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March 17, 2006

Jyme Schafer MD, MPH
Lead Medical Officer
Division of Medical and Surgical Services
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dear Dr. Schafer:

RE: Proposed Decision Memo for Lumbar Artificial Disc Replacement (CAG-00292N)

DePuy Spine, Inc. is an operating company of DePuy, Inc. one of the world's leading designers, manufactures and suppliers of orthopedic devices and supplies. We are known throughout the medical world for the development, manufacture, and marketing of innovative solutions for a wide range of spinal pathologies. The purpose of this letter is to provide comments concerning the Centers for Medicare and Medicaid Services' (CMS) Proposed Decision Memorandum for Lumbar Artificial Disc Replacement (CAG-00292N). The proposed non-coverage determination put forth by CMS will have a direct and significant impact on motion preservation technology for the spine and the CHARITÉ™ Artificial Disc, manufactured by DePuy Spine, as well as the thousands of patients who can benefit from motion preserving technology.

We request that CMS reconsider its position regarding the lumbar artificial disk replacement, stated in its Proposed Decision Memorandum. We believe that CMS' Proposed Decision Memorandum is the result of improper interpretation of the evidence presented to it. In addition, we believe that there are several legal and policy reasons why CMS should reverse its current proposal that we outline in more detail below.

Summary of Recommendations:
In summary, we request that CMS issue a coverage determination with limitations that properly reflects the supporting evidence for the technology. This coverage should:

- Follow the existing Food and Drug Administration (FDA) Inclusion/Exclusion Criteria for the device;
- Entail further evaluation (e.g., DEXA screening, Plain Radiographs and/or CT scans) of patients who are candidates for the procedure; and
- Include surgeon profile criteria based on recommendations from the IDE surgeons' experience.

Further detail on these three recommendations can be found in Exhibits D and E of this document.

In addition, DePuy Spine plans to initiate a patient registry that will include patients covered under Medicare. We would be willing to share data from this registry with CMS and would appreciate CMS' input on the design to ensure we are capturing pertinent information. This combination of limited national coverage and a patient registry is a responsible way to offer access to the technology for appropriate patients in need of the device.

LEGAL AND POLICY CONCERNS WITH THE CMS PROPOSED DECISION MEMO

We have the following legal and policy concerns with CMS' proposed decision memo:

- It gives insufficient weight to the underlying FDA pre-market approval (PMA) study and excessive weight to less rigorous evaluations of the product;
- An absence of conclusive evidence on a new technology should not be the basis of a non-coverage decision;
- CMS is inappropriately basing its proposed national non-coverage decision on an undefined standard of "net health benefit."

Insufficient Weight on FDA PMA Study
We believe that CMS' proposed national non-coverage determination is the result of improper interpretation of the evidence presented to it. In the case of the Blumenthal [1] study, which formed the basis of FDA pre-market approval, CMS has given the study's findings insufficient weight. Moreover, CMS has given excessive weight to certain studies, which are not predictive of the clinical outcomes likely to be attained by use of the CHARITÉ Artificial Disc. Reliance on Level IV (case series) and Level V (expert opinion) data, detailing sub-optimal results or high rates of complications reflects the early experience with the CHARITÉ Artificial Disc where the techniques and selection criteria were still being refined. The Level IV and V data as cited in the proposed non-coverage decision memo is not a strong basis for evidenced-based decisions and should be weighted appropriately compared to the Level I (high quality randomized and controlled) data. The Level I data strongly suggests that there are beneficial outcomes for properly selected patients in the Medicare population and they should not be denied access to this technology.

An Absence of Conclusive Evidence Should Not Lead to Non-Coverage
The absence of broad, conclusive evidence does not equate to the absence of clinical value. CMS should not make national non-coverage decisions unless it has definitive clinical information that a product or service is irrefutably *not* effective or that it causes patient harm. Deciding not to cover promising technologies due to "insufficient" evidence undercuts beneficiary access to appropriate care

by limiting patient and physician choice of procedure, technology, and medicine. Such coverage decisions actually make it more difficult for Medicare beneficiaries to benefit from these technologies, more difficult for real world studies to be conducted, and more difficult for evidence to be gathered. By applying a higher coverage standard to newer technologies than those covered for a longer period of time, this trend could also bias patient options to older less effective technologies.

Given that clinical data collection is still in its nascent stage, CMS' proposed non-coverage determination is premature. National non-coverage determinations are only appropriate in circumstances under which the evidence definitively shows that a product does not offer a clinical benefit, and not in circumstances where, as here, the evidence is simply still evolving. CMS should not deprive Medicare beneficiaries of this potentially beneficial technology at such an early stage**.**

Pursuant to administrative law principles, CMS has a duty to issue a coverage decision that is based on substantial evidence.[i] CMS' rules regarding acceptance of a National Coverage Determination (NCD) request are consistent with these principles. CMS states that it will not accept an NCD request unless the requestor is prepared to furnish ample supporting evidence along with the request.[ii] This allows CMS to reach a proper decision based on complete and accurate information and avoid making decisions that stifle the diffusion of potentially valuable technologies for which data are still being accumulated.[iii] Notably, CMS did not adhere to its rules in accepting the request for an NCD regarding the CHARITÉ Artificial Disc. The letter initiating the CHARITÉ Artificial Disc NCD indicated merely that there was insufficient evidence regarding the benefits of the technology, and not that there is strong evidence of its ineffectiveness.[iv] While reiterating these concerns with inadequate evidence in its proposed NCD, CMS as well does not point to definitive proof that the CHARITÉ Artificial Disc has only limited benefits or substantial adverse effects. Thus, any medical necessity determination based on currently available evidence would be speculative, discordant with applicable administrative law principles, and contrary to CMS' own policies.

CMS Should Not Apply An Undefined "Net Health Benefit" Standard to the CHARITÉ Artificial Disc

It is patently inequitable to base any determination on the application of an undefined "net health benefit" standard.[v] CMS has not defined this standard, which has rendered its determinations unpredictable. Statutory provisions enacted by Congress in the MMA, as well as traditional notions of due process and fair play, require greater transparency in the establishment of standards of such importance.[vi] In the absence of any such clearly defined standard, arguably the fairest standard in this

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[i] *See*, *e.g.* State of New York o/b/o Bodnar v. Secretary of Health and Human Services, 903 F.2d 122, 126 (2d Cir. 1990) (requiring that medical necessity determinations be based on "substantial evidence"); Arruejo v. Thompson, 2001 WL 1563699, *9 (E.D.N.Y. 2001).

[ii] 68 Fed. Reg. 55634, 55637 (Sept. 16, 2003).

[iii] Furthermore, accepting requests for an NCD only from a party prepared to support it also allows CMS to avoid entanglement in a conflict between two competitors. For instance, one company could seek to block entry into the marketplace of a competitor by seeking to obtain a noncoverage NCD for the competitor's technology before the competitor has had an opportunity to establish itself and accrue evidence of the value of its technology. CMS' rejection of NCD requests by parties not prepared to furnish ample evidentiary support helps ensure that it is not co-opted into serving a private party's interests.

[iv] Letter to CMS Coverage and Analysis Group from Dr. Richard Deyo, dated August 5, 2005.

[v] Proposed Decision Memorandum, pg 23. To ensure that the pagination of the decision memorandum reviewed by CMS is the same pagination as the version of the document we have reviewed, we are including a copy of the decision memorandum as **Exhibit A** hereto.

[vi] *See*, *e.g.*, Social Security Act, § 1862(*l*). Pursuant to this statute, CMS must issue guidance documents that lay out the NCD process, which includes the application of the "net health benefit" standard. This provision applies to all NCDs issued from January 1, 2004 forward.

case would be the one courts have applied in reviewing other coverage determinations, *i.e.*, whether the item in question is safe and effective.[vii] Since this is the same standard as that applied by the FDA in approving a new device, CHARITÉ Artificial Disc's FDA approval, which was based on an extensive review by an expert panel, should suffice to establish the propriety of Medicare coverage as well.

THE EVIDENCE SUPPORTS THE EFFECTIVENESS OF THE CHARITÉ ARTIFICIAL DISC

Publication of the CHARITÉ Artificial Disc IDE study results in *Spine* on July 15, 2005, [1] is a landmark event not only in spine arthroplasty, but also in the history of spine care. The CHARITÉ Artificial Disc is one of only two spine devices that have been subjected to the rigors of a prospective, randomized, controlled multi-center clinical trial.

We maintain that CMS' proposed national non-coverage memorandum is inconsistent with the evidence it has reviewed. The definitive study conducted thus far is the Blumenthal[1] study, which determined with statistical certainty that the CHARITÉ Artificial Disc was at least equivalent to the anterior lumbar interbody fusion. We disagree with CMS' findings with respect to any purported methodological flaws within the design of the study or the conclusions reached thereby. Further, we believe that the studies CMS has relied on to show a lack of patient benefit or potential patient harm are irrelevant because they largely reflect the results of prior versions of the CHARITÉ Artificial Disc and variable patient selection criteria.

Currently, there are two frequently used instruments to assess the treatment effect for chronic low back pain from degenerative disc disease, the Oswestry Disability Index (ODI) and the Visual Analog Scale (VAS). The ODI is a patient reported outcome measure commonly used to evaluate treatment response in the management of spinal disorders. The measure is an indication of the level of pain and the interference with several physical activities (e.g., sleeping, self-care, sex life, social life, traveling). The ODI is on a scale of 0-100, 0 indicating no disability and 100 signifying complete disability. [10] A change of 10 units from baseline has been shown to be the minimum change to demonstrate clinical improvement for ODI. [6] The other commonly used outcome measure in chronic back pain treatment effect is the patient reported VAS, which is a method to assess pain intensity. The severity of back pain is recorded with a VAS ranging from 0 mm to 100 mm. On this scale, "0" represents no pain and "100" indicates that the pain is the worst imaginable. A change of 18-19 points from baseline has been shown to be the minimum change to demonstrate clinical improvement. [6]

Minimal Clinically Important Difference

In a study by Hägg, et al,[6] the minimum difference that is considered clinically significant for ODI was 10 units. The minimum clinically important difference (MCID) of VAS back pain was 18-19 units. This difference was compared to baseline, **not** between treatment arms.[viii]

[vii] *See*, *e.g.*, Estate of Lillian Aitken v. Shalala, 986 F.Supp. 57, 59 (D.Mass 1997) (upholding the "safe and effective" standard in a challenge to an NCD); *see also* Arruejo v. Thompson, 2001 WL 1563699, *9 (E.D.N.Y. 2001).

[viii] Proposed Decision Memorandum pages 5-6, **Exhibit A**.

	Treatment	Unit of Measurement (0-100)	Baseline	24 Months	Difference
Blumenthal [1]	CHARITÉ	Mean VAS (SD)	72.0 (14.7)	31.2 (28.4)	40.8
	BAK	Mean VAS (SD)	71.8 (14.7)	37.5 (31.2)	34.3

	Treatment	Unit of Measurement (0-100)	Baseline	24 Months	Difference
Blumenthal [1]	CHARITÉ	Mean ODI (SD)	50.6 (13.1)	26.3 (22.0)	24.3
	BAK	Mean ODI (SD)	52.1 (13.7)	30.5 (22.7)	21.6

Clearly, the outcomes in both VAS and ODI far exceeded the MCID. At 24 months, the improvement is nearly twice the MCID.

Geisler, FH, Blumenthal, SL; Guyer, RD et al. Alternative Statistical Testing Demonstrates Superiority of Lumbar Arthroplasty at 2 Years vs Fusion for the Treatment of One-Level Lumbar Degenerative Disc Disease at L4-5 or L5-S1. Accepted for podium presentation at the Annual Meeting of the Spine Arthroplasty Society, Montreal, Canada, May 9-13, 2006; the 13th Annual International Meeting on Advanced Spine Techniques (IMAST), Athens, Greece, July 11-15, 2006; and Spine Across The Sea, July 23-27, Maui, Hawaii.[ix]

Non-Parametric Tests

The statistical analysis of the ODI and VAS scores performed for the FDA, and reported in the paper by Blumenthal et al, [1] used Student's t-test, which assumes a normal distribution. This methodology was pre-specified in the statistical plan for the trial. The ODI and VAS scores followed a normal distribution at baseline. However, at the two-year follow-up, the endpoint of the study, the distribution of ODI and VAS scores were somewhat skewed. Therefore, a non-parametric test such as the Wilcoxon Rank Sum test [6] is a more appropriate statistical methodology.

This analysis included 71 subjects enrolled in the non-randomized treatment arm, a concern that was raised by CMS in the Proposed Decision Memorandum.[x] Further, this secondary analysis provides strong evidence that in fact, subjects receiving the CHARITÉ Artificial Disc experienced improvement in pain and disability level compared to their baseline levels that was both statistically significant and clinically important at all time points through two-year follow up.

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[ix] Exhibit B.

[x] Proposed Decision Memorandum page 11, **Exhibit A**.

RESPONSE TO OBJECTIONS

I. BAK IS A VALID COMPARATOR

The BAK Cage[xi] was chosen as the control device in the CHARITÉ Artificial Disc IDE study [1] for several reasons:

- The ideal control treatment for the IDE study of the CHARITÉ Artificial Disc would have been applicable for all patients to be studied, have the same clinical and radiographic endpoints, be similar in invasiveness, minimize introduction of bias, be approved for use by FDA, and be considered a standard of care. At the time the IDE study of the CHARITÉ Artificial Disc was started, the BAK fusion cage was the best available option and satisfied all of these criteria except the radiographic outcomes. Today there is still no available control group that would satisfy the criteria for similar radiographic endpoints and in this study the clinical outcomes for subjects in the BAK treatment group compare well with the current "gold" standard therapies. Thus the control remains an appropriate informative comparison group.
- The results from the control group confirmed the original, FDA IDE study of the BAK device performed by Kuslich, [7] demonstrating that this fusion procedure is safe and effective in properly indicated patients.
- The similarity of surgical approach for both treatments enabled a fair comparison of hospital stay, blood loss, and other adverse events. Other options for the control (e.g., 360º fusion) would be less ideal as they involve destruction of the posterior musculature making a fair comparison of pain and/or disability difficult if not impossible. Also, it would be extremely difficult to reconcile the neurological complications in the control group with the treatment group if the approaches were different.
- Furthermore, Geisler [5] performed a meta-analysis of clinical results in the literature with more recent interbody devices as well as 360° fusion. This analysis showed that outcomes have not dramatically improved compared to the results with BAK. Thus, clinical outcomes with the CHARITÉ Artificial Disc were equivalent to or better than those related to 360° or stand-alone interbody fusion reported in the literature. The CHARITÉ Artificial Disc also carries the added benefit of restoring and maintaining segmental motion postoperatively.

Approach/Instrumentation	% Change Mean VAS	Change in Mean ODI
Anterior Fusion with Cage and BMP-2 (InFUSE IDE)	-53.8	-33.4
Weighted mean 360° fusion via ALIF, PLIF or TLIF	-49.1	-20.6
Mean % change: CHARITÉ Artificial Disc	-57.5	-24.8

- Both the CHARITÉ Artificial Disc and the BAK interbody fusion device required removal of the intervertebral disc.
- The same surgical approach and comparable surgical techniques allowed for assessment of risk of adverse events associated with surgical technique.

[xi] Proposed Decision Memorandum page 20, **Exhibit A**.

In the six years between the trial planning stages and FDA's approval, other alternatives for treating patients for DDD have emerged. However, patients should not be penalized for this, nor denied access to a therapeutic intervention that is safe and effective for the treatment of DDD.

II. CHARITÉ ARTIFICIAL DISC IS SAFE FOR ITS INTENDED USE

In order to appropriately compare Medical Device Reports (MDRs) with data from the IDE trial, adverse events should be reported as a rate, rather than an absolute number.[xii] In contrast with the older findings citied by CMS in its Proposed Decision Memorandum, DePuy Spine has analyzed the data from the MDRs associated with the CHARITÉ Artificial Disc and submitted to the FDA, in accordance with regulatory requirements, for the first 12 months following FDA approval of the device (October 26, 2004 – October 15, 2005). In addition, DePuy Spine has worked with a contract research organization (CRO) to conduct a Surgeon Survey of all surgeons who have been trained to implant the device at the DePuy Spine sponsored training courses beginning December 2004. The primary goal of this effort was to collect information directly from trained surgeons on their experience using the CHARITÉ Artificial Disc since its introduction to the US market and to compare this information with information provided to DePuy Spine through MDR reporting.

ADVERSE EVENTS	**Updated MDR (12-31-2005)**	**IDE (Randomized + Training)**
Anterior Migration	0.6%	1.1%
Sizing/ Malposition	0.5%	0.4%
Bone Fragment	0.0%	0.0%
Posterior Element Fracture	0.3%	0.4%
Subsidence	0.2%	0.0%
Vascular injury	0.3%	0.4%
Death*	0.1%	0.4%
Other	0.5%	1.1%
TOTAL	**2.5%**	**3.8%**

*Non-Device Related

The "other" category included reports of: endplate fracture, infection, neurological changes, patient selection errors, posterior migration, osteoporosis (unrecognized pre-op), removal for persistent pain and transitional segments.

The Surgeon Survey had a 13% response rate. This response rate was considered good based on the relatively short duration (8 weeks) and the fact that it captured a relatively large proportion, over 30% of the cases performed post FDA-approval. The survey also included high and low volume users. This yielded a sufficiently large and broad sample size for comparison to post-approval MDRs.

By the end of 2005, there were approximately 4,500 devices implanted in the US. The table above contains key adverse event rates from the IDE study, which included updated MDRs submitted to the FDA post-approval. Adverse events included major adverse events as defined by the FDA and other

[xii] Proposed Decision Memorandum page 17, **Exhibit A**.

adverse events as reported to the company as MDRs. These are preliminary data and may not reflect IDE rates given shorter follow-up.

The survey results confirm that the rate of complications reported through DePuy Spine's MDR reporting process are consistent with the experience of the surgeon community in broad commercial use. Further, the rates of complications reported during the survey and through the MDR reporting process are trending similar to the rates seen in the pivotal IDE clinical trial of the CHARITÉ Artificial Disc. The overall reported key adverse event rates were: IDE = 3.8%, updated MDR data for Dec 31, 2005 = 2.5%. The results from the CRO survey = 2.7%. In addition to the events listed in the table, posterior fixation has been reported in 0.1% of cases through December 2005, however, this represents less than 1 year of experience with the implant. In the IDE study, posterior fixation for pain was reported for 3.6% of the CHARITÉ Artificial Disc subjects and 9.1% (n=9) for the control.

With respect to patient deaths, there was one death in the IDE study attributed to an overdose of narcotic medication and illicit drugs. There were 3 deaths in the MDR group; two confirmed pulmonary embolism (PE) after a revision procedure and the second, a presumed PE two days after the index surgery (autopsy was refused).

III. A STATISTICAL ANALYSIS PLAN WAS INCLUDED IN THE ORIGINAL PROTOCOL

Despite CMS' statements to the contrary, [xiii] the fundamental elements of the statistical analysis plan for the study were included in the protocol prior to enrollment into the study. These elements included the study hypothesis, statistical methodology (i.e., Blackwelders), the primary endpoint, and secondary endpoints. These components were then further elaborated on in a separate document, the Statistical Analysis Plan (SAP).

The analysis plan was documented in the SAP that was prepared in October 2001. Although the analysis plan was not prepared prior to the start of enrollment it was written before enrollment was completed in April of 2002. Further, the plan was written over 2 years before the data were available for analysis in February 2004.

Although this plan underwent some modification prior to completion of the study, the bulk of the analyses that were conducted for the PMA were described in this first version of the SAP. In March of 2003 the SAP was amended to rearrange the formats of some of the tables and listings and to put some clarity in some of the sections that were previously described with insufficient detail. Additional amendments were made to the SAP in November 2003 that reflected the discussion and agreements made with the FDA at the pre-PMA meeting. None of these modifications to the plan were based on analysis of the data.

IV. THE CALCULATION APPEARS TO BE A STRICT INTENTION TO TREAT ANALYSIS[xiv]

The final dataset reported to FDA, and used to prepare the Blumenthal [1] and McAfee [9] manuscripts did not specify an intent-to-treat analysis, however, the principles were adhered to. Specifically:

1). All subjects received the treatment that they were assigned to, and their results were kept with their assigned group and

[xiii] Proposed Decision Memorandum page 9, **Exhibit A**
[xiv] Proposed Decision Memorandum page 9, **Exhibit A**

2). All subjects were accounted for in the final analysis with missing data treated as failures.

The impact of the missing data was assessed using a series of sensitivity analyses. These included a Last Observation Carried Forward, Repeated Measures Rates, incomplete data as failures, and incomplete data as failures. In all instances the study conclusion supporting the CHARITÉ Artificial Disc was strongly supported with p-values less then 0.05 in all cases (0.0001, 0.0012, 0.0005, and 0.0004 respectively).

V. A PROPER SENSITIVITY ANALYSES WAS CONDUCTED TO EVALUATE THE POTENTIAL IMPACT OF INCOMPLETE SUBJECTS

CMS raised the issue regarding the sensitivity analyses for patients that did not have complete follow-up data at the time of expedited review.[xv] The Proposed Decision Memorandum inaccurately states that the only imputation method was "last value carried forward." However, a variety of sensitivity analyses were performed in support of the non-inferiority claim. These included a number of variations using Blackwelder's Test based on different subject populations and imputations for missing values, a repeated measures model, and a multiple-imputation approach.

The following sensitivity analyses were completed in support of the non-inferiority claim using Blackwelder's Test to establish bioequivalence based on different subject populations and imputations. Each of the results supported the non-inferiority claim with $\delta = 0.15$.

- All Randomized Subjects, Non-Completers as Failures (protocol specified primary efficacy analysis)
- All Randomized Subjects, Last Observation Carried Forward (LOCF)
- All Randomized Subjects, Completers Only
- All Randomized Subjects, Completers in 24-Month Window

Based on a request from FDA, further sensitivity analyses were completed in support of the non-inferiority claim using Blackwelder's Test, this time with $\delta = 0.1$. Again, each of the results, with the exception of the worst-case scenario, supported the non-inferiority claim with $\delta = 0.1$.

- All Randomized Subjects, Non-Completers as Failures (protocol specified primary efficacy analysis)
- All Randomized Subjects, Non-Completers as Successes
- All Randomized Subjects, Last Observation Carried Forward (LOCF)
- All Randomized Subjects, Modified LOCF (see below)
- All Randomized Subjects, Completers Only
- All Randomized Subjects, Completers in 24-Month Window

For the Modified LOCF, results from 12-months were carried forward, but 6-month LOCF results were handled according to the worst-case definition.

In addition to the variations of Blackwelder's Test, a repeated measures model and multiple-imputation approach were used to estimate response rates at 24-months. For each of these analyses, the same hypothesis test was performed using contrasts. In the multiple-imputation analysis, all variables were included in the model specified by the FDA without regard to significance. While this

[xv] Proposed Decision Memorandum page 21, **Exhibit A**

reduced the degrees of freedom by including many estimated terms, it did not affect the overall non-inferiority comparison.

Results

The Blackwelder's test results for the various sensitivity analyses are summarized in Table A below. All of these sensitivity analyses support the non-inferiority claim. At the time of the FDA Advisory Panel Meeting, the FDA required calculation of the worst-case scenario (missing CHARITÉ Artificial Disc are considered failures and missing BAK are considered successes) because some patients had not yet been assessed for their final follow-up. Shortly after the panel meeting all subjects had their final assessment determined. All data presentations since that time (i.e., Blumenthal [1], McAfee [9] and Geisler [4] non-parametric analysis) have included all study subjects so this is an unwarranted asymmetric imputation is not justified by any observations from the study. The PMA approval by the FDA is evidence that the worst-case scenario does not bear merit.

Table A - Summary of Blackwelder's Test Sensitivity Test Results

Rule	CHARITÉ N / N (%)	BAK N / N (%)	Blackwelder's Test P-value (δ=0.15)	Blackwelder's Test P-value (δ=0.1)
Non-Completers as Failures	117/205 (57%)	46/99 (46%)	< .0001	0.0004
Non-Completers as Successes	138/205 (67%)	64/99 (65%)	--	0.0147
LOCF	129/205 (63%)	51/99 (52%)	< .0001	0.0002
Modified LOCF	129/205 (63%)	59/99 (60%)	--	0.0128
Completers[xvi] Only	117/184 (64%)	46/81 (57%)	0.0004	0.0052
Completers in 24-Month Window	103/164 (63%)	43/73 (59%)	0.0030	0.0217

The repeated measures analysis modeled success by visit for the all randomized subject population. This analysis provided showed that for 6, 12, and 24-month visits the estimated success rates for the CHARITÉ Artificial Disc arm were higher (69.2, 66.9, 63.5 respectively) than those of the BAK cage (47.8, 58.5, 54.6 respectively). In the repeated measures analysis, the p-value for the non-inferiority comparison of the arms was significant with a p-value of < 0.0001 for δ=0.15 and a p-value of 0.0015 for δ=0.1. A comparison of any treatment difference across the three visits was also statistically significant ($p<0.01$).

[xvi] A Completer is defined as a subject that has both the 24-month Oswestry Disability Index and the 24-month neurological exam completed.

VI. COST/BENEFIT OF SURGERY FOR DEGENERATIVE DISC DISEASE

Beyond our disagreement with CMS' analysis of the clinical evidence relating to the CHARITÉ Artificial Disc, we also question CMS' cost data. To gain further insight into potential costs, we have engaged an outside team of economists to project the likely costs to the Medicare program of this technology.

Covance Economic Model

Unlike many new technologies, which often result in an increased cost to patients, hospital, payers or a combination of these entities, the CHARITÉ Artificial Disc will likely lower costs. The CHARITÉ Artificial Disc is a novel treatment for lumbar DDD, and a technological advance. An economic model was created to determine the impact of this device on the cost of care. Covance Market Access Services, Gaithersburg, MD and San Diego, CA developed the economic model in collaboration with DePuy Spine and the clinical investigators.

The economic model assessed actual costs, not charges for a procedure. The model represents a reasonable estimate of costs based on available data and assumptions made in the absence of data.

- The four comparator groups included in the model are:
- One-level lumbar total disc replacement with the CHARITÉ Artificial Disc.
- One-level stand alone anterior interbody fusion with instrumentation containing autograft from iliac crest bone graft (ALIF w/ICBG).
- One-level stand alone interbody fusion with INFUSE® Bone Graft and LT-Cages® (ALIF w/BMP), Medtronic Sofamor Danek, Inc.
- One-level instrumented (pedicle screws) posterior lumbar interbody fusion (IPLIF) with ICBG.

Data was collected from a number of sources including: peer-reviewed medical literature; PMA clinical trial reports, protocols, summaries, etc.; clinical expert opinion; commercial payer claims data; clinical trial claims data; and hospital UB-92 claim forms. All currency is reported in 2005 U.S. dollars.

Results of the Model: Payer Perspective A 2-Year Time Horizon (DRG Payment)

	CHARITÉ Artificial Disc	ALIF with ICBG	ALIF with BMP	IPLIF with ICBG
Index Hospitalization*	$9,611	$22,338	$22,165	$24,663
Successful Surgery Follow-Up Care	$6,032	$6,899	$6,010	$6,010
Unsuccessful Surgery Follow-Up Care	$535	$911	$1,214	$1,214
Re-surgery	$1,106	$1,827	$2,437	$2,437
Complications	$194	$721	$370	$728
Total Payer Cost Per Patient	**$17,478**	**$32,697**	**$32,196**	**$35,052**

*The index hospitalization costs consists of a weighted average of hospital payments (DRGs) plus all relevant physician payments (CPTs).

CHARITÉ Artificial Disc: 42% of procedures falling under DRG 499 and 58% of the procedures falling under DRG 500 from the Federal Register August 12, 2005 CMS CY 2006 IPPS Final Rule plus CPT 22851 and the the T-Code of 0091T - Total disc arthroplasty (artificial disc), anterior approach, including discectomy, single interspace; lumbar.
ALIF with ICBG: 59% of procedures falling under DRG 497 and 41% of procedures falling under DRG 498 from the Federal Register August 12, 2005 CY 2006 IPPS Final Rule plus CPTs 20937, 22558, 22851.

ALIF with BMP: 59% of procedures falling under DRG 497 and 41% of procedures falling under DRG 498 from the Federal Register August 12, 2005 CMS CY 2006 IPPS Final Rule plus CPTs 22558, 22851.
IPLIF with ICBG: 59% of procedures falling under DRG 497 and 41% of procedures falling under DRG 498 from the Federal Register August 12, 2005 CMS CY 2006 IPPS Final Rule plus CPTs 20937, 22630, 22840, 22851.

Conclusions

- The model demonstrates that the costs associated to a payer with a DRG payment methodology for a single-level CHARITÉ Artificial Disc procedure are significantly less than costs associated with the three comparator groups.
- The introduction of the CHARITÉ Artificial Disc as a novel device for the treatment of lumbar degenerative disc disease does not increase costs associated with the treatment of these patients.

CMS PROPOSED NON-COVERAGE DECISION IS NOT SUPPORTED BY THE CITED EVIDENCE

As noted in the Proposed Decision Memorandum, CMS cited several cases series, which include Griffith et al. (1994), Cinotti et al (1996), Zeegers (1999), and Caspi (2003).

Zeegers reported on 50 patients with 2-year follow-up. As admitted in the conclusion, the indications for total disc replacement in the late 1990's were still widely variable, and did not represent the relatively narrow on-label FDA indications for the CHARITÉ Artificial Disc.

Cinotti and Caspi (as with Zeegers and Griffith) reported results from a time when indications were highly variable, only a limited number of device component sizes were available, and basic, rudimentary instrumentation was utilized.

A review paper by de Kleuver et al is cited. This literature review was performed in 2002 and published in 2003, over a year before the results of the prospective, randomized, controlled IDE trial of the CHARITÉ Artificial Disc were made public, and over two years before the results were published in the peer-reviewed literature (Spine, 2005). This article is outdated.

The paper by van Ooij reported operations in 27 patients is cited, as is the fact that these patients are from an original cohort of 500 patients. This yields a known complication rate in these patients of 5.4% (which is not cited in the memo). This is comparable to the complication rate seen in the IDE study. Again, the indications for lumbar disc replacement were highly variable when compared to the IDE study and current recommendations (unlike today). In addition, only a limited number of device sizes were available (unlike today), with basic first generation instrumentation (unlike today).

Throughout the memo, revision rates from various studies are cited. However, revision rates for lumbar fusion are equally high as reported by McAfee (2005, NASS) and as reported by Medtronic Sofamor Danek (INFUSE® SS&E, Federal Register, 10.4% re-operation rate for patients receiving LT-Cages and INFUSE for lumbar fusion). Federal Register, May 26, 2004. http://www.fda.gov/cdrh/pdf/P000058.html

The Griffith paper does not separate SB I and II data from SB III data. This paper reports outcomes that include 58 prototype devices, of different design, of different materials, and were never made commercially available. Knowledge gained from the early use of these devices helped inform the design of later generations of the device and instruments.

All of the papers named above were published prior to the completion of the IDE study and publication of the results in *Spine.* [1] These studies did not describe rigorous inclusion and exclusion criteria and patient selection as defined in the prospective, randomized controlled trial used for the IDE.

The paper by Putzier et al (*European Spine Journal*, published online, 2005) is given significant attention in the memo because it represents the longest published follow-up of patients implanted with a CHARITÉ Artificial Disc. Tables in the memo show a distinction between SB I, II, and III models of the device. The Proposed Decision Memorandum fails to take into account that this is the earliest clinical use of the SB III device. Indications, sizing, and instrumentation are all important distinctive issues compared to what is known and in use in 2005. Prof. Dr. Karin Büttner-Janz, a co-inventor of the device, disputes the accuracy of these data from the Charité hospital as it does not match with her data and these were her patients. Note: A letter to the editor from Dr. Büttner-Janz will be published in the April 2006 issue of *European Spine Journal.* [3, xvii]

Lemaire and David are criticized for reporting clinical results without the use of ODI, VAS, or SF-36 scores. At the time data collection began on these patients in 1989, none of these clinical outcome instruments were validated or in widespread use to measure pain and function in low back pain patients.

No formal training was available at the time these early studies were conducted. Since FDA approval of the CHARITÉ Artificial Disc, all spine surgeons who implant the device in the US must undergo a training course sponsored by DePuy Spine at the Center for Spine Arthroplasty in Cincinnati. This comprehensive training course includes didactic and hands-on training. During this training course, the primary emphasis is placed on appropriate patient selection.

The IDE study [1] of the CHARITÉ Artificial Disc is a landmark study in the history of spine surgery and represents the only prospective, multi-center, randomized, controlled study to date of two different surgical treatments for the treatment of low back pain. The Orthopaedics & Rehabilitation Panel of CDRH performed an exhaustive review of the results of the study and unanimously recommended approval of the device.

Levels of Evidence

Our classification of the studies available for CMS' review shows the following breakdown by quality of the analysis:

Level I: High quality randomized controlled trial

- CHARITÉ Artificial Disc IDE Study (Blumenthal et al, Spine 2005; 30:1565-75)

Level IV: Case Series

- Caspi et al, IMAJ 2003;5:9-11.
- Cinotti et al. Spine 1996;21:995-1000.
- David, Eur Spine J 2002:11(suppl 1):S18.
- Griffith SL et al. Spine 1994;19:1842-9
- Lemaire, *J Spinal Disord* 2005;18:353-59.
- Putzier M et al. Eur Spine J 2005: published online October 28.
- Sott AH, et al, International Orthopedics (SICOT) 2000;24:50-53.

[xvii] Exhibit C.

- van Ooij A et al. J Spinal Disord Tech 2003;16:369-83.
- Zeegers et al. Eur Spine J 1999;8:210-7.

Level V: Expert Opinion

- de Kleuver M et al. Eur Spine J 2003;12:108-16.
- Mirza S. Spine 2005;14:1561-4.
- Zindrick M et al. Spine 2005;30:E388-90.

We submit that CMS has not given the appropriate weight to the different levels of evidence. Level IV and V data are not reliable and sub-optimal results or high rates of complications found within these data should not be used to supersede findings in Level I data. In any event, the Level IV and V data CMS is now relying on are indicative of early experiences where techniques and selection criteria were still being refined. The Level IV and V data as cited in the Proposed Decision Memorandum is not a strong basis for evidenced-based decisions and should be weighted appropriately compared to the Level I data. The Level I data is encouraging for properly indicated patients in the Medicare population and they should not be denied access to the technology as further data is developed.

RECOMMENDATION

CMS must determine that the product is reasonable and necessary as a condition of coverage under section 1862(a)(1)(A) of the Social Security Act. We believe that the CHARITÉ Artificial Disc for lumbar artificial disc replacement meets the criterion for reasonable and necessary for a select patient population, as a condition of coverage determination with limitations, demonstrated in the Level I evidence from the FDA IDE clinical trial results. We further believe that the clinical benefits can be achieved in certain carefully selected Medicare beneficiaries (more likely under 65 and disabled than the over 65 elderly) and we support and emphasize the need for careful patient selection criteria.

We therefore recommend that, in lieu of a non-coverage determination, CMS should consider our proposed coverage determination with limitations. Exhibits D and E detail additional conditions for coverage that must be met to ensure that the CHARITÉ Artificial Disc is used only in patients for whom the device is indicated. Clearly defined indications and a keen focus on careful patient selection will help to ensure that the Medicare population will obtain optimal clinical results.

Finally, in addition to the recommended coverage determination with limitations, DePuy Spine will initiate plans for the registry. We would appreciate CMS' input on this design to ensure that we are capturing pertinent information. DePuy Spine would be willing to take a leadership position with CMS with regards to a broader registry, one that encompasses several treatments of back pain, not just specifically for the CHARITÉ Artificial Disc. Collaboration between CMS, the professional societies and industry would be essential for this project to be successful.

Thank you for the opportunity to provide commentary on consideration of lumbar artificial disc replacement for a National Coverage Determination.

Sincerely,

Richard M. Toselli, MD, MBA
Worldwide Vice President, Research & Development
DePuy Spine, Inc.

EXHIBIT A

PROPOSED DECISION MEMO FOR LUMBAR ARTIFICIAL DISC REPLACEMENT (CAG-00202N)

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EXHIBIT B

Alternative statistical testing demonstrates superiority of lumbar arthroplasty clinical outcomes at 2 years vs. fusion for the treatment of one-level lumbar degenerative disc disease at L4-5 or L5-S1

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Introduction: Publication of the results of the U.S. FDA study of the CHARITÉ Artificial Disc represents the only Level I data for lumbar arthroplasty in the literature. As published, the reported statistical significance between the randomized treatment and the control group with respect to ODI and VAS scores, were calculated by the a priori protocol-specified student's t-test. However, after examination of the complete study data distributions, it was apparent that a non-parametric test, the Wilcoxon Rank Sum Test, was a more appropriate test.

Methods: A total of 276 patients were enrolled in two arms of the IDE study, 71 in the TDR non-randomized arm, and 205 in the TDR randomized arm. A total of 99 patients were enrolled in the control group, ALIF with BAK cages and autograft, in the randomized arm of the study. A post hoc analysis of the ODI and VAS clinical outcome measures was performed at all time points using the Wilcoxon Rank Sum test (SAS v8.2). The analysis was performed using the same exact data previously reported by Blumenthal et al, with the non-randomized cases added.

Results: With respect to mean ODI scores, Blumenthal reported statistical significance between the randomized groups at 6 weeks (p=0.0198), 3 months (p=0.0014), 6 months (p=0.0017), and 12 months (p=0.0393), with no significance at 24 months (p=0.2670). This new analysis of all study patients demonstrates statistical significance between the two groups at all time points: 6 weeks (p=0.0015), 3 months (p=0.0004), 6 months (p=0.0004), 12 months (p=0.0203), and 24 months (p=0.0218). With respect to VAS scores, Blumenthal et al reported statistical significance between the randomized groups at 6 weeks (p=0.0222), 3 months (p=0.0177), 6 months (p=0.0044), and 12 months (p=0.0418), with no significance at 24 months (p=0.1074). The new analysis of all study patients demonstrates statistical significance at all time points: 6 weeks (p=0.0030), 3 months (p=0.0014), 6 months (p=0.0002), 12 months (p=0.0147), and 24 months (p=0.0089). No baseline correction was used in either of these analyses as the groups were balanced at baseline.

Conclusions: The conclusion by Blumenthal et al that lumbar arthroplasty at one level (L4-5 or L5-S1) for the treatment of DDD is at least as good as fusion is correct because of the non-inferiority study design and the definition of clinical success pre-specified in the protocol before the study began. However, this new analysis of all patients using the appropriate exact statistical test for the observed data distributions, demonstrates that lumbar arthroplasty with the CHARITÉ Artificial Disc at one level for the treatment of DDD, results in significantly superior clinical outcomes at all time points through the 2-year follow-up, compared to fusion, using well-recognized and validated outcome scoring methods (ODI and VAS).

EXHIBIT C

EUROPEAN SPINE JOURNAL

Büttner-Janz, Karin, Letter to the Editor concerning "Charité total disc replacement: clinical and radiographical results after an average follow-up of 17 years" (M. Putzier et al.). Will be published in the April 2006 issue of *Eur Spine J*.

EXHIBIT D

COVERAGE DETERMINATION WITH LIMITATIONS GUIDELINES

Indications and Limitations of Coverage

A. Nationally Covered Indications

Effective for services performed on or after May 16, 2006, CMS has determined that the evidence is adequate to conclude that the CHARITÉ Artificial Disc is reasonable and necessary for spine arthroplasty in skeletally mature patients with degenerative disc disease (DDD) on one level from L4-S1.

Degenerative disc disease is defined as discogenic back pain with degeneration of the disc as confirmed by history and radiographic studies with one or more of the following factors:

- Contained herniated nucleus pulposus
- Facet joint degeneration/changes
- Decreased disc height by ≥ 2 mm, and/or
- Scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule

Medicare coverage is provided only for those patients who meet all of the following selection guidelines:

In accordance with the Food and Drug Administration (FDA) approved labeling

Inclusion Criteria

- Symptomatic DDD confirmed discography
- Single level DDD at L4-L5 or L5-S1
- A minimum of 6 months of unsuccessful conservative treatment
- Leg pain and/or back pain with no nerve root compression
- Oswestry Low Back Pain Disability Questionnaire score ≥30 points
- Visual Analog Scale score ≥ 40 mm
- Able to tolerate anterior approach

In addition to the inclusion criteria, CMS mandates further evaluation to include:

- A DEXA screening for Medicare patients selected as candidates for this procedure. Exclude patients with a score less than (1.0) SD below the norm, which indicates osteopenia. This would, by default, also exclude patients with a score less than (2.5) SD below the norm, which indicates osteoporosis
- Plain radiographs and/or CT (contiguous fine cuts) scan to appropriately evaluate facet disease so that patients with moderate to severe facet disease can be excluded

CMS has determined that covered CHARITÉ Artificial Disc procedures are reasonable and necessary only when performed by a surgeon who:

- Is an Orthopaedic Surgeon or Neurosurgeon (Spinal Surgeons), licensed to practice medicine in those states in which the surgeon provides professional medical services who has completed a spine fellowship or residency program with a significant focus on complex lumbar spine procedures or have equivalent clinical experience.
- Has attended the DePuy Spine CHARITÉ Artificial Disc training course.

- Has observed 1-5 CHARITÉ Artificial Disc surgeries after attending the training course; this may be done locally (if available) or through an alternate visitation program provided by DePuy Spine.
- Has a practice with a primary spine focus that will provide a sufficient and regular volume of appropriately indicated patients for anterior lumbar procedures. It is the opinion of the experienced surgeons who were involved with the IDE trial that, in order to establish and maintain proficiency, a spine surgeon should perform anterior lumbar interbody fusions or artificial disc replacements on a regular basis.
- Must be willing, prepared, and qualified to manage potential revision procedures, including:
    - Posterior fusion with instrumentation,
    - Early-stage anterior revision to reposition the prosthesis,
    - Late-stage anterior revision, including: (i) prosthesis removal with anterior fusion and instrumentation, (ii) prosthesis removal with anterior and posterior fusion and instrumentation
- Is willing, as is important with any new technology, to maintain a current, best understanding of the state of the art in lumbar spine arthroplasty. This should be done via regular literature reviews and participation at continuing education events highlighting new techniques, technologies and clinical results.
- Has an identified approach surgeon at the spine surgeon's institution that has significant experience accessing the anterior lumbar spine or have own equivalent training and experience. The approach surgeon for the CHARITÉ Artificial Disc procedures must be willing, prepared and qualified to manage potential complications including approach related injury of the inferior vena-cava, iliac veins, iliac artery, ureter, peritoneum or other soft tissue or organ systems.

B. Nationally Non-Covered Indications

Medicare Beneficiaries with one or more of the following are excluded from coverage:

- Previous or other spinal surgery at any level, except prior discectomy, laminotomy, laminectomy or nucleolysis at the same level
- Multiple level degeneration
- Presence of Pars Defect/Fracture
- Previous trauma to the L4-L5 or L5-S1 levels in compression or burst
- Non-contained or extruded herniated nucleus pulposus
- Mid-sagittal stenosis of <8mm (by CT or MR)
- Spondylolisthesis >3mm
- Lumbar scoliosis (>11º sagittal plane deformity)
- Spinal tumor
- Active systemic infection or infection localized to the site of implantation
- Facet joint arthrosis
- Arachnoiditis
- Isthmic spondylolisthesis
- Chronic steroid use
- Allergy or sensitivity to implant metals
- Pregnancy
- Autoimmune disorders
- Psychosocial disorders
- Morbid obesity (BMI> 40)
- Bone growth stimulator use in spine
- Osteoporosis or osteopenia or metabolic bone disease
- Positive single or bilateral straight leg raise

Medicare beneficiaries not meeting all of the coverage criteria for the CHARITÉ Artificial Disc are deemed not eligible for Medicare coverage under section 1862(a)(1)(A) of the Social Security Act.

C. Other

All other indications for CHARITÉ Artificial Disc not otherwise indicated as nationally covered above remain at local contractor discretion.

EXHIBIT E

A CHECKLIST FOR A COVERAGE DETERMINATION WITH LIMITATIONS

Based upon the previously defined indications and contraindications for surgery, as well as the additional screening criteria, a grid could be constructed documenting pre-operative testing, patient selection criteria and absence of contraindications (see below):

Indications: Total disc arthroplasty in a skeletally mature patient with symptomatic degenerative disc disease at ONE (1) level, either L4-L5 or L5-S1.

A. Pre-Operative Work Up - documented in the medical record to include ALL of the following criteria. Dates for all diagnostics must be listed.

	Criteria	**Yes**	**No**	**Date**
1.	MRI – must show degenerative disc disease at L4-L5 or L5-S1			
2.	Discogram – must indicate concordant pain at L4-L5 or L5-S1			
3.	CT scan – address presence or absence of spondylolysis and facet disease. Must be contiguous fine cuts.			
4.	Plain X-Rays obtained.			
	a. Standing AP			
	b. Standing Lateral Flexion			
	c. Standing Lateral Extension			
	d. Any evidence of mechanical instability or alignment?			
	e. Documentation that the x-rays were taken in an upright position			
5.	Surgeon has clearly documented in the medical record all radiographic findings and abnormalities.			
6.	Ferguson view at the operative level is documented and notation addressing the shape of the endplates.			
	a. Ferguson view NOT needed if MRI or CT clearly indicates endplate spacing is adequate.			
	b. If documentation is NOT ideal for implantation, the surgeon MUST indicated how he will address the shape of the endplate.			
7.	DEXA bone density completed in all patients greater than 50 and those with risk factors for osteopenia or osteoporosis			
8.	Medical History must include discussion of any contraindications			
9.	Psychological Evaluation			
	a. History of schizophrenia			
	b. Bipolar condition			
	c. Evidence of severe depression			
	d. Evidence of a personality disorder			
	e. Evidence of inability to comprehend the disc procedure			
	f. Psychological clearance by psychologist to have the disc surgery			
	g. Final decision is the Surgeon's			

B. Patient Selection Criteria

		Yes	No	Date
1.	The patient is skeletally mature with symptomatic degenerative disc disease at one level.			
	a. L4-L5			
	b. L5-S1			
2.	No prior lumbar spinal fusion at the operative level			
3.	Chronic low back pain with or without leg pain and evidence of failing six (6) months of conservative therapy.			
	a. Physical therapy			
	b. Chiropractic manipulation			
	c. Oral anti-inflammatory medications			
	d. Injection therapy			
4.	Degenerative disc disease documented at operative level L4-L5 or L5-S1 by radiographic findings:			
	a. Plain x-rays			
	b. MRI			
5.	Surgeon qualifications/experiences/resources – Date of Training			

C. Patient Contraindications. The CHARITÉ Artificial Disc will NOT be covered when any of the following conditions are present:

		Yes	No	Date
1.	Osteopenia/Osteoporosis with a T-factor of <1			
2.	Scoliosis > 11 degrees of sagittal deformity			
3.	Spondylolysis at the affected level			
4.	Spondylolisthesis, retrolisthesis, or anterolisthesis at the operative level of > 3 mm.			
5.	Symptomatic central stenosis			
6.	Subarticular stenosis caused by facet joint hypertrophy with nerve compression in the lateral recess.			
7.	Tumor, neoplasm.			
8.	Presence of Pars Defect/Fracture			
9.	History of chronic steroid use. (If a history of long-term steroid use, may still have disc in now off of steroids, DEX scan with a factor ≥ 1.0, and not expected to require chronic steroid therapy in the future.			
10.	Advanced facet degenerative joint disease (unless facet pain is ruled out by negative facet injections)			
11.	Facet joint ankylosis			
12.	Metal allergy present			
13.	Pregnancy			
14.	Leg pain present due to nerve compression other than isolated foraminal stenosis at the affected level, or contained herniation, which can be removed by anterior discectomy			
15.	Noncontained or extruded herniated nucleus pulposus			
16.	Spinal infection			
17.	Autoimmune disorder			

		Yes	No	Date
18.	Calcification of abdominal vasculature per plain x-rays or CT scan			
19.	History of previous major anterior vessel surgery			
20.	Obesity (body mass index > 40 or 100 lb. over ideal body weight)			

EXHIBIT F

PREVIOUS PUBLIC COMMENTS SUPPORTING A COVERAGE DETERMINATION WITH LIMITATIONS

CMS received 138 public comments (08/16/05 – 09/16/05) in response to Dr. Deyo's letter. Over 50% (74) of those comments suggested a coverage determination with limitations, further supporting our recommendation.

Below are some of the suggestions reflective of this position:

- Careful patient selection and adhering to the inclusion/exclusion criteria outlined in the FDA IDE study will ensure that spinal arthroplasty is a safe and effective means of treating single level DDD in the lumbar spine.
- Patient safety and proper implementation is strongly supported by the professional societies, manufacturers and implanting surgeons.
- Osteoporosis and osteopenia are direct contraindications for this device as per the FDA labeling.
- Strict criteria should be used to properly select the patients that will benefit from the procedure to achieve the best outcomes.
- If patient selection is adhered to results will be predictable and will at least mimic the IDE and continued access studies.
- Limit coverage based on strict criteria to ensure the best clinical outcomes.
- Use a stringent list of selection criteria in order to screen patients, particularly the elderly for whom it may be contraindicated.
- Any procedure or implant in the hands of the poorly trained or misguided will result in problems. But we cannot limit those capable of helping many because of the inability of some to hurt few. I strongly support the controlled and careful utilization of artificial disc technology.
- It is only in the patients with the appropriate clinical and radiological criteria for use of the device.
- DePuy has gone out if its way to address some of the issues surrounding the artificial disc, stressing the very limited indications for implantation to all the surgeons it trains. As such, only a select few patients in the Medicare population would ever be considered for implantation.
- Osteoporosis is a definite contraindication for disc arthroplasty and DEXA bone scans can be obtained to ensure that no Medicare recipient with osteoporosis is selected for disc replacement surgery.
- The Charite serves as a very viable solution for a growing number of patients. What should be limited or closely monitored are the bone density values of the patients we might consider for this procedure. Young patients (<35yrs) sometimes present with poor bone stock due to metabolic bone disease, while the reverse can be said for select patients of the older population. Strict patient selection will bring better and consistent outcomes without restriction of age only.
- As I instruct medical students and residents in training, every weapon in our arsenal of medical gadgets is only as effective as the practitioner's ability to properly recognize the indications and limitations and apply it accordingly. If sufficient data exists to suggest that there is benefit from a modality or device, no matter how limited the indication(s), I would hope that consideration be given to not exclude such device from treatment options.
- Dr. Deyo is correct that most elderly Medicare patients will not be candidates for this procedure because they have osteoporosis, multi-level disc disease, spinal stenosis or other conditions that are contraindications to implantation of the device. Total disc replacement (TDR) is like any other surgical procedure where results are optimal only when strict indications for its use are followed and the surgery is performed correctly by competent surgeons.
- I agree with Dr. Deyo's assertion that many, if not most, Medicare eligible patients will not be good candidates for disc replacement surgery. However, a significant number will be prime

candidates. The main exclusion criteria used in the study were; osteopenia, spondylolisthesis, degenerative scoliosis, advanced facet arthropathy, herniated nucleus pulposus and significant canal stenosis. While these contraindications generally increase with age, turning 65 does not automatically disqualify a patient. Furthermore, a negative coverage decision would disenfranchise all those younger patients on disability receiving Medicare and Medicaid.

- Certainly consideration needs to be given to appropriate patient selection but there would seem to be much more appropriate means of monitoring usage than simply prohibiting the entire procedure from a large and important segment of the United States population.
- We are very excited about this as a true advancement for certain type of spinal problems, particularly collapsed degenerative lumbar disc disease which affects one level, particularly L5-S1 although it has been cleared for the two lower levels. Using very tight criteria for selection for surgery, we have now 35 patients who have been waiting patiently over the last nine-month period for clearance of surgical payment for these procedures.
- The data that was submitted in support of the disc is a solid randomized controlled study, verifying the efficacy of the artificial disc. There is no reason to think that the disc would not work just as well in a predominantly elderly population, as long as patient selection is appropriate, and that includes excluding those with osteoporosis. However, most of the Medicare population does not necessarily have osteoporosis, and to deny coverage for all based on one exclusion criteria which doesn't apply to the majority is uncalled for and unfair. The data from the FDA study, the European studies, and the presentations at scientific meetings from other discs all indicate that the artificial disc is a useful and appropriate device in selected patients.
- To remove artificial disc replacement from the approved procedures for Medicare beneficiaries, would limit care options for many patients who would qualify under the recommended strict indication guidelines.

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European Spine Journal
DOI 10.1007/s00586-006-1081-0

Letter to the Editor

Letter to the Editor concerning “Charité total disc replacement: clinical and radiographical results after an average follow-up of 17 years” (M. Putzier et al.)

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Received: 29 January 2006

The article to which this letter refers can be found at http://www.dx.doi.org/10.1007/s00586-005-1022-3. An author’s reply to this letter is available at http://www.dx.doi.org/10.1007/s00586-006-1082–z

I read with interest the paper by Putzier et al. [13] describing long-term clinical and radiographic results in the earliest patients implanted with the CHARITÉ Artificial Disc. As one of the two inventors of the device; the surgeon of record for all of the first 50 operated patients over several years in conjunction with my doctoral thesis [2]; and having knowledge of the other 21 patients including their clinical outcomes; I believe it is necessary to put the results described in the paper into the proper context.

First, it should be noted that the number of patients and the number of implanted model SB I disc prostheses is incorrect. There were 13 patients implanted with the SB I prosthesis, not 15. These 13 patients (5 males, 8 females) received 14 prostheses (not 16). The wrong number of cases is reflected in all relevant tables and is a basis for incorrect statistical calculations. Therefore all statistical conclusions made by the authors are flawed.

The authors used data from this study to come to the conclusion, “Proof that long-term results of TDR implantation in (patients with) DDD are at least as good as fusion results is still missing.”

The authors used the specific wording “at least as good as”. These words are normally reserved to describe the statistical results of a prospective, randomized, non-inferiority study, such as the U.S. FDA IDE study of the CHARITÉ Artificial Disc reported by Blumenthal et al. [1]. Instead, the study presented is Level IV data, a case series describing results with three different devices, which in no way resembles a prospective, randomized, non-inferiority design. Further, the authors attempt to demonstrate significance (or non-significance) with respect to various clinical and radiological results achieved with each of the three devices. However, with a lost to follow-up rate of 25.4%, incorrect patient/prosthesis numbers and extremely small sample sizes in each group, the power of their statistical analysis is highly problematic. The statement, “...there was no significant difference in the clinical or radiographic long-term outcome between these three different TDR types” is built upon a faulty statistical analysis. In addition, they attempt to correlate clinical and radiological results and compare TDR to fusion when patients in the fusion groups previously had a TDR procedure. Therefore, “proof” one way or the other certainly cannot be ascertained using these data. On the whole the comparison between the outcome after prosthetic implantation and fusion as stated in this publication therefore cannot stand.

The authors described the three different versions of the CHARITÉ Artificial Disc (SB CHARITÉ I, SB CHARITÉ II, and SB CHARITÉ III). It is not correct that model SB I had 5 and later 11 teeth. The authors noted that only the third-generation of the device was made commercially available beginning in 1987. This is an important distinction. Though, the design principles for each of the three devices are essentially the same, a mobile sliding UHMWPE core between two metal endplates, the authors seem to trivialize the change from pressed stainless steel plates to compact Cobalt Chromium alloy plates.

The same applies to the sizes of the prosthesis SB CHARITÉ III, which in the 1980s was only available in three sizes, with an increased surgical risk of implantation at the time with the dissection required in cases with the larger prosthetic plates. The SB I and SB II devices consequently provided insufficient endplate coverage with the limited selection of sizes. In the group of all patients with SB II devices 21 of the 88 SB II endplates (44 SB II prostheses) showed material damages beginning between 3 and 12 months after implantation. Now there are seven footprint sizes of the CHARITÉ Artificial Disc available, allowing for more complete coverage of the vertebral endplate to the cortical rim, which should reduce the incidence of subsidence. At the time these early cases were performed, only 0° and 5° lordotic endplates were available. Since then, 7.5° and 10° endplates

have been added, allowing for a more customized lordosis to be built into the disc space representing the patient's adapted anatomy. The instrumentation used to implant the prosthesis in the 1980s@ has been updated significantly, easing the technical difficulty of the procedure. In 1998, titanium@ calcium phosphate porous coating was added to aid in fixation of the prosthesis endplates to the@ vertebral endplates. Perhaps more importantly the indications and contraindications for TDR have@ been narrowed considerably since the device was first designed. Today for instance, diagnosing@ lumbar DDD is more effective by using MRI which was unavailable at the time the CHARITÉ@ Artificial Disc was implanted in the first patients. All of these changes combined yield an entirely@ different approach to TDR procedures compared to the very first cases performed with this device@ [3].@

At that time the prosthesis was invented, the approach was to learn by doing rather than learning@ from the experience of others. The knowledge now available regarding the loading and biomechanics@ of the lumbar spine with and without disc implantations was not available to the inventors or even@ known 20 years ago. Clearly, one cannot draw modern clinical conclusions based on the results@ from those very early designs. Just 30% (16 patients) of the total reported study population of@ Putzier et al. were implanted with a commercially available device, and their data show no cases@ of subsidence or implant fracture in patients receiving the third-generation device.@

Unfortunately, the reported data does not describe the positioning of the implanted prostheses@ within the intervertebral space, although the authors generally point out the high importance of@ the optimal implantation of the prosthesis. It is also unfortunate that the authors did not have@ personal experience implanting the CHARITÉ Artificial Disc. In the group of the first 50 patients@ with a CHARITÉ prosthesis, in whom 60 prostheses were implanted, a central position of the@ prosthesis in AP view was achieved in only 27 segments and a dorsal position of the disc in lateral@ view in only 12 segments. The figures of the SB III device in the paper published by Putzier et al.@ clearly show a positioning of the prostheses which are too anterior. McAfee et al. [11] demonstrated@ a statistical correlation between prosthesis positioning and clinical outcomes at 2 years. Patients@ with poor implant placement had statistically worse clinical outcomes than patients with optimal@ placement. Therefore the conclusion made by the authors: "...these patients (patients with functional@ implants) were significantly less satisfied with long-term outcome of the surgery than patients@ with spontaneously ankylosed motion segments or fusion after implant failure" must be doubted.@ Also of note, the authors did not write anything about the early outcomes or baseline clinical data,@ nor if the original indications match the indications of today.@

The paper was accepted for publication on August 8, 2005. Unfortunately, the authors did not have the opportunity to review the paper by Lemaire et al. [10] published that same month which describes clinical and radiographic outcomes in 100 patients implanted with the third-generation device and a minimum follow-up of 10 years. In 1989, the two inventors visited Dr. Lemaire to show him the CHARITÉ Artificial Disc and to discuss the clinical and biomechanical principles of the prosthesis. At that time, the 5-year learning curve for the development and application of the first Total Disc Replacement worldwide had already been realized, and there were no further changes to the basic design of the implant. Shortly thereafter, Dr. Lemaire, with surgical assistance from the inventors, implanted his first CHARITÉ Artificial Disc. His series had a lost to follow-up rate of 6.5%, a return to work rate of 91.6%, and 90% with an excellent or good clinical outcome. Lemaire reported in his paper five (5%) cases of secondary arthrodesis and only two (2%) cases of ossification affecting device mobility. With a mean ROM in extension/flexion of 10.3° at 10 years it is highly unlikely Lemaire's patients will show a much higher rate of spontaneous ossification at 15+ years.

Lumbar TDR, no matter the device used, has been maligned in the literature [7, 8, 12, 15, 16]. The majority of opponents of TDR make the erroneous assumption that a lumbar fusion procedure is a winning procedure for the patient each and every time, despite ample evidence to the contrary, most recently described by Geisler et al. [9]. Bringing forth the results in the earliest patients, as Putzier et al. have done, with the procedures performed prior to all of the changes described above combined with the collective knowledge gained over two decades; and pronouncing that the long-term results are not at least as good as fusion, demonstrates a misunderstanding of how to interpret clinical literature.

Using the logic of Putzier et al., total hip and knee replacement would not be the standard of care in elderly patients with degenerative arthritis. Organ transplantation would not be an option. Cardiac bypass surgery would not be performed. Laparoscopic and other minimally invasive surgical approaches would not be used. Pacemakers would not have been developed and implanted. The list of devices and surgical approaches that would not be in use today if results in the earliest of patients were used as reasoning for not performing the procedure, is endless. Advancements in Medicine would be stagnant.

The development of the CHARITÉ Artificial Disc was, and continues to be an important scientific advancement in the treatment of lumbar DDD in properly indicated patients. With this implant and the experiences gained through developing it, a new worldwide strategy for the treatment of spinal disorders has begun. Many implants for the functional maintenance of the

lumbar and cervical spine were created with new treatment concepts born from the first experience with lumbar TDR. Thousands of patients have been helped by the CHARITÉ Artificial Disc worldwide. It is too easy to cast stones using incomplete, and from the onset dubious results from the earliest available experience, and argue for maintaining the imperfect status quo for decades into the future, while at the same time ignoring evidence of good long-term outcomes such as the paper by Lemaire and presentations made at medical society meetings [4–6, 14]. However, those who invent or pioneer a procedure and know they are correct and those who come after them and see the future now, will remain undaunted.

It is my strong belief that lumbar arthroplasty is not going to go away, and it will stand the test of time with additional new developments.

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[Table 1 will appear here. See end of document.]

The table is prepared with the use of accurately conducted data forms, which each of these first operated 20 patients and the further 30 patients with the CHARITÉ Artificial Disc pre- and postoperatively received.

Summary (see also Table 1)

1. The first implantation of the CHARITÉ Artificial Disc was on the 19th of September in 1984, not on 21 September.
2. The last implantation of model SB I was on the 10 September 1985, but the first two implantations of a model SB II prosthesis were already on 5 and 9 September in 1985.
3. All together 14 SB I prostheses were implanted in 13 patients (patient 8 with a two level surgery) - and not 17 SB I prostheses in 16 patients as written by Dr. Putzier.
4. Dr. Putzier described that he allegedly involved 15 patients with 16 SB I prostheses in his evaluation. All together there are incorrect statistical calculations in the publication of Putzier et al. due to the wrong number of SB I prostheses/patients.
5. If 15 of the first operated 16 patients could be examined it is questionable whether the authors of the publication did carry out x-rays in every patient or the authors could recognize the different models of the CHARITÉ Artificial Disc.

Table 1 Overview of the first 20 patients with the CHARITÉ Artificial Disc (SB I and SB II)

Number	Patient	Gender	Age at surgery	Date of surgery	Level(s)	Model SB	SB I: teeth on plates	X-ray marker ring (sliding core)
1	W.W.	M	41	19 Sept 1984	L4/5	I	11	–
2	H.B.	M	42	21 Sept 1984	L5/S1	I	11	–
3	I.B.	F	47	22 Jan 1985	L4/5	I	11	–
4	H.L.	F	46	23 Jan 1985	L4/5	I	11	–
5	M.N.	F	43	19 Feb 1985	L4/5	I	11	–
6	K.D.	F	30	27 Feb 1985	L5/S1	I	11	–
7	E.W.	F	37	27 Feb 1985	L4/5	I	11	–
8	I.S.	F	44	15 Mar 1985	L4/5, L5/S1	2xI	11	–
9	W.D.	M	50	29 April 1985	L4/5	I	11	+
10	C.G.	F	48	13 May 1985	L4/5	I	11	+
11	H.L.	F	33	13 May 1985	L4/5	I	11	+
12	W.B.	M	53	05 May 1985	L4/5	II		+
13	J.W.	F	47	09 Sept 1985	L5/S1	II		+
14	M.A.	M	33	09 Sept 1985	L4/5	I	5	–
15	D.S.	M	45	09 Oct 1985	L4/5	I	5	–
16	G.B.	F	36	24 Sept 1985	L3/4	II		+
17	M.M.	F	46	30 Oct 1985	L4/5	II		+
18	J.R.	M	42	18 Nov 1985	L5/S1	II		+
19	J.L.	M	41	18 Nov 1985	L4/5	II		+
20	H.-G.Z.	M	55	12 Sept 1985	L3/4	II		+