

The recent CMS decision to not provide coverage of Lumbar Artificial Disc Replacement surgery for Medicare patients over the age of 60 seems cynical. There may be no definitive proof that mobility of a particular segment delays, mitigates or prevents adjacent segment degeneration, but there is proof that the proper use of lumbar artificial disc does provide similar clinical outcomes (as does lumbar fusion) and patients recover more quickly from surgery.

michael_hobert@lifenet.org

I generally concur with your decision to deny payment for lumbar disc arthroplasty procedures at this time. I have been a practicing orthopedic surgeon with an emphasis on degenerative lumbar disorders for the last twenty-five years. The majority of my surgical patients have been Medicare eligible. I do not see lumbar arthroplasty procedures at this time as a good surgical alternative for this elderly patient group. James F. Marino, M.D.

I had the disk replacement done in Feb 2006. If not for the replacement being done I would not have been able to deal with the pain I was in. On top of all that I had gone over a year before having the surgery and now I am paying the cost for that with damage done to some of my nerves. If anyone can know what a person goes through with the pain they would not deny anyone the surgery and would want to help them no matter what age they are. It's not something you would want a loved one to have to suffer through. I feel anyone who needs the disk replacement done should have it done. Making anyone to suffer is not right at all.



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June 22, 2007

Steve Phurrough, MD, MPA
Director
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Administrative File: (CAG-#00292R)
P.O. Box 8011,
Baltimore, MD 21244-1850.

Re: Proposed Decision Memo for Lumbar Artificial Disc Replacement (LADR)
(CAG-00292R)

Dear Dr. Phurrough,

Synthes Spine appreciates the attention the Centers for Medicare & Medicaid Services (CMS) is paying to the issue of treatment for low back pain including holding a recent meeting of the Medicare Coverage Advisory Committee (MCAC) (now the Medicare Evidence Development and Coverage Advisory Committee) on the subject of spinal fusion.¹ We appreciate the effort CMS has undertaken in the Proposed Decision Memo for Lumbar Artificial Disc Replacement (LADR) (CAG-00292R), however, we strongly disagree with the discussion of the evidence, analysis and the conclusions. Synthes Spine believes that there is indeed sufficient and compelling evidence in our randomized controlled trial (RCT) for CMS to make a positive national coverage decision (NCD) for this procedure for Medicare beneficiaries 60 years old or under using ProDisc-L® Total Disc Replacement an important technological advancement in the area of spine care. Fifty years ago the vast majority concluded that fusion was the only effective treatment for degenerative hips only to be superseded by scientific study demonstrating that the preservation of motion in the hip had benefits going beyond the relief of pain due to degeneration of the hip joint. Today, total hip replacement using motion preservation technologies is the most effective orthopedic treatment available.

We understand that CMS considers this national coverage determination (NCD) part of its effort to assess available evidence on the treatment, especially surgical treatment, of low back pain. However, we are concerned that CMS is incorporating applications beyond the indications approved by the Food and Drug Administration (FDA) in its

¹ CMS Medicare Coverage Advisory Committee Meeting, Baltimore, MD, November 30, 2006

considerations for ProDisc-L and, therefore, is inappropriately concluding that the evidence is insufficient to support Medicare coverage.² In addition, we disagree with CMS' criticisms of the methodology of our randomized controlled trial and we offer further clarification to address these criticisms. We close by recommending a Medicare coverage policy that will encourage the development of additional evidence on the effectiveness of surgical interventions for degenerative disc disease (DDD) and other causes of low back pain in the Medicare population.

Appropriate Application of ProDisc-L Study Findings

As CMS acknowledges there are millions of Americans who suffer from low back pain. Many people suffer symptoms at some time in their life. It is well known that the vast majority of those persons will require no intervention at all. Some people affected will seek some intervention ranging from a few OTC pain relievers, through exercise, physical therapy, chiropractic and in some cases narcotics, and most of the symptoms will be relieved to a tolerable level or disappear. However, there is a small subset of patients for whom conservative care has not and will not alleviate the pain no matter how long the course of therapy is continued. Conservative care is no longer a treatment option for them. Many of these patients suffer from DDD. In many cases their pain is disabling and life revolves around looking for relief. This small subset of DDD patients is currently being treated, most often, with spinal fusion. Physicians and patients know fusion is not a "cure" but for these patients it is their only option. Artificial disc replacement (ADR) with ProDisc-L offers another option and one with a proven superior result to fusion for the treatment of DDD. The FDA approved ProDisc-L for use in patients with degenerative disc disease at one level in the lumbar spine (from L3-S1) and with no more than Grade 1 spondylolisthesis at the involved level. Since FDA has not approved other indications (including other causes of low back pain), it is appropriate only to focus on the covered indication at this time. Our RCT showed that for such patients ProDisc-L is not only non-inferior but is actually statistically superior to circumferential fusion.³ Based on this evidence Medicare should nationally cover ProDisc-L for those patients under 60 who meet this specific indication.

ProDisc-L is not an alternative to fusion surgery for low back pain. Rather, ProDisc-L is an alternative to fusion surgery for patients with DDD. The superiority to fusion for this specific subset of patients is an important point. We discuss in more detail below specific elements of our study design and methodology and want to clarify why we chose circumferential fusion as the treatment for the control group in our RCT. For patients with unresolved low back pain, circumferential spinal fusion is considered the gold standard of care. We acknowledge CMS' concern that there is limited evidence supporting circumferential spinal fusion as it pertains to the Medicare population. However, Medicare currently covers fusion and CMS emphasized at the recent MCAC meeting that it is not considering a change in coverage at this time. A decision to limit coverage for a treatment determined to be superior to a treatment covered with no limitations is irrational. In its summary of safety and effectiveness, FDA found that "a

² Food and Drug Administration, "Summary of Safety and Effectiveness Data" for ProDisc®-L, (<http://www.fda.gov/cdrh/pdf5/p050010b.pdf>)

³ Food and Drug Administration, "Summary of Safety and Effectiveness Data" pg. 19

statistically significant difference in Overall Success rates between the PRODISC®-L and control groups was found.”⁴ It is illogical to cover fusion for treatment of DDD but limit coverage for ProDisc-L, a treatment shown to be statistically superior to fusion for the treatment of DDD.

The expansion of the NCA, we believe, spills over into areas that have little clinical relation to the narrow application for ProDisc-L. This argument is supported by statements such as, “Outcomes that are usually heavily weighted by CMS - morbidity and mortality - are difficult to examine in the context of treatment for chronic low back pain which is a symptom, not a disease.” However there are, indeed, accepted diagnostic methods for identifying the pain generator and diagnosing the disease at the root of the pain, and from this identifying an appropriate patient. Of course, quite often no one diagnostic test is perfect or can be used alone, so a combination of diagnostic methods might be needed, and must be taken into account along with the judgment and experience of the physician, as is the case with all other diseases. Additional statements concerning the unknown etiology of lower back pain, the difficulty in identifying the pain generator, and the lack of specific diagnostic methods are further indication of the expanded yet not applicable indications and treatments influencing the NCD. A close reading of the analysis suggests that CMS may be going beyond the indications for ProDisc-L to include all indications for which fusion surgery is presently used. We sincerely hope to confirm that CMS is not making the assumption that board certified spine surgeons will use ProDisc-L for all forms of lower back pain. The indications for ProDisc-L are very specific:

The PRODISC®-L Total Disc Replacement is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L3-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than 3mm of spondylolisthesis at the involved level. Patients receiving the PRODISC®-L Total Disc Replacement should have failed at least six months of conservative treatment prior to implantation of the PRODISC®-L Total Disc Replacement.

ProDisc-L is indicated for only the treatment of chronic, non-responsive, debilitating symptomatic degenerative disc *disease*. Degenerative disc disease is not a symptom; it is a well characterized disease involving the degeneration of the intervertebral disc. Each patient studied under the FDA approved IDE study was confirmed to have DDD. The inclusion criteria established the confirmation of degenerative disc disease as:

Back pain with or without leg radicular pain; and

Radiographic confirmation of any 1 of the following by

CT, MRI, discography, plain film, myelography and/or flexion/extension films:

- **Instability (≥ 3 mm translation or $\geq 5^\circ$ angulation);**
- **Decreased disc height > 2 mm;**
- **Scarring/thickening of annulus fibrosis;**
- **Herniated nucleus pulposus; or**
- **Vacuum phenomenon**

⁴ Food and Drug Administration, “Summary of Safety and Effectiveness Data” page 19

Although these criteria may contain elements associated with symptomatology there is the empirical requirement for radiographic confirmation of the disease state.

CMS statement that, “Treatment of symptoms relies primarily on a subjective measure - clinical judgment,” might be true if the clinician were to rely solely on the presentation of symptoms without confirmation of the disease state. However, as studied in the IDE and as required by the indications for use in the FDA approved ProDisc-L labeling, DDD must be, “confirmed by patient history and radiographic studies.”

The issue is not limited only to the application of expanded indications for ProDisc-L. In fact, CMS relies on several published articles to question the effectiveness of fusion surgery as an effective treatment for low back pain in general. The analysis is distorted by considering data on the use of spinal fusion for other indications rather than concentrating on the single, well established indication for which fusion surgery has proven to be effective. Again we make or claim that the decision does not reflect the narrow indications for ProDisc-L and the proven results with this device.

Response to Critique of Methodology

We appreciate CMS’ preference for better evidence regarding medical treatments. However, we believe the results of our RCT provide compelling evidence for coverage of artificial disc replacement with ProDisc-L in the appropriate patient population, i.e., those under 60 years of age with DDD at one level who have failed a course of conservative treatment. Synthes seeks to clarify our methodology to ensure CMS understands our approach. We take issue with the discussion of several of our methodological decisions and address these concerns below in the order they appear in the proposed decision memo.

II. Background

We agree with CMS and Haldeman that for many patients the origin of low back pain is often unknown. We also agree with Boden and CMS that, “While from a simple mechanical aspect it could be hypothesized that DDD is a cause for pain, disc degeneration is also observed in individuals without pain.” The pain generator may be as CMS states a “conundrum.” However, it is our experience that physicians take care to identify, as best as possible, the pain generator in the confirmation of DDD. What matters most is that when a patient has lumbar pain and there is confirmed evidence of DDD and a surgical intervention is planned, and the patient meets the criteria, the clinically superior intervention would be total disc replacement (TDR) with ProDisc-L as demonstrated by our RCT and FDA approval.

In the last paragraph in this section marked **II. Background**. CMS imparts the impression that the procedure for LADR is risky and “has the potential to be life threatening.” While any surgery has the potential to be life threatening the anterior access procedure to expose the spine is no more life threatening than would be any other procedure that involves exposure of the great vessels.⁵

⁵ Addendum 1 & Addendum 2, S. Brau, MD, Presented at NASS meeting, September 2006

To date there are no known reported deaths with the ProDisc-L surgery. Revisions are sometimes necessary. The rate of revision in the US has been about 2% in over 2000 patients and all of those revisions have been successful. Dr. Brau, a well regarded access surgeon, has had a similar experience with both the ProDisc-L and other artificial discs.⁶

In addition Synthes Spine was developed a very rigorous training program for both physicians and access surgeons. No physician can implant the device unless he/she has previous anterior access experience and he/she completes a training forum for a day and a half. During the training physicians critically review patient histories they have selected as potential candidates. They experience hands on training with the instrumentation and most often there is a live surgery to observe. Physicians are asked pointedly to stay within the labeled indications. Synthes has taken every precaution to ensure the procedure is performed by carefully trained surgeons.

VI. General Methodological Principles

In this section, CMS sets out the features they look for in a RCT. They look for a clinically relevant cohort as did the sponsor of the ProDisc-L trial. The cohort chosen was carefully screened.

- 18-60 years old
- DDD in a single segment from L3-S1
 - Back pain with or without leg pain
 - Radiographic confirmation
- > 6 mos of conservative therapy
- Oswestry Score > 20/50
 - >40% impaired

The sponsor purposely used only a “single good reference standard” which was a 360° fusion. No other fusion procedure was chosen or allowed as it was widely accepted that a 360° fusion is the procedure that the majority of the patients would have undergone had they not participated in the trial. As a demonstration of how strong the single reference standard is the 97.1% fusion rate achieved in those patients who were fused is the highest fusion rate published to date in a RCT. Lastly it should be stated that a third party was chosen and blinded when reading and measuring the test results. Synthes believes that its study meets all of the assessment criteria stated by CMS.

VII. Evidence

In this section CMS states “Outcomes that are usually heavily weighted by CMS - morbidity and mortality - are difficult to examine in the context of treatment for chronic low back pain which is a symptom, not a disease.” We agree that there is difficulty in examining the morbidity and mortality associated with this procedure because both of these conditions do not play a major role in the outcomes. While we agree that there can always be more evidence, the evidence that exists demonstrates that the procedure is safe and effective as approved by the FDA and a discussion of mortality based upon the evidence is inappropriate.

⁶ Brau, S., et al, *The Spine Journal*, 4 (2004) 409-412

CMS also states in this section, “In chronic low back pain, sustained improvement in pain perception and a reduction in the pain-related functional restriction are generally the focus of study outcomes. Measuring a reliable improvement in chronic pain is problematic as pain is subjective and is particularly responsive to the placebo effect; therefore, clinical trials with appropriate controls utilizing independently assessed validated instruments are most heavily weighted.” While FDA did not require that a measure of pain be included to determine overall success, data on pain as measured by the Visual Analog Scale (VAS) is available. This data was included in the peer-reviewed article presenting the RCT findings and has been reprinted below. We also provide data on the Oswestry Disability Index (ODI) results because pain is one element of disability. As shown, the ProDisc-L treatment group exceeded the control group in both decrease in VAS scores and an improvement in ODI results.

The VAS scores

ProDisc-L 51% decrease VAS satisfaction 67 for fusion and 77 for ProDisc Fusion 43% decrease

The Oswestry Disability index results

ProDisc-L 46% improvement

Fusion 38% improvement

81% of the patients would have the treatment again while only 69% of the fusion patients would have the surgery again.

B. Discussion of Evidence

1. Question

CMS posits the question as follows: “Is the evidence sufficient to conclude that LADR with the ProDisc lumbar artificial disc will improve health outcomes in the Medicare population with low back pain due to degenerative disc disease?” Synthes submits that the question should be qualified and include *.....in the under 60 Medicare population* and if asked that way the answer would be in the affirmative based upon the results of the RCT, the European experience and the physician and patient comments previously received by CMS.

2. External Technology Assessment

CMS has opened this NCA with a specific qualification that they would not be re-assessing the Charite device yet they bring into the discussion of evidence the BCBS TEC assessment which covered only Charite. BCBS TEC has not yet published a technology assessment which specifically speaks to the ProDisc-L and we are perplexed at this inclusion. Additionally, we suggest that because Medicare has demonstrated interest in reviewing the role of fusion in the control of back pain that it would be appropriate to enlist the capabilities of the Agency for Healthcare Research and Quality (AHRQ) to study the role of TDR in the treatment of DDD.

VIII. Analysis

Throughout the analysis section of their decision CMS raises questions about the study design, execution and results. CMS focuses on the choice of the fusion control, the non-inferiority study design, patient follow-up, and overall study success criteria and results.

Fusion Control:

CMS states, “The ProDisc randomized clinical trial has as a comparator 360 degree – circumferential – fusion, a type of fusion that generally has higher successful fusion rates. The trial is designed to demonstrate that the disc is not inferior to this type of fusion; however, it is not clear that a trial designed to demonstrate noninferiority is valid given that the effectiveness of fusion in degenerative disc disease is not well-established in comparison to no treatment (MCAC fusion 2006).” We note that every patient in the IDE study had failed at least six months of conservative care before being enrolled in the study. This represents a 0.0% success rate for patients receiving non-operative treatment. At pre-operative baseline, while receiving conservative care, the patients in the fusion control group had a mean ODI score of 62.7/100. At 24 months post-operative, these same patients had a mean ODI score of 39.8. The following table shows the distribution of percent change in ODI at 24 months for patients enrolled in the study.

TABLE 7-10
Oswestry Disability Index
Distribution of Percent Change at 24 Months

	Fusion (n=71)	PRODISC-R (n=149)	PRODISC-NR (n=48)
Deteriorated	8 (11.3%)	13 (8.7%)	3 (6.3%)
No Change	3 (4.2%)	0 (0.0%)	0 (0.0%)
>0 – 4.9% improvement	0 (0.0%)	5 (3.4%)	0 (0.0%)
5 – 9.9% improvement	7 (9.9%)	8 (5.4%)	2 (4.2%)
10-14.9% improvement	7 (9.9%)	8 (5.4%)	2 (4.2%)
15-19.9% improvement	3 (4.2%)	8 (5.4%)	4 (8.3%)
20-24.9% improvement	4 (5.6%)	4 (2.7%)	1 (2.1%)
≥ 25% improvement	39 (54.9%)	103 (69.1%)	36 (75.0%)
Total - Any Improvement	60 (84.5%)	136 (91.3%)	45 (93.8%)

From this table it is clearly evident that patients in the fusion control responded very well to the operative treatment after receiving no benefit from non-operative treatment. The argument that, “the effectiveness of fusion in degenerative disc disease is not well-established in comparison to no treatment (MCAC fusion 2006),” is untenable for this application.

Non-inferiority Study Design:

CMS claims, “For a noninferiority comparison, the investigational treatment where the results are not inferior to another treatment is generally considered acceptable if there are other obvious advantages. For the lumbar artificial disc, the advantages are not obvious. Though the disc has been in clinical use in other countries well over 10 years, the design promise of spinal mobility leading to improved outcomes over fusion remains an

unproven idea. The available evidence thus far does not provide a direct link between spinal mobility and improved clinical outcomes.” This conclusion ignores the outcome of the ProDisc-L study. Regardless of whether the IDE study was intended to prove non-inferiority, the results conclude that the ProDisc-L was superior to the circumferential fusion control. Investigational studies are powered to ensure that a statistically significant difference can be discovered if one exists. Despite the fact that the study was powered to ensure that inferiority of ProDisc-L to the fusion control could be detected, the results show that the study was adequately powered to demonstrate superiority.

The study design assumed an 85% success rate in both treatment groups as a basis for establishing sample size in the non-inferiority study. When the overall success rates begin to diverge, such as happened here, the sample size necessary to detect a statistically meaningful difference begins to decrease. Every clinical study design must consider several assumptions about the performance of the investigational device and the control device. In the ProDisc-L IDE, the study authors assumed an equal performance in the two groups. The 85% assumed success rate was based on published clinical results. Indeed, the clinical success rate for patients in the ProDisc-L study exceeded this assumed success rate (91.3% of all ProDisc-L patients showed some improvement in ODI scores). Given the stringent requirements for overall study success (ODI, SF-36, Neuro, Re-operations, maintenance of Disc Height, absence of Subsidence, absence of Migration, absence of Radiolucencies, and Range of Motion) the assumed overall study success rates were not achieved. Nevertheless, because of the actual differences in performance, the study was adequately powered to demonstrate statistical superiority.

Patient Follow-up:

CMS states, “Incomplete patient accountability further complicates interpretation of this study. Zigler 2005, an early report of the IDE trial, reported that 500 patients were enrolled as of March 2003. It is presumed that those not reported in this study are in the two level study, but we don’t know. The clinical trial report doesn’t list denominators, only percentages, so it’s difficult to know who was included in their analysis. The FDA summary does have some denominators. From this summary, we conclude that 9/80 patients are completely excluded from the fusion group, and 12/160 excluded from the ProDisc group (presumed for missing data).”

The ProDisc-L IDE study had superior patient follow-up. Over the course of four years, only 8/242 (3.3%) of all patients were lost to follow-up. The study involved 242 (80 Fusion, 162 ProDisc-L) patients that were operated. Of these, 8 (2 Fusion, 6 ProDisc-L) were early failures, 6 (5 Fusion, 1 ProDisc-L) were major protocol violations, leaving 220 (71 Fusion, 149 ProDisc-L) patients that were seen in the clinic for their 24 month follow-up. Under FDA requirements, only patients that had all data necessary to calculate the overall study success or who had known outcomes (early failures) were included in the calculation of overall success. Several sensitivity analyses were performed including an analysis where all missing patients are treated as failures in both treatment groups, an analysis where all missing patients are treated as successes in both treatment groups, and a worst case analysis where all missing patients in the Fusion group are treated as successes and all missing patients in the ProDisc-L group are treated as failures. Under all sensitivity analyses, ProDisc-L was proven to be non-inferior to the fusion control.

Overall Success Criteria:

CMS states, "While there are numerically more measures than in the Charite randomized trial, the requirements are not more stringent." We respectfully strongly disagree.

The ProDisc-L IDE study employed the most stringent overall success criteria in the history of spine studies in the United States. In order for a patient to be considered an "overall study success" the patient needed to be a success in all ten of the primary success criteria. A failure in any single component resulted in the patient being considered a study failure. This means that a patient could be a success in 9/10 criteria and would still be an "overall" study failure. The study requirements employed in the IDE study were exceptionally rigorous and included measurements of pain (ODI, SF-36), neurologic performance, radiographic performance (subsidence, migration, radiolucencies, disc height) and the restoration of normal lumbar spine motion. Additionally we do not understand why CMS appears to dismiss the importance of the motion criteria. At 24 months 94% of ProDisc-L patients had normal motion of 7.7° while the control experienced decreasing range of motion over the same period.

Conclusion:

In the conclusion CMS states that "Some evidence does exist for patients age 60 and under. However, rather than confirm the results of earlier case series studies, the ProDisc FDA IDE noninferiority clinical trial creates more uncertainty in benefit due to certain issues including trial design and reporting." Most device trials are designed to show non-inferiority as we discussed above. The treatment effect in this study is 18.4% with a confidence interval of 4.1% to 32.3%. We submit that as convincing evidence that ProDisc-L is superior to its' fusion comparator. CMS also questions the reporting in the study. Synthes will be pleased to work with CMS to report anything required.

CMS misses the clinical application of the artificial disc and dismisses the evidence relative to the indications for the device. LADR is meant to be an alternative to fusion for the treatment of DDD in the lumbar spine from L3 to S1. The clinical goal is to stop or reduce pain as well as or better than fusion. It is meant to preserve the biomechanics of the spine which fusion cannot do. It is meant to possibly reduce the damage to the adjacent levels which it is known fusion contributes to, (severe DDD at a level also contributes to adjacent level degeneration for the same reason a fusion does: the diseased level no longer moves appropriately, transferring load onto adjacent levels) and finally it is meant to produce a health benefit in carefully selected patients which thousands of patients will testify that it does. The above statements can be proven in the literature, definitively in the RCT, in the FDA Summary of Safety and Effectiveness and from physician and patient experience both here and abroad.

On behalf of patients and their physicians we ask what further evidence CMS wishes to see. Synthes, we believe, is not unique in wondering why when a product is declared safe and effective by a fellow government agency, with effective being the operative

word, and has compelling strong scientific/clinical evidence to prove its' clinical value, what additional evidence CMS requires to render a decision of reasonable and necessary?

Coverage with Evidence Development

As stated previously, Synthes acknowledges the time CMS took in this evaluation. We appreciate the avenue left open to patients to seek coverage at the local level. Nonetheless, we feel the conclusion that LADR with ProDisc-L should not be a covered benefit is not justified because strong evidence exists to support coverage. However, we recognize CMS' desire for more evidence on this and all potential treatments for DDD specifically and for low back pain in general.

We recommend that CMS consider coverage with evidence development for ProDisc-L. We pledge to work with CMS to provide the data necessary for a registry or other information gathering tool to inform physician practice and Medicare coverage of these important treatment options.

We acknowledge the medical controversy surrounding spinal fusion. The small numbers of patients that have fusion do so because they cannot get relief from pain any other way. No one undertakes spinal fusion lightly, neither physicians nor patients. Yet it exists and it works or it would not still be part of the treatment regimen for this disabling condition. CMS witnessed the controversy at the recent MCAC meeting. It should be in the spirit of furthering the treatment options for this disabling disease that Synthes and CMS work together under the novel approach of coverage with evidence determination to determine what is clinically effective for Medicare beneficiaries 60 years of age and under suffering from DDD at one level.

We invite and look forward to the opportunity to work with CMS to study the causes of the larger area of lumbar back pain as well as the narrower area of the treatment of DDD in the lumbar spine.

Sincerely,



Michael Heggie
Director of Reimbursement

Approach Complications in Lumbar Total Disc Replacement

Purpose

To determine the incidence of approach complications in a large series of patients undergoing lumbar total disc replacement (TDR)

Methods

- 334 Patients (190 male / 144 female)
- May 2001 - Dec 2005
- All but 16 were part of IDE study, continuation or compassionate use
- Three different devices
 - Charite - 66
 - ProDisc - 248
 - FlexCore - 20
- 100% follow-up rate
- All complications were tabulated concurrently
- Minimum follow-up 6 months

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Results

Number of Approaches

Level	Approaches (#)
L5-S1	124
L4-S1	105
L4-5	45
L3-L5	19
L3-S1	24
L2-S1	1
Hybrids	7
Prior fusion	3
Misc	6
Total	334

Complications

- Iliac vein laceration
 - All at L4-5 (3 during approach)
 - Minimal blood loss (200 to 400 cc)
 - No sequelae, no transfusion
- Left iliac artery thrombosis
 - At L3-4 - pt. had prior ALIF from L4 to S1
 - Vessels could not be mobilized fully without stretch
 - Diagnosis made by pulse oximeter
 - Rt. by stat thrombectomy with no sequelae

4 (1.2%)

1 (0.2%)

Results (cont'd)

Complications (cont'd)

- Retrograde ejaculation 0
- Ureteral injury 0
- Arterial injury in primary cases 0
- Nerve root injuries 0
- Ileus (transient, no N-G suction) 5 (1.5%)
- Bowel injuries 0
- Clinical DVT 2 (0.6%)
- Hernia (so far) 0

Conclusions

- This study compares favorably with published reports of complications, in experienced hands, for Anterior Lumbar Interbody Fusion (ALIF) and for the Charite IDE study.
- The approach is, therefore, safe and effective when performed by experienced access surgeons.
- L4-5 is again shown to present the higher risk and technical difficulty.
- Surgeons with little or no experience in anterior lumbar surgery should be very leery of performing lumbar TDR, especially at L4-5.

Incidence of Revision and Approach Strategies in Lumbar Arthroplasty

Methods

- 393 Patients:
- 1 to 4 level TDR's
 - May 2001 - December 2005
 - Age Range: 19 - 60
 - Follow-up range:
 - 3 mo - 4 yrs 7 mo
 - 100% follow-up rate

Results (cont')

	Patients	Revisions	Revision %
Charite	66	5	7.50% *
Flexicore	20	1	5.00% **
ProDisc-L	307	2	0.60%
Total	393	8	2.03%

* Highly significant Δ between ProDisc-L and Charite (p<0.001)
 ** Significant Δ between ProDisc-L and Flexicore (p<0.01)

Results

8 Anterior Revisions - 2.03% (8/393)

	Revisions	Time to Reop	Device
Extrusion	5	≤ 3 wks	3 Charite 1 Flexicore 1 ProDisc-L
Migration	2	8 mos	1 Charite 1 ProDisc-L
Persistent pain	1	15 mos	1 Charite

There were no complications relative to the approach in any of the 8 revisions.

- 6 at L5-S1
- 2 at L4-5
- L4-5 is most challenging and requires significant experience on the part of the access surgeon

Recommendations

- Imaging studies:
 - MRV. Radial color coded CT
 - Venogram (especially anterior device extrusion at L4-5)
 - Ureteral catheters (especially in returns to L4-5 or above)
 - Pulse oximeter (identify artery, monitor vessel occlusion time at L4-5.)
- Balloon (Fogarty) catheters (control of venous bleeding)
- Cell saver
- Percutaneous venous catheters (control bleeding with balloons or stents via femoral veins, prep groins.)
- Avoid rt. side except for L5-S1
- IVC filter (when clot is seen in iliac vein on imaging proximal to extruded device)
- Avoid same incision after 10 days
- L5-S1 - opposite side retroperitoneal
- L4-5 - far lateral retroperitoneal or transperitoneal
- L3-4, L2-3 - far lateral retroperitoneal

Conclusion

- Revisions in arthroplasty are inevitable
- Significant difference in revision rate depending on device
- Pre-op planning of revision is very important.

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June 21, 2007

Jyme Schafer, MD, MPH
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Dear Dr. Schafer:

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

DePuy Spine, Inc. is an operating company of DePuy, Inc. one of the world's leading designers, manufacturers and suppliers of orthopedic devices and supplies. We are known throughout the medical world for the development of innovative solutions for a wide range of spinal pathologies.

The current national coverage determination (NCD) has had a significant impact on motion preservation technology for spine patients and the CHARITÉ® Artificial Disc, manufactured by DePuy Spine. For Medicare beneficiaries sixty years of age or under, there is no national coverage determination, leaving such determinations to be made on a local basis. The purpose of this letter is to provide comments concerning the Centers for Medicare and Medicaid Services' (CMS) reconsideration of the Proposed Decision Memo for Lumbar Artificial Disc Replacement (CAG-00292R).

CMS is now opening this NCD for reconsideration with a thorough review of the evidence on the ProDisc™-L Total Disc Replacement and any other lumbar artificial discs that receive FDA approval during this national coverage analysis process. We would like to request the following:

- Give careful consideration to the discussion and conclusions from the recent Medicare Coverage Advisory Committee (MCAC) on Spinal Fusion; particularly being aware that the arthroplasty IDE studies exceeded established minimal standards for health-related disability as determined by the Oswestry Disability Index (ODI) and for pain outcomes, as determined using the Visual Analog Scale (VAS).
- Apply the same evidentiary standards for review of the ProDisc-L data as were applied to the CHARITÉ Artificial Disc data.
- Note the design limitations and lack of conclusive findings of randomized trials comparing lumbar fusion surgery to nonoperative care.
- Provide coverage to both the CHARITÉ Artificial Disc and ProDisc-L Total Disc Replacement, recognizing that they both meet the standard of "reasonable and necessary".

MEDICARE COVERAGE ADVISORY COMMITTEE (MCAC)

On November 30, 2006, CMS convened an expert panel for the MCAC on Spinal Fusion for the Treatment of Low Back Pain Secondary to Degenerative Disc Disease. The MCAC addressed concerns that directly pertain to the control arms in all of the lumbar artificial disc trials. In the formal Technology Assessment, when assessing treatment effectiveness for chronic low back pain, two validated instruments were used: the ODI and VAS for pain assessment¹.

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., personal care, sleeping, sex life, social life, traveling). The ODI is on a scale of 0-100, 0 indicating no disability and 100 signifying complete disability. A change of 10 units from baseline has been shown to be the minimum change to demonstrate clinical improvement for ODI. 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. The minimal change to demonstrate clinical improvement is referred to as the Minimal Clinically Important Differences (MCID). The Technology Assessment noted that the arthroplasty IDE studies exceeded established minimal standards in ODI and VAS.

As described in the tables below, when the principles of the MCID are applied to the clinical results from the CHARITÉ Artificial Disc and the ProDisc-L Total Artificial Disc IDE studies, all devices exceed Hägg's definition of MCID for ODI and VAS by two-fold from baseline. Although these are two different studies for which direct comparison is not possible, they are being presented here in table form in order to apply the Hägg criteria.

MINIMAL CLINICALLY IMPORTANT DIFFERENCES

Health-Related Disability (ODI)

The MCID for ODI was 10 units. A minimum level of clinical significance is generally a more rigorous measure of treatment efficacy than statistical significance.

ODI	Treatment	Mean at Baseline	Mean at 24 Months	Mean Point Reduction	Mean % Reduction
Blumenthal <i>et al</i> ²	CHARITÉ	50.6	26.3	24.3	48.0%
	ALIF with BAK	52.1	30.5	21.6	41.4%

ODI	Treatment	Mean at Baseline	Mean at 24 Months	Mean Point Reduction	Mean % Reduction
Zigler <i>et al</i> ³	PRODISC L	63.4	34.5	28.9	45.6%
	360° fusion	62.9	39.8	23.1	36.7%

¹ Hägg O, Fritzell P, Nordvall A et al. The clinical importance of changes in outcome scores after treatment for chronic low back pain.[see comment]. *European Spine Journal* 2003;12:12-20

² Blumenthal S, McAfee PC, Guyer RD et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITÉ artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes. *Spine* 2005;30:1565-75

³ Zigler J, Delamarter R, Spivak JM et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. *Spine* 2007;32:1155-62

VAS - Pain Outcomes

The MCID of VAS back pain was 18-19 units. A minimum level of clinical significance is generally a more rigorous measure of treatment efficacy than statistical significance.

VAS	Treatment	Mean at Baseline	Mean at 24 Months	Mean Point Reduction	Mean % Reduction
Blumenthal <i>et al</i> ²	CHARITÉ	72.0	31.2	40.8	56.7%
	ALIF with BAK	71.8	37.5	34.3	47.8%

VAS	Treatment	Mean at Baseline	Mean 24 Months	Mean Point Reduction	Mean % Reduction
Zigler <i>et al</i> ¹	PRODISC L	75.1	36.1	39.0	51.9%
	360° Fusion	73.2	41.2	32.0	43.7%

At 24-months, the clinical VAS and ODI outcomes in arthroplasty groups were equal or greater than twice the MCID value.

Since a randomized controlled trial has not been conducted comparing CHARITÉ Artificial Disc and ProDisc-L Total Disc Replacement, conclusion statements directly comparing the two studies with respect to any clinical outcomes are not possible. However, there are several similarities in the study designs that support our request:

- Non-inferiority studies
- Age 18-60 years old
- 24 month duration
- Five-year follow-up request by FDA as a condition of approval

In addition, published literature on CHARITÉ and ProDisc-L share the following attributes:

- Limited evidence for the elderly population and
- European case series for long-term data.

The control arms differ: the CHARITÉ Artificial Disc study control is an ALIF with BAK and iliac crest autograft, while the ProDisc-L Total Disc Replacement control is a 360° fusion (anterior/posterior fixation); however, both trials compared a motion device to fusion.

CONTROVERSY OF TRIALS COMPARING LUMBAR FUSION SURGERY TO NONOPERATIVE CARE FOR TREATMENT OF CHRONIC BACK PAIN

Highlighted below are a few examples from the MCAC transcripts and a recent publication by Mirza *et al* that emphasize the challenges in evaluating the effectiveness of nonoperative care for patients with low back pain and drawing meaningful conclusions from such studies.

During his technology assessment presentation at the CMS meeting in November 2006, Dr. McCrory had the following comment on nonsurgical therapy for low back pain: “And finally, you know, also for this technology assessment, we were interested in the comparison between surgical therapy and nonsurgical

¹ VAS scores at baseline obtained from Summary of Safety and Effectiveness Data (www.fda.gov) and VAS scores at 24 months obtained from ProDISC IDE Study Brochure (www.synthesprodisc.com)

therapy. The nonsurgical controls were really not terribly well standardized and described and could not be easily reproduced, at least in the papers that we looked at.”⁵

During the same session, Dr. Mirza further stated that: “There are five trials which have asked the lead question, which is, does surgery work better than nonsurgical treatment? And I think those studies are very, very hard to do. And as the SPORT publication showed just last week, it is very hard for us in the United States to conduct that kind of randomized trial in other countries...I doubt that we would be able to that kind of study in the U.S.”⁶

In the Technology Assessment presented by Dr. Crory *et al.* for the MCAC meeting, the following statement discussed the limitation of clinical studies evaluating nonsurgical vs. surgical care for low back pain: “In controlled studies comparing lumbar spinal fusion to non-surgical treatment, differences in not only the patient populations but also in the non-surgical treatments used hamper the ability to compare the results of the studies.”⁷

In addition, a recent publication by Mirza *et al* reviewing all trials comparing lumbar fusion to nonoperative care provided the following conclusions⁸:

- Compared to unstructured, heterogeneous nonoperative care, lumbar fusion surgery may be more efficacious for treatment of chronic back pain.
- Fusion may not be more effective than a structured rehabilitation program that includes cognitive-behavior therapy.
- Limitations of some randomized trials comparing these treatments prevent definitive conclusions as to which is more efficacious.

In summary, findings from the MCAC session comparing fusion to nonoperative care have clouded the issue on the clinical benefit of lumbar artificial disc replacement. As noted above from the MCAC transcripts, the Draft Technology Assessment by Crory *et al* and the review publication by Mirza *et al.*, randomized trials comparing nonsurgical treatments to fusion contain methodological limitations that could potentially discredit any study conclusions.

It is our goal to refocus the issue back to the positive clinical outcomes observed following total disc replacement with the CHARITÉ Artificial Disc or the ProDisc-L Total Disc Replacement in both, VAS and ODI. The improvements from baseline to 24 months far exceeded the MCID for all procedures, including the fusion control arms. At 24 months, this improvement was twice the MCID for the arthroplasty groups. Clearly, an improved health outcome was achieved.

LUMBAR ARTIFICIAL DISC REPLACEMENT FOR THE ELDERLY POPULATION

Although both studies excluded patients over the age of 60, the clinical community believes that the clinical benefits for both the CHARITÉ Artificial Disc and the ProDisc-L Total Disc Replacement can be

⁵ MCAC meeting on 11/30/2006 - Spinal Fusion for the Treatment of Low Back Pain Secondary to Lumbar Degenerative Disc Disease. Douglas C. McCrory, M.D., M.P.H. Assistant Professor Medicine, Duke University (00043: 21-25, 00044: 1-2)

⁶ MCAC meeting on 11/30/2006 - Spinal Fusion for the Treatment of Low Back Pain Secondary to Lumbar Degenerative Disc Disease. Sohail K. Mirza, M.D., M.P.H., University of Washington (00071: 4-6)

⁷ McCrory DC, Turner DA, Patwardhan MB et al. Draft Technology Assessment - Spinal Fusion for Treatment of Degenerative Disease Affecting the Lumbar Spine - Duke Evidence-based Practice Center . 2006. Agency for Healthcare Research and Quality

⁸ Mirza SK, Deyo RA. Systematic review of randomized trials comparing lumbar fusion surgery to nonoperative care for treatment of chronic back pain *Spine* 2007;32:816-23

achieved in carefully selected Medicare beneficiaries. This was further reinforced during the Spinal Fusion MCAC, when the expert panel voted that it is "Reasonably Likely" that the results of lumbar fusion procedures for the treatment of low back pain secondary to degenerative disc disease in the under 60 population would apply to the Medicare over 65 population.

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. The CHARITÉ Artificial Disc and the ProDisc-L Total Disc Replacement meet the criterion for reasonable and necessary for a select patient population as demonstrated in the Level I evidence from the FDA IDE clinical trial results. We further believe that the clinical benefits can be achieved in carefully selected Medicare beneficiaries (including the under 65 disabled population and a more limited number of patients 65 and older) and we strongly support the need for careful patient selection criteria. These patient criteria were detailed in DePuy Spine's previous comment on the NCD.

As CMS considers the merits of this NCD, we request that CMS apply consistent coverage standards when evaluating the levels of evidence for both the ProDisc-L Total Disc Replacement and the CHARITÉ Artificial Disc.

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

Sincerely,



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