively.^{1, 9-10} In the SOURCE Registry, which includes both high risk and inoperable patients, transfemoral 30-day mortality rates were 6.3%.²¹ Similarly, among TA patients in Cohort A, 30-day mortality rates were 8.7% (as-treated analysis) compared to 10.3% in SOURCE.^{9-10, 21}

One-year survival was also comparable on an as-treated basis. Among transfemoral patients in Cohort A[§], one-year mortality was 21.3% compared to 18.9% in SOURCE. Similarly, among TA patients in Cohort A, one-year mortality was 29.1% compared to 27.9% in SOURCE.^{9-10, 22} Thus, upon closer scrutiny, The PARTNER Trial results are consistent with the commercial experience in Europe as reflected in the SOURCE Registry, and the US investigational study appears to be generalizable.

C. Non-PARTNER Trial Concerns Raised in the Proposed Decision Memo

1. Appropriate Comparisons Between TAVR and Open Surgical AVR

To define the standard therapy to which TAVR has been compared in published clinical trials, CMS included reviews of open surgical and minimally invasive AVR in the proposed decision memo.

Unfortunately, the four referenced studies²³⁻²⁶ do not constitute a valid TAVR comparison group because they are not carefully designed evaluations of high-risk AVR cases. Rather, they describe AVR results in elderly (aged 80 years and older) patients and importantly, age alone is not a contraindication for surgery nor does it necessarily denote high surgical risk. In fact, as these papers attest, excellent surgical outcomes have been demonstrated in octogenarians.

Two of the four referenced studies (Filsoufi et al. and ElBardissi et al.) provide operative risk information for the patients studied; the other two studies—Melby et al. and Thourani et al.—do not. In Filsoufi et al.,²⁵ the mean logistic EuroSCORE was 23%. However, 12.9% of the overall cohort had a logistic EuroSCORE between 3 and 8, and 55.8% had scores between 9 and 25. This demonstrates that many patients at moderate surgical risk could have been included in the analysis. Similarly, in ElBardissi et al.,²⁶ the mean STS score was 10.5%; however, the interquartile range (7-17%) indicates a mixed population of moderate and high-risk patients. By contrast, TAVR patients consistently present with high or prohibitive surgical risk. To date, this has resulted in high surgical risk scores (i.e., STS score $\geq 10\%$, Logistic EuroSCORE $\geq 20\%$)

[§] One-year mortality rates on an as-treated basis were not provided in Cohort B

and/or the presence of comorbidities known to increase surgical risk but not currently captured in the existing algorithms (i.e., porcelain aorta, chest wall radiation, cirrhosis, and others).

A more appropriate benchmark study was referenced in our initial comment letter and noted in the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document. This study, Thourani et al.,²⁷ is a recent review of high-risk surgical AVR results in four US centers with significant experience. The mean age was 76 and all patients had an STS predicted risk of mortality $\geq 10\%$ (mean 16.3%). The Consensus Document summarized the study as follows: “Complications included stroke in 4.4%, new permanent pacemaker in 5%, multisystem organ failure in 6.9%, pneumonia in 7.5%, and dialysis in 8.2%. Postoperative length of stay was 12.6 days and in-hospital mortality was 16.4%. One-, three-, and five-year survival were 70.9%, 56.8%, and 47.4%. This study was performed between 2002 and 2007 in four centers before participation in The PARTNER Trial commenced and, therefore, serves as a reasonable baseline for comparing the results of TAVR.”^{14, 27}

D. TAVR Improves Health Outcomes for Medicare Patients

The proposed decision memo suggests the evidence is insufficient to conclude that TAVR improves health outcomes in patients with symptomatic severe AS.

Given the evidence presented in The PARTNER Trial section above, we believe there is little doubt that the benefits of TAVR clearly outweigh the risks, and that appropriately selected Medicare beneficiaries will experience improved health outcomes. For inoperable patients with symptomatic severe AS there is no established alternative to TAVR. The dramatic survival benefits at one year and two years (absolute difference of 20% and 24%, respectively) and significant improvement in QOL demonstrate that TAVR is substantially more beneficial than standard therapy.^{1, 5, 11} The QOL results are especially important, as they account for both the harms and benefits of TAVR and confirm that transcatheter patients can expect meaningful improvements in net health outcomes from the patient’s perspective. Similarly, the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document, endorsed by 12 Societies in total, concludes that the benefit from TAVR in inoperable patients “greatly exceeds the risk.”¹⁴

For high-risk patients with symptomatic severe AS, surgical AVR is the gold standard. Both TAVR and AVR are associated with important, but different, peri-procedural hazards as noted earlier in this document. Overall, survival is comparable between groups at 30-days and one-year, with improvements reported for TAVR at 30-days in functional status and exercise capacity.¹⁰ Both TAVR and AVR patients also reported substantial improvement in disease-specific and generic QOL over one-year follow-up.¹² The 2012 ACCF/AATS/SCAI/STS Expert Consensus Document concludes that the data from Cohort A of The PARTNER Trial “support TAVR as an acceptable alternative to surgical AVR in selected high-risk operable patients.”¹⁴

II. Coverage of Clinical Studies

Edwards remains firmly committed to continued evidence generation on TAVR and agrees that clinical trials must be well-designed and adequately powered. However, as described more fully

below, Edwards is concerned with CMS' proposed requirement limiting coverage for unlabeled uses to superiority trial designs. CMS' proposal undermines the agency's efforts to promote continued US-based clinical investigations in Medicare beneficiaries aimed at better understanding key determinants of health and QOL outcomes.

Noninferiority and other clinical trial designs play an important role in the advancement of medical technology. The FDA has routinely approved noninferiority trial designs as the basis for device approvals, considering them the best methodological approach in situations where existing standards of care are well-established and effective. Therefore, we believe patients will benefit from ongoing evidence generation for new indications and next generation TAVR devices through continued coverage of Category B Investigational Device Exemption (IDE) trials approved by the FDA, including noninferiority trial designs.

Edwards recognizes that an IDE trial may not be possible for some important, but small, patient populations that otherwise would not be eligible for coverage under the proposed decision. We support the Society of Thoracic Surgeons and the American College of Cardiology's ("the requestors") initially proposed National Coverage Determination (NCD) language addressing Medicare coverage for certain unlabeled indications that would be most appropriately provided under Coverage with Evidence Development (CED). Specifically, in addition to those identified in the requestors' draft NCD, we believe that the covered clinical circumstances should also include "valve-in-valve" patients, End-Stage Renal Disease (ESRD) patients, and patients with untreated clinically significant coronary artery disease requiring concomitant revascularization. Medicare coverage under CED for these populations should be allowed in situations where patient outcomes will be assessed through well-designed and controlled observational studies with participation in a prospective national registry.

A. Superiority Trial Designs Generally Are Not Appropriate for Investigation of TAVR

The proposed decision memo for TAVR specifies that for unlabeled uses of TAVR, studies must have a "...Superiority (not non-inferiority) TAVR study design" as a condition for coverage. Superiority trials have an important place in the development of clinical evidence, but the proposed decision memo's restriction to reimbursing only superiority trials is unnecessarily restrictive, would subvert the intention of CMS' IDE policy, and would inappropriately deny access for some beneficiaries. Further, it could pose a serious risk that important clinical trials would move outside of the U.S.

Superiority trials are the accepted standard when testing a new drug or device against the natural progression of the disease. However, when an accepted, highly effective treatment already exists, such as open-heart surgery, a well-designed, adequately powered noninferiority trial typically is used to determine the new therapy's comparability while also collecting additional data that can demonstrate an overall benefit to patients. Especially when the new therapy is substantially less invasive than the existing therapy, establishing comparability on the most important clinical endpoint (e.g., mortality) allows for the collection of data in other areas such as QOL or cost effectiveness. Combined, this data can demonstrate an overall superior

outcome and benefit for patients. However, in these circumstances the primary clinical endpoints will almost always be assessed using a noninferiority standard.

In most cases, superiority trial designs are no longer appropriate in the investigation of new indications or “next generation” TAVR devices, because the clinical trials are no longer testing a new therapy against the natural history of the disease or optimal medical management, but rather against a highly effective established standard of care. In cases where the difference between the expected primary outcome of two therapies is relatively small, powering a trial for a superiority endpoint may create an impractically large trial, thereby dramatically increasing the costs and time required.

The FDA routinely has approved noninferiority trial designs as the best methodological approach for device approvals when existing standards of care are well-established and provide demonstrable health benefits. For example, PARTNER II Cohort B originally was designed as a superiority trial against medical management (similar to PARTNER I Cohort B); however, after results of PARTNER I were reported, clinical experts and the FDA deemed the design unethical and suggested a change to a noninferiority design.

CMS has also provided coverage for technologies in cases where the evidence supporting improved health outcomes is drawn primarily from well-designed and conducted noninferiority trials. We are not aware of any NCDs in which CMS has instituted coverage requirements for clinical trials solely on the basis of their design. Rather, CMS typically has required adherence to an established set of standards of scientific integrity and relevance to the Medicare population, and allowed appropriate discretion for clinical trial sponsors to decide which trial design is most appropriate to answer relevant research questions.

B. PARTNER Trial Design Addresses Most Important Clinical and QOL Questions

As discussed in Section I, in collaboration with the FDA, a superiority design was chosen for the Cohort B arm (inoperable patients) of the PARTNER I trial. Cohort B was designed as a superiority trial in order to establish TAVR’s effectiveness relative to medical management for inoperable patients. That trial demonstrated statistically significant survival improvements in patients randomized to TAVR versus standard therapy, making it no longer ethical to randomize inoperable patients to medical management in future clinical trials.

On the other hand, for operable high-risk Cohort A patients, for whom the highly effective surgical AVR is the gold-standard therapy, statistically significant differences in the mortality endpoints between TAVR and AVR were not anticipated. Thus, the Cohort A arm was designed in collaboration with the FDA to assess noninferiority compared to AVR.

The Cohort A results demonstrated that “transcatheter replacement is an alternative to surgical replacement in a well-chosen, high-risk subgroup of patients with aortic stenosis.”⁹ The study showed that each therapy has important but different peri-procedural hazards and post-operative requirements that are likely to impact patient and physician decision making.

Thus, noninferiority trials are ideally suited to situations when a new treatment has at least comparable efficacy to the standard of care and has other distinct advantages such as, in this case, a far less-invasive procedure. Unlike open-heart surgery, TAVR does not require full sternotomy, placing the patient on heart-lung bypass, a prolonged period under general anesthesia, and a longer and more complicated recovery time.

C. Limiting Coverage to Studies with a Superiority Design Would Have a Chilling Effect on Evidence Generation

Edwards is deeply concerned that a superiority design requirement in the final NCD would undermine CMS' and FDA's efforts to stimulate future clinical investigations that have the potential to benefit patients. Restricting Medicare coverage to studies with superiority designs would have the immediate impact of limiting Medicare beneficiary enrollment—the primary patients of relevance for TAVR—in most ongoing and future investigations of TAVR, including the Category B IDE trials that are currently underway and for which reimbursement is currently being provided by local contractors. A requirement for superiority design also may create incentives for researchers and industry to design trials that meet CMS superiority requirements, but utilize inappropriate or inadequate endpoints. Such an incentive may prevent answers to the most important clinical and QOL questions.

Edwards is among many manufacturers either in the design or enrollment phases of studies investigating device or delivery system improvements or additional indications for TAVR. The company has a large, randomized US-based trial underway, PARTNER II**, which is evaluating the SAPIEN XT, a device already approved for use in many countries outside the US. SAPIEN XT was designed to reduce the delivery system profile for both transfemoral and transapical applications. These reductions in the size of the delivery system, and the addition of new valve sizes, may reduce adverse events as well as support expansion of the study population to include patients previously excluded due to anatomical limitations. The trial design calls for the enrollment of up to 3,000 patients in two cohorts of inoperable and intermediate-risk operable patients. The primary endpoints to be evaluated are a composite of death and major stroke, with secondary endpoints that include valve performance and QOL indicators.

PARTNER II was designed, in consultation with the FDA, with a noninferiority design for the primary endpoint (composite of death and stroke) given the existence of alternative therapies with established benefit for both cohorts of patients (SAPIEN for Cohort B; AVR for Cohort A). A primary objective of the trial is to further evaluate both the risks (e.g., stroke rate, vascular complications) and benefits (e.g., mortality, QOL, reduction in procedure time) of an improved device in a broader population of patients. A decision by CMS to limit coverage to studies with superiority designs could delay or halt the enrollment of PARTNER II and other trials currently underway or in the design stages, thereby slowing the advancement of this therapy in the US.

** Clinicaltrials.gov identifier NCT00530894

In addition, CMS should consider the impact that inconsistent trial design standards for device approval and coverage determinations may have on clinical trial development and resulting evidence for a broad range of medical technologies. This inconsistency also may run contrary to recent efforts by the FDA and CMS to improve the approval and coverage process.

We urge CMS to remove language in its proposed decision that limits Medicare coverage for unlabeled uses to studies with a superiority design.

D. CMS Should Cover Additional Indications for TAVR in the Context of Category B IDE Trials

CMS' Category B IDE trial regulation^{††} is intended to provide Medicare beneficiaries with access to the latest advances in medical technology while facilitating the collection of data on these devices through clinical trials. Another of CMS' stated intentions in promulgating the regulation is to provide incentives to manufacturers to continue to pursue clinical development. Indeed, this regulation has led to broader coverage of certain investigational devices, particularly in the area of cardiac devices, leading to better and more evidence to inform clinical practice.

Coverage for IDE trials does not pose an undue cost burden to the Medicare program. The regulation recognizes that payment for an IDE trial should be no greater than payment for an alternative therapy the beneficiary would otherwise have received; in the case of PARTNER II, TAVR for eligible inoperable beneficiaries and AVR for high-risk operable patients.

TAVR is a rapidly developing technology and additional improvements and indications are likely to be assessed by the FDA in the coming years. Coverage of TAVR in Category B IDE trials would ensure that, in the future, additional Medicare patients could benefit quickly from improvements in this less-invasive approach after they are determined by the FDA to be safe and effective. Finally, we do not believe the requestors' intentions were to limit Medicare coverage of Category B IDE clinical trials in this area. IDE trials will assist in growing the evidentiary base for the use of TAVR that can inform improvements in clinical practice and help Medicare beneficiaries and providers make the most appropriate therapeutic decisions. As CMS finalizes its coverage policy for TAVR, we urge CMS to maintain coverage for FDA-approved Category B IDE trials.

E. CMS Should Encourage Data Collection in Small, But Important, Populations Through CED

The requestors' proposed NCD language explicitly addressed the issue of CED for small patient subpopulations for certain unlabeled indications. The specific indications included: 1) Aortic valve is a congenital unicuspid or bicuspid valve, or is non-calcified; 2) Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency; 3) severe ventricular dysfunction with LVEF < 20; 4) Renal insufficiency (Creatinine > 3.0) and/or

^{††} 42 CFR 405.201

ESRD requiring chronic dialysis; 5) Low gradient low output aortic stenosis; and 6) Patients who have significant associated valvular lesions that cannot be treated surgically.

As CMS notes in the CED guidance document^{##} made available in the proposed decision memo, Medicare coverage may be extended to patients enrolled in a clinical research study for certain indications where sufficient evidence may not be available because: 1) available clinical research studies may not have included specific patient subgroups or patients with disease characteristics that are highly prevalent in the Medicare population; and, 2) the available clinical research may have failed to adequately address the risks and benefits to Medicare beneficiaries for off-label or other uses of a drug, biologic, service or device.

Edwards understands that a Category B IDE trial may not be practical for some of these important, but small populations, and supports coverage for these beneficiaries through CED. We encourage CMS to cover through CED those populations outlined in the requestors' proposed NCD language. While some evidence in the literature suggests this therapy could provide benefits to these subpopulations of patients, these populations were excluded from enrollment in the PARTNER and PARTNER II trials. Therefore, limited clinical evidence exists to support or refute claims of possible benefits to these patients. As discussed with the requestors and described in our previously submitted comments, we support expansion of the covered clinical circumstances to include "valve-in-valve" patients, ESRD patients, and patients with untreated clinically significant coronary artery disease (CAD) requiring concomitant revascularization.

As indicated in the proposed decision memo, the optimal management of CAD in the setting of TAVR is not well defined, since patients with recent or untreated clinically significant CAD requiring revascularization (as well as significant peripheral vascular disease) were intentionally excluded from The PARTNER Trial. The European clinical experience demonstrates that among carefully selected patients, revascularization by means of percutaneous coronary interventions (PCI) is feasible and safe when performed in addition to TAVR either as a staged or a concomitant intervention.²⁸⁻³¹ Based on these findings, we believe the presence of CAD should not preclude otherwise eligible patients from receiving treatment. In fact, the CED provisions in the proposed decision memo appear to be the perfect setting to further evaluate the optimal management of TAVR concomitant with CAD.

Absent coverage under CED, many of these inoperable patients will die and evidence collection for these populations will not be generated or available to help further define appropriate populations who could benefit from TAVR. Coverage under CED for these populations that otherwise would not be eligible for coverage under the proposed decision should be allowed under circumstances where outcomes will be assessed through a well-designed and controlled observational study with participation in a prospective national registry.

We are confident that, as currently designed, the STS/ACC TVT Registry captures the relevant outcomes with respect to mortality, functional improvement, stroke, other major adverse

^{##} <http://www.cms.gov/determinationprocess/downloads/ced.pdf>

cardiovascular events, length of hospital stay, and other important clinical and health outcome related events. As such, we believe that given the registry linkage to CMS data for long-term follow-up, data will be sufficient to assess the long-term outcomes and adverse events in these small populations without initially requiring further clinical evidence through additional studies.

III. Recommended TAVR Program Facility and Heart Team Criteria

Edwards appreciates CMS' principled approach to developing a comprehensive set of facility and operator criteria designed to achieve a balance between adequate patient access and safety. The proposed criteria are a good start in providing reasonable assurance that TAVR is used safely and responsibly in institutions where adequate clinical expertise resides. However, we believe that some of the proposed criteria undermine CMS' effort to encourage a multi-disciplinary heart team approach and may disqualify many sites that have already been providing TAVR with high-quality results, including many facilities that participated in The PARTNER Trial.

Based on our experience conducting pivotal clinical trials and providing TAVR in hundreds of centers around the world, excellent patient outcomes are best achieved when TAVR programs are located in institutions that are highly experienced in cardiac care, with high-functioning multi-disciplinary heart teams dedicated to and experienced in TAVR. We therefore respectfully recommend that CMS amend its proposed facility and individual operator requirements to reflect a heart team-centric approach.

A. Qualified Facility Criteria

Our experience indicates that hospitals with strong cardiac programs are more likely to possess the qualities that predict TAVR success: related procedural experience (e.g., AVRs and PCIs), familiarity and skills in advanced cardiac techniques, a well-developed and adaptable cardiac care infrastructure, cardiac imaging expertise, and institutional commitment to comprehensive, patient-focused cardiac care. Institutions with these attributes tend to recruit the best talent, achieve the best work-up and post-operative management of complex heart valve disease patients, and—most importantly—achieve positive patient outcomes. Therefore, facility-based procedural volume requirements are good qualification measures in the absence of demonstrated TAVR performance.

After a qualified hospital initiates an active TAVR program, and as long as the TAVR program is delivering positive patient outcomes measured and reported in a national registry, maintenance of non-TAVR procedure volumes becomes less relevant. However, it does remain important for hospitals to maintain an ongoing valve surgery capability to support a strong TAVR program.

We support limiting coverage to hospitals that performed ≥ 50 AVRs , $\geq 1,000$ catheterizations, and ≥ 400 PCIs (at least 20 of which were structural heart cases) in the year before the initiation of a TAVR program. To maintain general proficiency in relevant

cardiac care, facilities must also maintain minimum volumes of either ≥ 20 AVRs a year or ≥ 40 AVRs every 2 years.

B. Heart Team Composition

Excellent patient outcomes in a TAVR program also depend on assembling a cohesive and committed TAVR heart team. Edwards is dedicated to the heart team concept, which has been developed through our experience managing The PARTNER Trial in the US and commercializing TAVR globally. The most successful heart teams are typically comprised of clinicians that have committed themselves to the extensive training, proctoring, patient screening, communication, and scheduling that is required to start and maintain a robust and disciplined TAVR program.

Edwards believes the TAVR facility is in the best position to identify and assemble an experienced heart team. A qualified site's first significant step toward building a successful local TAVR heart team is the initiation of the TAVR site activation program, where a qualified site is educated on the TAVR procedure, required time commitment, and necessary structure and skills of their heart team. In our experience, heart team membership may change substantially after these meetings, with the facility better understanding the commitment and team dynamics required for success.

We believe that at least two engaged cardiothoracic surgeons and two interventional cardiologists at each site must lead and coordinate all clinicians to form a high-functioning multi-disciplinary heart team. Additional support personnel, such as clinical cardiologists, echocardiographers, anesthesiologists, intensivists, valve clinic coordinators, and other clinicians should be made available as needed.

C. Heart Team Experience

In the heart team-focused treatment model, the collective experience of the entire team is more important than the individual clinician experience. A TAVR team comprised of clinicians with large volumes of related procedures do not necessarily achieve optimal patient results. To date, Edwards has had a great deal of success with TAVR programs globally without the imposition of rigid criteria for individual operators, thus allowing for flexibility in maximizing effective team dynamics.

Edwards has an enormous amount of respect for clinical societies' expertise in matters related to their individual specialties. We have worked closely with the Society of Thoracic Surgeons and the American College of Cardiology over the last several months to develop an understanding of what they believe is the most appropriate approach to developing a fully-functioning heart team.

While we believe that societies are expert at developing and maintaining minimum credentialing criteria for individual clinicians within their respective specialties, we respectfully disagree with the proposed approach of setting additional experience criteria for individual members of the

heart team. We believe that requiring a facility to demonstrate that it has the requisite infrastructure and experienced heart team should be sufficient.

Based on our extensive experience, Edwards has firsthand insight into what constitutes minimum requirements for a heart team qualified to perform TAVR. We therefore recommend that heart team-based criteria should replace the proposed individual experience requirements.

Prior to initiating a TAVR program, eligible heart teams must have performed the following procedures: ≥ 25 AVRs in the prior year and ≥ 75 PCIs in the prior year. Thereafter, the heart team must maintain TAVR experience, with minimum volumes of either ≥ 20 TAVRs a year or ≥ 40 TAVRs every 2 years.

D. Continued Heart Team Performance

Edwards encourages CMS to adopt patient outcomes criteria—as detailed in the summary below—which heart teams are continually measured against in a national qualified TAVR registry. Establishing and monitoring heart team-based performance would promote the improvement of national outcomes over time. In order to adequately assess collective heart team experience, we recommend the evaluation of heart teams every two years. If a heart team does not meet pre-determined patient outcome criteria, then the team must re-train and re-proctor, and ultimately develop a remediation plan, if necessary.

E. Summary of Proposed Facility and Heart Team Criteria

- For a facility to be qualified for TAVR it must:
 - Be a leader in cardiac care, with minimum, past procedural experience:
 - ≥50 AVRs in the prior year
 - ≥1000 catheterizations in the prior year
 - ≥400 PCIs in the prior year, at least 20 of which are structural heart cases
 - 1. Structural heart cases include but are not limited to BAVs, patent foramen ovale closure (PFO), atrial septal defect repair (ASD), ventricular septal defect (VSD), and percutaneous mitral valve repair (PMVR)
 - Designate a TAVR heart team
 - Two cardiac surgeons and two interventional cardiologists to lead the team
 - 1. At least one of the heart team's cardiac surgeons must be board-certified or eligible in cardiac surgery
 - 2. At least one of the heart team's interventional cardiologists must be board-certified or eligible in interventional cardiology
 - Identify other relevant clinician team members, which frequently include clinical cardiologists, echocardiographers, anesthesiologists, intensivists, valve clinic coordinators, and other clinicians, as needed
 - To qualify as a team at the initiation of a TAVR program, collectively, members of the heart team must have the following past procedural experience:
 - 1. ≥25 collective AVRs in the prior year
 - 2. ≥75 PCIs in the prior year
- After a qualified facility's TAVR program is established, the facility must:
 - Perform ≥20 TAVR procedures per year or ≥40 TAVR procedures every 2 years
 - After the program has been running for two years, the heart team must demonstrate the following patient outcomes, based on TAVR registry data (two-year average):
 - 30-day all-cause mortality ≤15%
 - 30-day significant neurological events ≤15%
 - ≥90% follow-up
 - ≥60% one-year survival rate for inoperable patients
 - Maintain ≥20 AVR procedures per year or ≥40 AVR procedures every 2 years
 - Participate in a national qualified TAVR registry
 - Provide CMS a written affidavit attesting that criteria outlined in this section (TAVR volumes, patient outcomes, and AVR volumes) have been met
 - Certification to be provided on June 1 two years after TAVR program initiation and every other year thereafter
 - CMS retains the ability to grant individual facilities, under certain circumstances, exceptions to the above facility-based criteria

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