GAG# LADR Thierry Marnay Contribution. txt
From: Dr Thierry MARNAY. [th
Sent: saturday, December 23, 2006 11:10 AM
TO: OCONNOR, DEIRDRE E. (CMS/OCSQ)
subject: GAG# LADR Thierry Marnay Contribution
Attachments: TMarnay comments 1.doc
Dear Mrs O'Connor
TO be sure you will receive my contribution to the information about the LADR prodisc® I joined to this mail the file I tried to put on CMS web site (but I received no confirmation about it I preferred to send it to you directly) I hope you will read and take in account those information and comments. I am ready to answer to all the questions you would like to ask related to Total disc replacement

Sincerly yours
Season Greetings
Dr Thierry Marnay
Dr Thierry MARNAY
spine surgeon
Associated Professor NYU Hospital for Joint Diseases
Chief of spine surgery Department
Centre de Chirurgie Vertebrale
Clinique du Parc - BP20
34171 CASTELNAU LE LEZ (France)
Tel : +33 (0)4 67 33 13 63 (secretariat) Fax: +33 (0)4 67 72 95 41 Email

NCA
Lumbar Artificial Disc Replacement (LADR)
ProDisc-L®
by Thierry Marnay, MD [t]

As inventor[E] of ProDisc-L, using it for almost 17 years with an experience of more than 1000 levels implanted, I strongly believe that it must be offered to the patients under an insurance coverage. The quality of the results demonstrated in all the studies and especially the US FDA IDE, reinforces the conviction that this is a terrific progress in treatment of the Degenerative Disc Disease and this treatment must be delivered to those who need it and are good selected candidates. Even though I have not yet been a Medicare provider, I think that I must participate to this debate according to my long experience and as witness of the development of this technology in the major countries including USA.
The qualities of the ProDisc-L cannot be discussed, and this is confirmed by the US randomized Study which has been conducted in a perfect way with impressive data and showed its superiority over the control group. The 360 fusion control group was the standard of care when the study was designed. As a matter of fact, the results of this control group are the best results never published about fusion, and the ProDisc-L showed "statistical superiority" to its control group. That amplifies, in a positive manner if needed, the long experience that the international and US spine surgeon community has had with this implant if we follow the publications on this device. The US study design included patients between 18 and 60 years old. However two studies have been conducted (Marnay, Bertagnoli) concerning patients over sixty years old and their results confirm that, following drastic conditions of selection, ProDisc-L should be delivered and reimbursed for this population too.

Preamble

Intervertebral disc degeneration is a major cause of pain and disability in adults. The population suffering of low back pain is growing with the development of the economy of the societies. But this universal disease is also the cause of the principal costs in medical and social expenses in the developed countries and becomes a real problem in those in development (Ehrlich [I]). The adult population concerned by this disc degeneration disease starts with patients since 18 years old. However the oncoming growth of the population between 60 and 70 years old increases the rate of patients to be treated.
"Regional back pain: predicament at home, Nemesis at work" (Hadler [ii]) The initial treatment for lumbar degenerative disc disease is non-operative and successful main part of the time. A lot of other procedures have been used for decades with limited success. As a surgical point of view, the posterior classic discectomy treats in majority the roots compression (leg pain) and the laminectomy treats the canal stenosis symptoms. When the degeneration of the disc requires a surgical treatment, the arthrodesis technique has been proposed and used for more than 60 years. It has proven its efficiency after conservative treatment failure (Fritzell P. [iii]). Despite a multiplication of the techniques to achieve its primary goal, which is fusion, the arthrodesis cannot solve all the problems created by thedisc degeneration. The pain relief is inconstant and often partial, the spinal balance is not achieved, the essential permanent small motion to adapt instantaneously the spinal curves to all the small displacements of everyday life and the disc rotation at each footstep are no more possible. That increases the charge of the adjacent levels, (which proceeds of the same degenerative disease), accelerates their degeneration despite a good restoration of the disc space and the elimination of the instability at the level operated on after interbody fusion. Hypertrophic facets arthropathy, dynamic hypennobility nor instability, spinal stenosis, disc degeneration and osteophytes fonnations have been reported to occur at levels

adjacent to fusion. These pathological evolutions may result in pain and roots compressions and require revision surgery in adjacent levels in a lot off cases (Lee C.K [IV] Kumar M.N. [v]). Artificial disc replacement with the ProDisc-L implant is used for 17 years with strong long-term data. We reported this long term 7 to 11 years of follow up of the ProDisc-L® implantation in 64 patients, concerning 93 implants, as an effective and safe procedure (Tropiano P. [vi]). An analysis of the evolution of the adjacent levels after Total Disc Replacement of this long term cohort showed the protection from degeneration when the mobility has been maintained at follow up (Huang R. [vii]). More than any other technique, total disc replacement in Lumbar spine with the implant ProDisc-L® has been the focus of scientific studies [viii].

The responsibility of the surgeons has always been to improve the surgical treatments of the diseases they had to deal with. We created the conditions for a safe and effective replacement of the failed part of the mobile unit of the spinal joint, the disc space, with a Total Disc Prothesis. We have performed the laboratory tests and afterwards the clinical studies that started 17 years ago. The spine surgeons involved in the development and the clinical studies obtained successful results with the satisfaction of a perfected conducted clinical research and more than that, the joy to participate to a work that was changing completely the future of their patients, victims of a disease with no real satisfying treatment, till the ProDisc-L has been an option. And the results of the studies they participated to, comforted them in the choice they have made of a Total Disc replacement. Industry has performed its role in research, development and studies support. Regulatory organizations did a great job in their control and analysis of the results (FDA [iX]). Insurance companies have now the responsibility and the duty to provide this possibility, Total Disc Replacement, for all the patients it may be indicated.

Requirements for a Total Disc Replacement
Design & Biomechanical Bases:

The choice of the type of implant is the first step. The choice of a mechanical implant corresponds to several fundamental criteria:

-The well known and long time successful follow up of the mechanical type of implants in the other joints replacement using implantable materials : two Cobalt Chrome alloy endplates (CoCrMo), one ultra high weight Polyethylene (UHWPE) inlay which characteristics are tested and fully under control. (Compared to all the viscoelastic materials that have permanently failed in the past because of the weakness of their mechanical characteristics).

- The use of a ball and socket artificial joint to neutralize the shear forces and so protect the remaining part of the mobile unit, the facet joints.

- The capability of the implant to reproduce flexion, extension, lateral bending and rotation.

- The choice of an adapted positioning of the center of rotation of the implant and the calculation of the radius of the polyethylene dome that must fit, after the restoration of the disc height, with the rotational path of the facets in all the degrees of liberty. The disc diseases includes most of the time a ligament failure. But beyond that, the surgery may need the posterior longitudinal ligament resection (to allow the disc height to be restored), face its degeneration or a prior damage after a posterior discectomy already performed in the history of the patient for a disc herniation. The anterior longitudinal ligament may be also damaged by the degeneration of the disc and must be sacrificed in the anterior access of the disc space during the surgical procedure. Those elements explain the choice of stability induced by the ball and socket design and the part of constrain of the ProDisc-L® implant to take the role attributed to those two ligaments in the natural disc.

-The design adapted to the surface of the vertebral plates with the choice of sizes, the different possibilities of height to restore an adapted one and a lordotic angle chosen according to the disc shape.

-The capacity of the implant to create a physiological translation according to all the biomechanical work published in literature and reproduced in our tests (Pearcy M. [X]).

Biomechanical and Laboratory Tests:

All the tests required for the proof of safety and effectiveness have been performed since the beginning of the history of the implant which started in the eighties. They have been up dated according to the evolution of the technology and periodically reconducted. They have been included in all the FDA PMA procedure. They concerned the wear tests, the compression shear tests, the compression shear fatigue test, the inlay push out test, the hysteresis test, the expulsion test, and the creep relaxation test. The conclusions of this long work including millions of cycles is the safety of the implant to be set in the human body disc space, under long-term functional behavior. The measurement of the debris produced during the wear tests showed a large margin of safety with a very small volume of debris produced especially compared to the standards accepted for the other types of implants.

Implantation Feasibility

This concerns the capacity of the surgical spine community to implant perfectly and in a reproducible manner the ProDisc-L® from patient to patient, without complications.

-The anterior approach for a spine access in surgery is universally known since the beginning of the 50's (Cauchoix J. [xi] Harmon p. [xii]). With the use of the anterior interbody fusion that as been generalized in the last decades, the technique for a safe anterior access to the disc has been standardized (Brau S. [Xiii]): the preoperative protocol has been developed as the use of an angio-scanner for the vessels topography (Datta J. [xiv]), and an adapted instrumentation has been created.

- This access in the hands of "access surgeons" has been the object of specific educational courses with the development of appropriated tools [u]. The level of safety reduced the complications risks as it has been proven in all the studies published especially about the total disc replacement, with the lowest rate of vascular injuries and infection, (that should be compared to the rate of theses complications of all the other techniques currently used in the same type of indication)[l3].

- The implantation technique of the ProDisc-L® has been developed, studied, and taught for now 17 years and the work with the US surgeons started in 2000 with the training courses organized for the teams involved in the American randomized study. The specific part of the implantation is reduced in three surgical steps sustained by a simple and efficient instrumentation (Tropiano P.[XV]). The training courses organized for the spine surgeons are the guarantee of a perfect use of those instruments and of a perfect setting of the implant.

Safety of the implant

The implant design incorporates the essential elements of a perfect stability when in place following the standards of orthopedic implants designed for joint replacements.

-The keel for the guidance and primary anchorage is one of the key points of the connection bone-implant. The role of the keel during the surgical procedure is to guide the prothesis during its setting in the same spot that the one chosen during the preparation following the path prepared by the chisel cut. Without this specificity present on the implant ProDisc-L® since the beginning, the disc prothesis may slide during its insertion and may not follow the centering of the implant that is decided at the beginning of the procedure after a fluoroscopic control. The keel cut prepares the bony anchorage with an immediate press-fit on the keel that insures the immediate stability of the disc prothesis. Afterwards in the 6 first weeks, the anterior part of the cut in front of the keels, heals and "closes the door" to any expulsion of the implant.

-The bone integration is promoted by the plasma sprayed titanium coating surface of the implant endplates facing the vertebral endplates. That creates the secondary stability and will support the anchorage of the implant during the patient's life.

-The presentation in a three components way of the implant is a fundamental point that should be respected by all intra-discal total joint replacement processes. The capability to introduce the plates without the core of polyethylene, allows a perfect setting for them, as deep as needed and guided to avoid any damage to the bony surface, as the introduction does not need a strong and forced hammering. The instrumentation helps the insertion of the poly core, once more without any strength, and permits the perfect snapping of it. Additionally, in the rare cases when a revision could have been needed, this composition of a three pieces implant may the removal of the disc easier with no vertebral bone resection, just by the possibility to remove the polyethylene core first, and after to take off the plates one after the other.

The thousands implantation performed all over the world, including those performed during the US IDE study and those made under "the continued access" procedure have confirmed the safety of the design of the implant and of its implantation procedure.

Patients' selection

The selection of the patient in a surgical procedure and the choice of the appropriated treatment have always been and remain the key point of the success of any treatment. The delay between the first signs of the disease and the first surgical visit, and the well performed state of the art conservative treatment (minimum 6 months) are the starting points before any further surgical discussion. The interview (historical review of the disease, treatment already performed), and the management of the patient in his global nature (general health, social, professional, family), the identification of the pain origin (Bertagnoli R. [xVi]), filling the index of disability to confirm its level and justify a surgical choice (Oswestry disability index-ODI (Little D. [xvii]), visual analogical scales-VAS), the explorations of the spine (X-Rays, CT scan, MRI analysis (Marnay T. [xviii])) the respect of the frame delivered by the studies including the bone quality checked by DEXA have detennined the "indications-contra indications". These are the elements for the surgeon's choice and the guarantee of the success of the procedure. All of these has been well defined during the process of the ProDisc-L® approval and remains the center point of all the education process of the surgeons community to this technique [x].

Studies results

A lot of publications in the international scientific literature may be analyzed with the goal to confirm the effectiveness and safety of the ProDisc-L® total disc replacement. The quality of their results demonstrates that this technology is neither experimental nor investigational. Long term follow up, international studies with cohorts of hundreds of patients, a randomized study versus 360° fusion conducted in United States with results inspected with a microscope by all the observers, contribute to confirm those points.

Long-term follow up

The series of patients operated on between 1990-93 have been the object of researches in connection with an American Spine Team (Joint Disease Hospital of New York). Beyond the analysis of the clinical results at follow up, the long tenn safety analysis without any delayed complications related to the procedure or the implants, the measurement of the range of motion (ROM) have been perfonned (Huang R. [xix xx Xxi]). The space motion is still maintained after years and the ROM measurement has been correlated to the quality of the long-term outcomes and the adjacent disc protection from a degenerative process.

Randomized Study Results

Several publications have concerned the preliminary results of the FDA IDE study of ProDisc-L Total Disc Replacement versus Fusion (360°) as treatment of discogenic pain at one level between L3-S1 (Delamarter R.xxii, Zigler J. [xxiii]). The randomized study so conducted on 286 patients has showed the "Effectiveness and Safety" of this technique in the proper selected patients. The table (table 1) below shows the quality of the results and the statistically superiority of the ProDisc-L Total disc Replacement on the 360°Fusion[xxiv].

Table 1: Results of ProDisc-L® US randomized study (source FDA)

	Fusion	ProDisc-L® L (Randomized)	ProDisc-L® L (Non-randomized)
ODI success (≥ 15% improvement)	46/71 (64.8%)	115/149 (77.2%)	41/48 (85.4%)
ODI success (≥ 15% pointd improvement)	39/71 (54.9%)	101/149 (67.8%)	36/48 (75.0%)
Device success (no reoperation, revision, removal or supplemental fixation)	73/75 (97.3%)	155/161 (96.3%)	50/50 -100%
Neurological Success (maintain or improve - motor, sensory, reflex, and straight leg raise)	57/70 (81.4%)	135/148 (91.2%)	40/48 (83.3%)
SF-36 success (score improved)	49/70 (70.0%)	118/149 (79.2%)	43/48 (88.9%)
Radiographic success (using FDA's definition of ROM success)1.5	59/69 (85.5%)	125/143 (87.4%))	40/45 (88.9%
Radiographic success (using Sponsor's definition of ROM success)2.5	50/69 (85.5%)	131/143 (91.6%)	43/45 (95.6%)
Overall success [3]	32/71 (45.1%)	94/148 **(63.5%)**	30/45 **(66.7%)**
Overall success [4]	29/71 (40.8%)	79/148 (53.4%)	25/45 (55.6%)

1 (24 month flexion/extension ROM -Preop flexion extension ROM) >0 (with ± 3' measurement error applied)

2 Flexion/extension ROM at 24 months "normal", where "normal" ROM defined as follows:

L3/L4 normal if ROM> 60 (±3° error) and < 20' (design limit of device)
L4/L5 normal if Z> 6' (±30 error) and 5200 (design limit of device)
L5/SI normal if> 5' (±30 error) and S 200 (design limit of device)

3 Synthes Spine proposed criteria: Analysis conducted per the investigational protocol, including> 15% ODI score improvement, sponsor's definition of ROM success and a non-inferiority margin of 12.5%

4 FDA requested criteria: Analysis conducted as above, except: _> 15 point ODI score improvement, FDA's definition of ROM success, and a non-inferiority margin of 10%

5 Four of the patients had a partial post-24 month analyses and radiographic analysis was completed post 24 months (range 33-45 months postoperatively).

Source: FDA http://www.fda.gov/cdrh/pdf5/p050010c.pdf page 11-12

The "overall success" concerned ten items and was especially more difficult to achieve than all the current "overall success" of the other IDE determined for competition or fusion products. The criteria chosen (ODI, Device success, Neurological success, SF36, no migration, no subsidence, no translucency, no loss of height, fusion status success, ROM success) were much more selective than ever done in the past (especially for the other disc, approved with only four criteria, which could explain its controversial nature and by extension, the global suspicion about total disc replacement which in the case of the ProDiscL ® cannot be justified).
One of the most important other aspects of the ProDisc-L® randomized study results is the analysis of the range of motion. It has been shown in the long-term studies performed already evocated, that a maintained range of motion was the key of the protection of the adjacent level from degeneration, in opposition of what has been described as the "fusion disease" about the pathologic evolution of the level above a lumbar fusion. Even those long-term studies could bring the proof a motion restored and maintained with years of use of the implant, the Flexion/Extension range of motion analysis in the US randomized study confirmed the restoration of motion at 24 months (7.7°).

« *Although the study was not designed to show a difference, a statistically significant difference in Overall Success rates between the PRODISC-L-L and control groups was found using a one-sided Fishers Exact Test, for both the applicant's proposed and FDA'S requested definitions of Overall Success" (p=0.0053 and p=0.0438), respectively) 'from* FDA ProDisc-L® approval documentation: Summary of safety and effectiveness data p 19
http://www.fda.gov/cdrh/pdf5/P050010.html

Comparative study of Prodsic® Total Disc replacement
in patients Below versus Over 60 years old
Single Level versus Multi levels

We conducted a prospective study that started in 1999, with the use of ProDisc-L® as Total disc Replacement including 476 patients with a degenerative disc disease, respecting the same indications-contraindications as the USA randomized study but including patients over 60 years old. Two hundred and thirty five (235) needed a one level disc procedure of which about twelve (12) were more than sixty years old (60), and two hundred and forty one needed a multi level procedure of which about twenty three (23) were more than sixty years old. There is no statistically significant difference "in the results presented between the two groups, below versus over sixty years old (table 2). The surgery on multi levels indications, supposed to give worse results in the elderly group (this is a presupposed paradigm without scientific base as demonstrated in this study) shows that the results are equivalent to all other groups (the one level over 60 and the two groups below 60). The selection part of the process is the more important component of this success. In the patients over 60, the pre-operative explorations analyze especially Dexa (-1), pulmonary explorations, cardiologic explorations, and angios-canner of the pelvic vessels (access strategy but also research of calcifications on the aorta and the iliac arteries). The patient must also present a dynamic profile in his activities to justify this therapeutic choice.

Table 2: Prospective study conducted by the author including patients over 60 years old.

< 60 Years	>60 Years
1 level 223 patients 113 M 110 F Age 42 y ±8,86 (19-59)	**1 level 12 patients 2 M 10 F Age 64 y ±5,3 (60-78)**

	Pre	3m	6m	12m	24m		Pre	3m	6m	12m	24m
Oswestry/*50* ±	28 8,67	16 11,92	11 11,09	8 8,58	7 7,1	**Oswestry/*50* ±**	27 2,12	8 5,97	5 6,65	2 2,31	5 7
VAS *L/10* ±	7,4 2,35	1,9 2,67	1,5 2,34	1,2 1, 53	0,9 1.53 ±	**VAS *L/l0* ±**	6,2 3,46	1,5 0,65	1,2 1,72	0,4 0,64	1,9 3,34
VAS R/*10* ±	6,3 3,38	2,6 3,19	1,9 3, 06	1,9 3, 05	1 1, 63 ±	**VAS R/*10* ±**	6,6 2,33	0,7 1, 45	0,4 0,94	0,7 1,21	0,8 1, 55

Multi Levels	**218 patients 124 M 94 F Age 45 y ± 8,54 (22-59)**	**Multi Levels**	**23 patients 16 M 7 F Age 63y ±3,22 (60-71)**

	Pre	3m	6m	12m	24m		Pre	3m	6m	12m	24m
Oswestry/*50* ±	30 6,94	18 12,12	10 10,37	7 6,98	8 7,6	**Oswestry/*50* ±**	33 5,73	12 8,65	5 6,07	4 5 32	6 6,61
VAS *L* ±	7,2 2,38	2,6 2,85	1,2 1,75	0,9 1,84	0,8 1,24	**VAS L ±**	9,3 0,5	1,4 1,46	1,7 2,05	1,0 1,56	1,4 1,99
VAS R ±	6,8 2,69	3,6 3,87	1,7 2,55	1,8 2,92	1,1 1,72	**VAS R ±**	7,1 2,92	3,1 2,22	1,5 3,33	0,6 1,03	0,4 0,94

All the categories detailed in this study, below and over 60 years old on one hand, one level or multi-levels on the other hand, improved dramatically. Those conclusions about the quality of the results for the patients over 60 treated with a ProDisc-L® procedure are corroborated by the publication of R. Bertagnoli. [xxv] This confirm the possibility to use the ProDisc-L® as a total disc replacement over 60 years old under the conditions of selection of the patients already detailed.

Discussion

The studies performed and detailed here could be completed by all the others published in literature or communicated in congresses. But the conclusion is obviously that the ProDiscL ® technology has proven its safety and efficiency, that the phase of experimentation and investigation is behind us and delivered its answer which are the results shown here. And the team in charge of the organization of the surgeons training has been professional in the way of teaching. All the technologies are permanently evaluated, and reevaluated, that the role of scientific societies and journal were the results are published. After more than 50 years of use the total joints replacements are the subject of studies, research, and that the pride of a profession to permanently reevaluate their procedures to deliver the best treatment to the patients. And even with supposed

limited life time of some of those joints, the long-term studies have demonstrated the low rate of revision in hips and knees (despite the number of procedure) and proven the benefit for the population. And that's why, despite their approval, after some years, some techniques can disappear when another one comes, with better results. That's the permanent evaluation of the surgeons whose practice could not survive if their results for their patients were not "satisfying". And this evaluation will be performed permanently as usual, probably more precisely as we enter in a new technology with the concepts of the XXI century[K].

Where is the risk? Do you create the possibility for everyone who needs it and fits with the criteria of selection, to have access to this technology or only let this technology accessible for those who will pay for it? To let the surgeons make what they have always done, use an approved and proven safe technology and test it on the mass of the patients with the quick answer of the "market" or keep on running a slow process of "no accessibility", accepting not to deliver the best treatment to a mass of population, without objective reasons? But the real choice is also in the hands of the citizen. With the information that is delivered now in real time on all topics, the patients have access to the data published, to the results of those already operated on, they moved from the "word of mouth" to the" word of net". And so what are the main consequences of those new ways of communication? The patients will know that there is a better technique than those proposed and reimbursed and they do not benefit of it. What will they do in a few years if they will have a bad result with their fusion or have a degeneration on the level above which needs a new procedure, when they could have got a procedure that reduces this risk? "Why I could not get the best treatment when I have been operated on, did I need to pay for it as those who could receive it, so why did I pay for insurance?" (This question has already been asked by the patients in a lot of countries before the reimbursement process). And where will be the responsibility in those cases? When the scientific randomized studies have been well conducted, when all the other publications confirm those results, when the professionals describe the need, their confidence and enthusiasm for a procedure they were waiting for years, when the patients who already benefited of it, testify, what else can be more convincing?

The reimbursement of the ProDisc-L® procedure is a necessity now. But if we want to make this successful for years and confirm on bigger numbers of patients operated on what we have seen as results, we need to follow the process of selection of the patients already defined (and that is even more fundamental for the patients over 60) , to follow the process of trainings of great qualities, to maintain the control of the "good practice of the users" and the permanent studies and publications. But, all of that is the current practice for the main part of surgeons work, does not seem new, but it just needed probably to be repeated once more.

RR public comment. txt
From: R R
Sent: Wednesday, December 06, 2006 5:45 PM
TO: OCONNOR, DEIRDRE E. (CMS/OCSQ)
This is in response to your request for public comment on the lumbar artificial disc. Results so far have been mediocre. It is difficult to find people enthusiastic about the procedure outside of the industry involved. The risks of revision surgery and mediocre results so far seem to make the technology questionable. Perhaps FDA criteria for approval of new devices ought to be superiority of any new product introduced, rather than equivalence with current technology.

From: Saphire-Bernstein, Inger
Sent: Wednesday, December 27, 2006 1:51 PM
To: CMS CAGInquiries
Cc: Aronson, Naomi
Subject: Lumbar Artificial Disc Replacement (LADR)

Naomi Aronson, Ph. D., Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, would like to submit the attached resource materials to CMS for use in reconsideration of the NCA on Lumbar Artificial Disc Replacement (LADR). Attachments include the April, 2006 TEC Assessment of Artificial Vertebral Disc Replacement and the link to a recent article in Forbes: "Dangerous Devices" Herper and Langreth, Forbes 11/27/06 http://www.forbes.com/forbes/2006/1127/094_print.html. We hope these materials are helpful.

«20_01.pdf»

Naomi Aronson, Ph. D.
Executive Director
Technology Evaluation Center
Blue Cross and Blue Shield Association
225 N. Michigan
Chicago, IL 60601
P:
E:

Technology Evaluation Center

Assessment
Program
Volume 20, No. 1
April 2005

BlueCross
BlueShield
Association

An Association
of Independent
Blue Cross and
Blue Shield Plans

Artificial Vertebral
Disc Replacement

Executive Summary

Low back pain is an extremely common condition that affects up to 20% of the U.S. population. Degenerative disc disease (DDD) is a major common cause of low back pain. Replacing the disc with an artificial disc is one proposed method to alleviate the pain associated with DDD. This Assessment will review the available evidence to determine if disc replacement is an effective treatment for chronic degenerative disc disease.

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether the artificial disc or treatment of degenerative disc disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental bodies.

In October 2004, the U.S. Food and Drug Administration (FDA) granted Premarket Application (PMA) approval for the Charite Artificial Disc, stating that the device is indicated for spinal arthroplasty in skeletally mature patients with DDD at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. As a condition of approval, the manufacturer has agreed to conduct a postapproval study, using a maximum of 366 patients (201 randomized investigational subjects, 67 training investigational subjects, and 98 control subjects). Postapproval study patients will be evaluated for a period of 5 years post-implantation.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Current evidence supporting the effectiveness of artificial vertebral disc is insufficient. Case series evidence is inadequate to establish efficacy. There is only one completed randomized, clinical trial that evaluates the Charite artificial disc compared to BAK fusion cage. No other disc replacements have better or more rigorous evidence of efficacy.

The only randomized, controlled trial has several methodologic issues that make it difficult to interpret the results. The Charite artificial disc had a success rate of 63%, compared to a success rate of 53% for BAK fusion, using a composite measure of outcome that incorporated improvement of symptoms and absence of complications. The first concern is that the analysis showed noninferiority compared to BAK fusion using the composite measure of success, but did not show statistically significant superiority in most outcome measures. A noninferiority trial design implies that there is a trade-off between efficacy outcomes and some other advantage of a new technology, for example, morbidity or invasiveness, such that a less-stringent threshold for efficacy is acceptable. However, at this time, no such advantage has been demonstrated for the Charite artificial disc. So the reported success rate shows that the artificial disc is not inferior to the BAK procedure, not that it is better.

The second concern is that the lack of a prespeci11ed analysis plan, unexplained closure or the database before all patients reached completion, and lack of intent-to-treat analysis may cast some doubt on the analysis. Although the sponsor provided TEC with additional analysis that included patients that were excluded from the analysis presented to the FDA, it was unclear how many additional patients actually provided 24-month outcome data and what imputation was performed for missing or discontinued data.

Finally, although fusion is considered a standard surgical treatment for back pain due to DDD, doubts remain about its effectiveness, as clinical trials comparing fusion to nonsurgical alternatives show conflicting results. Moreover, substantial variation in frequency, success, reoperations, and complications has recently been reported for spinal fusion procedures. The use of the BAK procedure as a comparator to the Charite disc highlights the problem, as no randomized, controlled trials exist comparing the BAR to other spinal fusion techniques or to conservative management. Given the broader clinical context, and the concerns with the sole randomized, controlled trial, the evidence is not sufficient to conclude that the use of artificial vertebral disc improves health outcomes. Low back pain is a common condition. Given the population affected, additional and more rigorous trials of the outcomes of the use of artificial disc in the treatment of DDD are needed.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The evidence is insufficient to determine whether the use of artificial vertebral discs improves the net health outcome or whether they are as beneficial as any established alternatives.

5. The improvement must be attainable outside the investigational settings. Whether the use of artificial vertebral discs improves health outcomes has not been established in the investigational settings.

Therefore, the use of artificial vertebral discs for degenerative disc disease does not meet the TEC criteria.

Contents

Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

TEC Staff Contributors

Author-David Mark, M.D., M.P.H.; TEC Executive Director - Naorni Aronson, Ph.D.: Managing Scientific Editor-Kathleen M. Ziegler, Pharm. D.; Research/Editorial Staff-Claudia J. Bonnell BSN, M.L.S.: Maxine A. Gere, M.S.

Blue Cross and Blue Shield Association Medical Advisory Panel

Allan M. Korn, M.D., F.A.C.P. – Chairman, Senior Vice President, Clinical Affairs/Medical Director, Blue Cross and Blue Shield Association; Alan M. Garber, M.D., Ph.D.-Scientific Advisor, Staff Physician, U.S. Department of Veterans Affairs: Henry J. Kaiser Jr., Professor, and Professor of Medicine, Economics, and Health Research and Policy, Stanford University; Steven N.Goodman, M.D., M.H.S., Ph.D. – Scientific Advisor, Associated Professor, Johns Hopkins School of Medicine, Department of Oncology, Division of Biostatistics (joint appointments in Epidemiology, Biostatics, and Pediatrics) – American Academy of Pediatrics Appointee.

• **Panel Members** Peter C. Albertsen, M.D., Professor, Chief of Urology, and Residency Program Director, University of Connecticut Health Center; Edgar Black, M.D., Vice President, Chief Medical Officer, Blue Cross Blue Shield of the Rochester Area; Helen Darling, M.A., President, National Business Group on Health; Josef E. Fischer, M.D., F.A.C.S., Mallinckrodt Professor of Surgery, Harvard Medical School and Chair, Department of Surgery, Beth Israel Deaconess Medical Center – American College of Surgeons Appointee; Willard K. Harms, M.D., M.M., Medical Director, Medical Policy and Adjudication, Blue Cross Blue Shield of Illinois; Michael A.W. Hattwick, M.D., Woodburn Internal Medicine Associates, Ltd. American College of Physicians Appointee; I. Craig Henderson, M.D., Adjunct Professor of Medicine, University of California, San Francisco; Mark A. Hlatky, M.D., Professor of Health Research and Policy and of Medicine(Cardiovascular Medicine), Stanford University School of Medicine; Bernard Lo, M.D., Professor of Medicine and Director, Program in Medical Ethics, University of California, San Francisco; Barbara J. McNeil, M.D., Ph.D., Ridley Watts Professor and Head of Health Care Policy, Harvard Medical School, Professor of Radiology, Brigham and Women's Hospital; Brent O'Connell, M.D., M.H.S.A., Vice President and Medical Director, Pennsylvania Blue Shield/Highmark, Inc.; William R. Phillips, M.D., M.P.H., Clinical Professor of Family Medicine, University of Washington – American Academy of Family Physicians' Appointee; Maren T. Scheuner, M.D., M.P.H., Visiting Associate Professor, Department of Health Services, UCLA School of Public Health – American College of Medical Genetics Appointee; J. Sanford Schwartz, M.D., Professor of Medicine, Department of Medicine, University of Pennsylvania School of Medicine and Professor, Health Care Systems, Health Management & Economics, The Wharton School; Earl P. Steinberg, M.D., M.P.P., President, Resolution Health, Inc.; A. Eugene Washington, M.D., M.Sc., Executive Vice Chancellor, University of California, San Francisco; Jed Weissberg, M.D., Associate Executive Director for Quality and Performance Improvement, The Permanente Federation.

CONFIDENTIAL: This document contains proprietary information that is intended solely for Blue Cross and Blue Shield Plans and other subscribers to the TEC Program. The contents of this document in any manner to any other parties without the express written consent of the Blue Cross and Blue Shield Association.

©2005 Blue Cross and Blue Shield Association. Reproduction without prior authorization is prohibited.

Technology Evaluation Center

Assessment Objective

Low hack pain is an extremely common condition that affects up to 20% of the U.S. population. Degenerative disc disease (DDD) is a major common cause of low back pain. Replacing the disc with an artificial disc is one proposed method to alleviate the pain associated with DDD. This Assessment will review the available evidence to determine if disc replacement is an effective treatment for chronic degenerative disc disease.

Background

Low Back Pain

Low back pain is an extremely common condition, with an incidence approaching 15% to 20% in the U.S. (Deyo and Tsui-vVu 1987). The physiologic basis for low back pain is highly complex, in large part because the lumbar spine itself is an unusually complex anatomic structure. The spine is the only organ composed of bones, joints, ligaments, fatty tissue, multiple layers of muscles, and nerves (including peripheral nerves, nerve roots, sensory ganglia, autonomic ganglia, and the spinal cord). Furthermore, these structures are supplied by an intricate arterial and venous system and lie in close proximity to the skin with its sensory receptors. Diagnosis and treatment of low back pain require an understanding of many different types of tissue, as well as knowledge of the biomechanics of complex spinal structures, the manner in which they can be injured, and the variety of biochemical manners in which each of these structures responds to trauma and to aging. In addition, certain other psychosocial factors that affect the manner in which pain is processed centrally in the brain should be considered (Haldeman 1999).

Spinal structures and tissues that possess either unmyelinated nerve innervation or documentable substance P or related peptides are assumed to have the capacity to cause pain. Such structures include the posterior facet joints, bones and periosteum, muscles, tendons, fascia, ligaments, nerve roots, dorsal root ganglia, dura mater, and the intervertebral disc (lJaldeman1999).

The Vertebral Disc as a Source of Low Back Pain

Disc pain is a potential cause of low back pain. There is a lack of consensus in the medical literature as to what extent the intervertebral disc is innervated (Pope and DeVocht 1999). Once believed to be inert because nerve endings could not be demonstrated in the nucleus or inner annular fibers, the intervertebral disc is now known

to contain fine nerve endings in the outer one-third of the annulus. These nerve endings are immunoreactive to a number of pain-related neuropeptides (substance P, calcitonin-gene-related peptide rCGHP], and vasoactive intestinal peptide [VIPI) (Weinstein et al. 1988). Impulses from these free nerve endings in the outer third of the disc and the adjacent longitudinal ligaments reach the spinal cord through a number of sensory nerves in the following manner:

• the posterior and posterolateral annulus, together with the posterior longitudinal ligament and the ventral dura, is innervated by the sinu-vertebral nerves;

• the anterior and lateral aspect of the disc, together with the periosteum of the vertebral bodies, is innervated through the gray rami communicantes.

The sinu-vertebral nerves have been shown to innervate tissues one or two layers above or below their origin, a finding that may explain the poor localization of lumbar pain.

Evidence that these nerve endings observed in the outer one third of the disc may be a source of low back pain is based upon several clinical observations. First, it has been demonstrated in human volunteers that injection of 11% sodium chloride into the intervertebral disc causes, after a few seconds, very severe pain with deep aching across the back and poor localization (Hirsch et al. 1964). There is an early case report describing a patient who had low back pain produced by pulling on a nylon suture that was looped through the intervertebral disc (Smyth and Wright 1958).

More recently, Kuslich and Ahern (1994) observed that 33-40% of patients in their large back surgery series had significant pain when the affected central or lateral annulus was stimulated. Finally, other investigators have reported that examination of pathologic discs reveals unusually profuse innervation (Yoshizawa et al. 1980). Grigg and colleagues (1986) suggest from evidence in animal studies that the intervertebral disc contains a relatively rich supply of what they termed "silent noci-ceptors"- nerve endings that are not readily excited by mechanical stress, but which, when exposed to pain-inducing substances accompanying inflammatory, degenerative, or traumatic processes, become exquisitely responsive (Grigg et a1. 1986).

Types of Intervertebral Disc Damage

A number of disc injuries can potentially lead to pain. These include annular tears, disc protrusions with extrusion of nucleus pulposus into radial tears in the annular fiber of the disc, and disc herniation, in which nucleus pulposus tissue escapes the confines of the annulus. These events cause pain by stretching or tearing peripheral innervated disc fibers or by generating an irritating inflammatory reaction in adjacent spinal tissues (Swenson 1999).

Degenerative changes in the collagen fibers of the intervertebral disc may also lead to increased focal segment instability. As the intervertebral disc ages, nuclear hydrostatic pressure is lost, leading to buckling of the annular lamellae, increased shear stress across the annular wall, and eventually annular delamination and fissuring of the annular wall.

All of these changes have been shown to alter disc mechanics, making annular disruption, a precursor of disc herniation, more likely. Degenerative disc disease is thought to result from the inability of the disc's reparative capacity to keep pace with the trauma that occurs with activities of daily living.

Degenerative disc disease (DDD) can be accompanied by spinal stenosis, a narrowing of the spinal column that causes nerve compression, and spondylolisthesis, a displaced vertebral disc. These conditions cause additional symptoms in addition to back pain. Total disc replacement is not considered a treatment for DDD accompanied by these other conditions; thus this report will not discuss further these conditions.

Alternative Treatments for Low Back Pain
Due to Degenerative Disc Disease

Gibson et al. (1999) in a Cochrane review of surgery for low back pain, distinguish between treatments directed specifically at disc pro-lapse (herniation) versus treatments directed at degenerative lumbar spondylosis (same as DDD). Total disc replacement is intended only to treat DUD but without accompanying spinal stenosis or severe spondylolistesis. Thus, treatments for disc prolapse such as chymopapain and various techniques for discectomy are not alternative treatments to total disc replacement. Treatments for spinal stenosis or spondylolisthesis such as decompression with or without fusion are also not alternative treatments to total disc replacement.

Nonsurgical therapies are the first-line treatment for back pain associated with DDD. Such treatments include physical therapy, massage, and manipulation. Some controlled trials have shown these modalities to be effective (Cherkin et al. 2003). However, many patients do not respond to such treatments.

lntradiscal electrothermal treatment (IDEI') is another alternative treatment (TEC Assessments, Vol. 18, No. 19; 200--+). Stronger evidence of its efficacy is still needed, as there are few rigorous randomized, clinical trials evaluating this treatment.

Surgical arthrodesis, or fusion, is the current standard surgical treatment for DDD that is not responsive to other treatments. Elimination of motion across the disc space and reduction of loads on disc tissues theoretically result in pain relief. Evidence supporting the efficacy of fusion is relatively sparse.

A review of spinal fusion surgery by Deyo et al. (2004) found that national survey data shows that use of spinal fusion has increased rapidly (i.e., annual numbers of procedures increasing by 77% from 1996 to 2001), owing to new technological advances (e.g., bone morphogenetic protein), financial incentives, and controversial expansion of indications (e.g., discogenic back pain without evidence of sciatica), and a high rate of reoperations. The authors state that, "Fundamental problems plague the study of spinal fusion, including the lack of definitive methods to confirm a solid fusion, a weak association between solid fusion and pain relief, and the placebo effect of surgery for pain relief."

They further state that, "Evidence-based practice for degenerative spine disorders might reserve the use of spinal fusions for spondylolisthesis and only rare cases of disk herniation or spinal stenosis without spondylolisthesis," and that "More evidence from clinical trials should be required for degenerative disk disease to be an accepted indication" (Deyo et al. 2004). Regarding the use of "emerging spinal implants," such as artificial discs, the review states that, "If ongoing trials suggest results equivalent to those of spinal fusion, it may be faint praise, given the paucity of evidence that spinal fusion is safe and effective for common indications" (Deyo et al. 2004).

A 1992 review by Turner et al. could find no randomized trials of fusion. Combining many studies of fusion performed for many different clinical indications, they found an average of 68% of patients reported a satisfactory outcome. A 1999 Cochrane review (Gibson et al.) concluded that at that time there was no acceptable evidence of any form of fusion for degenerative lumbar spondylosis, back pain, or "instability." The authors could find no randomized clinical trials comparing fusion to a non-surgical alternative, only trials that compared surgical techniques of fusion to each other.

Since the Cochrane review, there have been 2 published clinical trials comparing lumbar fusion to a nonsurgical alternative treatment for patients with chronic back pain due to DDD. Fritzell et al. (2001) conducted a multicenter randomized controlled trial comparing 3 techniques of lumbar fusion to nonsurgical treatment. Enrollment criteria included patients with chronic pain, severe disability, pain attributed to DDD, and no neurologic compromise due to herniated disc, spondylolisthesis, or spinal stenosis. There was no specified non-surgical treatment, but it was described as commonly used physical therapies. Overall results of the trial are shown in Table 1. Patients receiving fusion therapy reported mean changes from baseline in the range of 18-33% for various pain and disability scores, whereas patients in the control group had changes ranging from -21 to 8% for the same outcomes, all between-group changes being statistically significant. In terms of patients' overall assessment, 6,3% of patients receiving fusion reported being better or much better, compared to 29% of control patients. Critics of the study have pointed to the modest effect of surgery (up to 30% mean score change), and the fact that control patients may not have received optimal nonsurgical treatment (Deyo et al. 2004).

The other randomized trial by Ivar Brox et al. (2003) assigned a specific cognitive and exercise regimen to the nonsurgical patients. Enrollment criteria for this study were roughly similar to the other clinical trial, and outcomes were assessed at 1 year. In this study, patients receiving fusion reported improvements ranging from 36 to 49% on pain and disability scales, but patients in the control arm also reported similar improvements in these scores, resulting in differences that were not statistically significant for most outcomes. Although this trial was much smaller than the study by Fritzell et al. (2001), the point estimates of effect for each arm are very similar to each other, and confidence intervals sufficiently narrow to rule out a large clinical benefit of surgery. The authors believe that the difference in results between the 2 studies is caused by the specific intervention used in the nonsurgical group, which produced improvements similar in magnitude to the surgical fusion group.

Study		Outcomes of Fusion		Outcomes of Control		Between-group p-value	
Fritzell et al. (2001)	2 years			2 years			
Surgery n=201		pre	pos		pre	pre	
Control n=63	Back pain	64.2	43.2		6.6	58.3	0.0002
	Leg pain	35.3	29.0		6.6	42.6	0.005
	Oswestry	47.3	35.7		4.4	45.6	0.015
	MVAS	63.7	45.6		65.5	60.4	0.004
	GFS	49.1	34.1		47.6	45.5	45.5
Ivar Brox et al. (2003)	1 year			1 year			
Surgery n=35		pre	post		pre	post	
Control n=26	Back pain	62.1	39.4		64.1	48.7	0.14
	Leg pain	43.5	26.6		34.0	35.5	0.002
	Oswestry	42.0	26.4		43.0	29.7	29.7
	GFS	35.9	18.3		44.6	22.6	0.50

GFS: General Function Score; MVAS: Million Visual Analog Score

The relative sparseness of controlled clinical trial data regarding the effectiveness of fusion for DOD makes uncertain the validity of it as a valid comparator to total disc replacement. It cannot be ruled out that the improvements associated with lumbar fusion are due to natural history, placebo effects, or co-interventions such as rehabilitation and exercise programs. Complicating the evaluation of fusion is the variety of techniques and devices used to perform the procedure. Pedicle screws and intervertebral fusion cages are two types of devices implanted during some procedures. Clinical trial results comparing use of these devices have not produced consistent results.

Common complications of fusion include instrument failure (7%), complications at the bone donor site (11 %), neural injuries (3%), and failure to achieve a solid fusion or pseudarthrosis (15%) (Deyo et al. 2004). Fusion is thought to cause increased rate or disc degeneration in spinal segments adjacent to the fusion.

The clinical trial of the Charite disc compared the disc with BAK fusion. There is no clinical trial evidence comparing the BAK fusion device to other methods of fusion. The clinical trial that led to U.S. Food and Drug Administration (FDA) approval was a single-arm trial enrolling 947 patients, with comparison to literature-based controls who received fusion by a similar (anterior or posterior) approach. In the single-arm analysis, total success as assessed by 1) successful fusion, 2) improvement in pain, 3) maintenance or improvement in function, and 4) maintenance or improvement in muscle strength, was achieved by 72% of patients (184/254) at 24 months. Despite differences in patient selection and outcome assessment, outcomes of BAK fusion were reported to be roughly similar to literature controls, but this comparison lacked matched controls or other methods to control for differences in patient selection and outcome assessment.

Outcome Assessment

Outcomes of treatments for back pain have been compared using a variety of techniques. Most common are pain scales measured on a visual analogue scale. Various questionnaires have been developed to additionally capture measures of physical functioning. One of the more common measurement scales in use specific to patients with back pain is the Oswestry Disability Index, originally developed in 1976. The validity, consistency, and reproducibility of the Oswestry Disability Index were extensively reviewed by Roland and Fairbank (2000). This review cites an article by Meade et al. (1986) that suggests that a 4-point difference in the Oswestry Disability Scale is the minimum difference carrying clinical significance. This article (Roland and Fairbank 2000) also cites a personal communication from the FDA, which states that the FDA has chosen a minimum 15-point change in spinal surgery patients as a clinically meaningful difference.

Total Disc Replacement

Prosthetic discs are meant to replace the function of the native disc. Such discs are meant to perform the function of a natural disc including range of motion and transmission and absorption of compressive loads. There are several disc replacement products that have been developed or are in development and testing. They include Charite, ProDisc, Maverick and Flexicore. All discs consist of metal end plates that affix to the vertebral bones and some mechanism in between that allows for motion in several planes. The Charite artificial disc uses a polyethylene core that can shin dynamically within the disc space during spinal motion. This report will only evaluate the evidence on the Charite disc as it is the only product to have FDA approval at this time. None of the other disc replacements have better or more rigorous evidence of efficacy.

The Charite disc was developed in the 1980s and has been used more extensively than other artificial discs. It has been estimated that the disc has been implanted in more than 5,000 patients since 1987. During this period of use, no randomized clinical trials have been published. Only results from case series are available. Through this clinical experience, the clinical indications and contraindications for use of the disc have developed. It is indicated only on a subset of patients for whom fusion is often performed. The disc is indicated in individuals with degenerative disc disease at a single level, at either L4-5 or L5-S1. It is contraindicated in individuals with instability (caused by spondylolisthesis, fracture, or tumor), osteoporosis, prior major spine surgery, facet joint arthritis, and spinal infection.

Beyond the evaluation of the disc as an effective treatment for back pain due to DDD, the disc raises unique concerns. According to de Kleuver et al. (2003), who did a systematic review of disc replacement, these issues are 1) loosening, 2) subsidence (migration of prosthesis), 3) polyethylene wear, 4) mobility, 5) adjacent disc degeneration, 6) complication rate, and 7) salvage procedures in case of failure. In their review, de Kleuver et al. found no mention of loosening, subsidence, and polyethylene wear. Not all papers addressed the mobility provided by the disc. The operated segment appears to move with a reported average range of motion of 5-12 degrees, but mobility of the segment is frequently lost due to the need for subsequent surgical fusion or spontaneous fusion. None of the studies address whether disc replacement can reduce the rate of adjacent segment degeneration, which is considered to be a problem of fusion. The complication rate was highly variable. For 411 patients in the studies considered in the review, there were no infections, 8 vascular injuries, and 6 thrombotic complications. Regarding a safe salvage procedure, several studies reporting doing a posterolateral fusion.

The manufacturer of the Charite disc sponsored a randomized clinical trial comparing the disc to anterior fusion using the BAK fusion cage. The results of this unpublished study are available

from the FDA Web site along with a detailed statistical critique by an FDA statistician. Geisler et al. (2004) reported selected findings from this clinical trial, but the numbers differ slightly from the FDA document, and the focus of the publication was the neurological complications. The results of this clinical trial led the FDA to approve the Charite disc in October 2004. A detailed description and assessment of this trial will be reported in the Review of Evidence section of this Assessment.

As a condition of approval, the manufacturer has agreed to conduct a postapproval study, using a maximum of 366 patients (201 randomized investigational subjects, 67 training investigational subjects, and 98 control subjects) (U.S. Food and Drug Administration 2004c). Postapproval study patients will be evaluated for a period of 5 years post-implantation. The primary endpoint of the study will evaluate "overall success," defined as:

• improvement of at least 15 points in the ODI score compared to baseline;
• no device failures requiring revision, reoperation, or removal;
• absence of major complications, defined as major vessel injury, or major neurological deterioration (e.g., nerve root injury); and
• maintenance or improvement in neurological status versus baseline, with no permanent neurological deficits compared to baseline status.

Also, annual reports will be submitted with data from all subjects enrolled in the postapproval study.

Methods

Search Methods

The MEDLINE database was searched from 1980 through March 2005, using the search terms "Charite" or "intervertebral disk/[MeSH] OR spinal OR spine OR lumbar." The search was limited to English-language citations involving human subjects. In addition, *Current Contents* and bibliographies of key articles were reviewed for relevant citations.

Study Selection

The one randomized controlled trial of the Charite disc is unpublished but available from the FDA Web site. From other literature found, studies of consecutive case series of artificial disc procedures using the Charite disc were included if they reported patient outcomes.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 8, 2005. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusion of this Assessment.

Formulation of the Assessment

Patient Indications

Potential candidates for artificial disc replacement have chronic low back pain attributed to degenerative disc disease, lack of improvement with nonoperative treatment, and none of the contraindications for the procedure, which include multilevel disease, spinal stenosis or spondylolisthesis, scoliosis, previous major spine surgery, neurologic symptoms, and other minor

contraindications. These contraindications make artificial disc replacement an option for a subset of patients for whom fusion is indicated. Patients who require procedures in addition to fusion, such as laminectomy and/ or decompression are not candidates for the Charite disc.

Technologies to be Compared
The current surgical alternative is fusion. Comparison to fusion is complicated by the uncertain efficacy of fusion, as documented in the "Background" section of this report. Nonsurgical alternatives include a variety of cognitive, behavioral, exercise, manipulation, and physical therapy approaches.

Health Outcomes
Benefits. The benefits of treatment for low back pain include pain relief and restoration of function (increased mobility and flexibility, enhanced exercise or sitting tolerance and return to work). The mobility and flexibility of the artificial disc potentially improves physical functioning and also may reduce adjacent spinal segment degeneration, but these outcomes have not been specifically assessed.

Harms. Potential harms that could occur after artificial disc replacement include worsened symptoms and complications due to the procedure. However, these harms may also occur with surgical fusion.

Assessment Question
Does artificial disc replacement using the Charite disc improve health outcomes in terms of pain relief and restoration of function among patients with chronic discogenic low back pain, compared with fusion or other treatments?

Review of Evidence

Case Series Reports
Results from case series reports of disc replacement surgery are shown in Table 2. It is not possible to make inferences regarding the success of the procedure in these types of studies because there is no control group. Differences in patient selection criteria may confound assessment of the procedure.

However, these case reports might provide generalizable information regarding complication rates and may provide useful information on the longitudinal trajectory of outcomes among patients receiving the procedure. In the 6 case series reported in the table, none reports rigorous preoperative and postoperative pain or functional scales, but report postoperative states only. A variety of complications are reported, including vascular and neurologic outcomes. Migration of the prosthesis is reported in several of the studies. It is difficult to calculate rates of any particular complication because of the varied format of reporting between studies.

The review by de Kleuver et al. (2003) included a few additional case series reported in foreign-language journals. They did not find any comparative trials either. In addition to the lack of any controlled comparative studies, they noted high rates of secondary arthrodesis either due to spontaneous bony bridging or to the need for subsequent surgical arthrodesis. They concluded that there were insufficient data to assess the performance of disc replacement.

Charite Clinical Trial
The stated purpose of the clinical trial was to investigate the safety and effectiveness of the Charite artificial disc compared to the BAK Interbody Fusion Device for the treatment of single-

level degenerative disc disease. Patients were to be randomized in a 2:1 ratio and treated in 15 different geographic sites. Outcomes were to be assessed at regular intervals out to 24 months. At each site, 5 patients were to receive the Charite disc before patients were randomized.

Methods and Statistical Analysis Plan. The principal outcome to he assessed in the study was a composite outcome, where success was determined if all the following were found:

1. Improvement in the Oswestry Disability Index =25% at 24 months compared to baseline
2. No device failures requiring revision, reoperation or removal.
3. Absence of major complications, defined as major blood vessel injury, neurologic damage, or nerve root injury.
4. Maintenance or improvement in neurological status at 24 months, with no new permanent neurological deficits compared to baseline.

Other outcomes included work status, visual analog scale rating of pain, SF-56 scores, and adverse events.

The study was designed as a noninferiority trial with a d=0.15, which means that the confidence interval of the difference between the Charite disc and BAK fusion cage must rule out that the success rate of the Charite disc is greater than 15% worse than the BAK fusion cage. Assuming a 70% success rate for both treatment groups, the Charite disc could have a success rate that was up to 4.9% worse than BAK fusion and still he considered to be noninferior. In the trial publication, p-values for the composite outcome were based on a noninferiority calculation that rejects the hypothesis that Charite disc is inferior. However, p-values calculated for all other outcomes including the separate components of the composite outcome used the traditional calculation used for "superiority" trials.

A trial that is designed and analyzed as a noninferiority trial usually establishes a less-stringent standard for demonstrating efficacy than a standard clinical trial. Such trials are often employed when there is some margin of acceptable inferiority of a new technology in its principal outcome that is offset by some other advantage, such as less morbidity, less invasiveness, better acceptability to patients, or lower cost. In the case of the Charite disc, there are no offsetting advantages that are immediately evident or proven, as it is simply proposed to provide greater relief of back pain. The Charite disc might provide greater flexibility than conventional fusion, but there is no firm evidence to show this.

The inclusion and exclusion criteria were fairly typical of the type of patients for whom this artificial disc or fusion alone is indicated. Patients had symptomatic degenerative disc disease at a single level unresponsive to conservative treatment, but did not have nerve root compression, spinal stenosis, or severe spondylolisthesis. Patients could have had prior discectomy, laminotomy, laminectomy, or nucleolysis at the same level.

Clinical Trial Results. Of the original 304 patients randomized, 267 were analyzed in the "intent-to-treat" population. Subjects who discontinued the study early were included in the analysis hut considered failures; however, patients who were overdue for their 24-month evaluation and patients who had not reached 24 months' evaluation were excluded from the analysis (Table 3). This exclusion of randomized subjects violates the intent-to-treat principle. Apparently, the sponsor closed the database early so that final evaluations of these subjects were not performed.

Patients receiving the artificial disc had an overall composite success rate of 63%, and patients receiving the BAK cage had a success rate of 53%. This met the specified non-inferiority criteria with a p-value of 0.0001 (Table 4). Although the Charite disc had a higher success rate than the BAK cage, this difference would not have met traditional criteria for a superiority trial. Analyses of the separate components of the composite outcome showed that the difference was mostly attributable to the improvement in the Oswestry disability score, with a success rate of 70% for the artificial disc and 58% for the BAK cage (p=0.054).

The FDA document states that sensitivity analyses were carried out with various imputations for patients without full follow-up information. The success rate for the artificial disc varied from 63% to 68%, and the success rate for the BAK cage ranged from 48% to 54%. Analysis of the success rates over time showed a consistent increment of success at the 6- and 12-month observation visits as well as the 24-month visit. In examining just the change in the Oswestry scores, the artificial disc groups had significantly greater change at the 6-week, 3-month, and 6-month timepoints, but the differences were not significantly different from control at 12 months and 24 months.

In terms of the other secondary outcomes reported, differences in VAS pain scores and SF-36 scores were not significantly different between groups. Greater numbers of patients receiving the artificial disc reported being satisfied (73% versus 65%, p=0.009).

Table 2 Patient Outcomes of Charite Artificial Disc as Reported in Case Series

Study	Sample Size	Back Pain Outcomes		Complications/ Poor Outcomes
Cinotti et al. (1996)	46	2-year outcomes self-rating	24% excellent 39% good 30% fair 7% poor	8 pts eventually had fusion 1 bilateral radiculopathy 1 anterior dislocation/reop 4 spontaneous fusion 0 loosened prostheses
David (1993)	22	1-year outcomes self-rating	65% exc/good	0 migration 0 infections 1 case of L5 sciatica requiring removal 1 case dislocated prosthesis
Lemaire et al. (1997)	105	Mean follow-up 51 months % with good improvement	79%	5 vascular complications 2 temporary neurologic symptoms 4 cases bone complications 0 loosening 0 migration of prosthesis
Griffith et al. (1994)	93	Mean follow-up 1 year Average pain reduction 6 preop to 3 postop		1 device failure 5 migration of prosthesis 1 dislocation 30 other procedural complication 3 patients with reoperations
Sott and Harrison (2000)	14	Mean follow-up 48 months Good outcome Fair outcome Poor outcome (good: >75% pain relief, return to work, :s slight physical restriction, no analgesics)	 10/14 2/14 2/14	1 migration-asymptomatic
Zeegers et al. (1999)	46	2-year outcomes 65% improved low back pain 64% improved leg pain 81% return to work 83% "no regret"		2 not properly positioned no signification migration 7 reoperations for complications

Table 3 Clinical Trial, Population Characteristics, and Patient Follow-up Characteristics

	Charite Disc	BAK Cage
Enrolled and randomized	205	99
Completers	177	78
Early discontinuation (all imputed as failure in analysis)	5	7
Not at 24-mo follow-up yet*	13	6
Overdue for 24-mo follow-up* "ITT" (completers + early failure)	182	85
Characteristics of "ITT"		
Men%	46%	55%
Mean age	39.5	40.1
Level L4L5 operated	29%	33%
Level L5S 1 operated	71%	67%
*Excluded from ITT population		

The sponsor provided TEC with additional analysis providing some additional data on patients who were excluded from the analysis shown in the FDA analyses (Personal communication, Christianson W; February 2005). However, it remains unclear as to how many additional patients actually provided outcome data at 24 months and what imputation was performed for missing or discontinued patients.

In addition to adverse events that were incorporated into the composite outcome, other adverse events occurring in all 205 randomized patients were tabulated (Table 5). It appears that the adverse events labeled "device failures" correspond exactly to the definition incorporated into the composite outcome, but the numbers vary slightly because of the slightly larger denominator. The category "severe or life-threatening events" is apparently a much broader category Table 4. Results of Clinical Trial at 24-month Endpoint of events than the "major complications" used in the composite outcome, and "device-related adverse events" does not correspond to any part of the composite outcome. As shO"\'\'11 in the table, the artificial disc had higher rates of severe and life-threatening events (15% versus 9%) and device-related adverse events (7.3% versus 4%), but lower rates of device failure (4.9% versus 8.1 %). Statistical significance of these differences is not reported, but none of these differences is statistically significant. The rates of device failure reported in these data are similar to the rates of device failure reported in the ITT population as part of the composite outcome.

FDA In-Depth Statistical Review. The FDA performed an in-depth statistical review of this clinical trial to expedite the Premarket Application (PMA) approval. The review made several important comments regarding the conduct and analysis of the trial. The review noted that there was no statistical analysis plan in the original protocol documents. A statistical analysis plan appears to have been finalized at a date by which most trial data were probably available; thus, the sponsor needs to clarify when the statistical analysis plan was finalized and whether the analysis plan was developed or modified based on preliminary review of the data.

The study was designed without any planned interim analysis, but the analysis was conducted before all randomized patients had achieved 24 months' follow-up. It should be clear that there was no interim analysis.

The FDA reviewer wanted more detail on the sensitivity analyses performed to account for missing observations, particularly more specific data on the "last value carried forward"

technique of data imputation. The reviewer calculated some scenarios imputing missing data, and found that a "worst-case" scenario favoring BAK fusion, imputing success for BAK fusion missing observations and imputing failure for artificial disc missing observations did not meet noninferiority criteria. The reviewer also takes issue with the "ITT" population as specified in the analysis, and that exclusion of patients who missed or had not yet reached 24-month follow up "will likely lead to strong bias." Imputation of discontinued patients as failures as performed in the analysis favored the artificial disc group, as there were a lower percentage of patients receiving the artificial disc that were discontinued. Finally, the reviewer found a few calculation errors, and suggested alternative modeling techniques to account for imbalances between groups.

Summary

In sum, the evidence supporting the effectiveness of the Charite artificial disc is limited. Case series provides little evidence of efficacy, particularly in the case of back pain due to degenerative disc disease, where outcomes can be influenced by patient selection, placebo effects, or natural history.

There are several disc replacement products that have been developed, but to date the Charite artificial disc is the only product to have FDA approval. The Charite disc is also the only disc for which there is evidence from a randomized, controlled trial. None of the other disc replacements have better or more rigorous evidence of efficacy. The one clinical trial of the artificial disc has several potential issues affecting a straightforward interpretation of its results. The analysis showed noninferiority compared to BAK fusion, but did not show superiority. A noninferiority criterion usually implies some trade-off in the principal outcomes for some other tangible trade-off. However, there is no immediately evident advantage to use of the artificial disc. Lack of a prespecified analysis plan, unexplained closure of the database before all patients reached completion, and lack of correct intent-to-treat analysis cast some doubt on the analysis. The point estimate of 63% success does not show the artificial disc to be a highly successful treatment.

Finally, although fusion is considered a standard surgical treatment for back pain due to DDD, doubts remain about its effectiveness, as clinical trials comparing fusion to nonsurgical alternatives show conflicting results. It might be desirable to have a nonsurgical alternative in a clinical trial evaluating the effectiveness of any surgical treatment. Back pain is an important clinical issue that merits additional clinical trials for which patients are followed for both short-term and long-term outcomes.

Table 4 Results of Clinical Trial at 24-month Endpoint

	Charite Disc	BAK Cage	p-value
Composite outcome (ITT)	63% (114/182)	53% (45/85)	noninferior*
Composite outcome (completers only)	65% (115/177)	59% (46/78)	noninferior*
Components of Composite Outcome, ITT Population			
>25% improvement Oswestry scale	70% (127/182)	58% (49/85)	0.054
Lack of device failure	96% (174/182)	91% (77/85)	0.163
Lack of major complication	99% (180/182)	99% (84/85)	1.00
Lack of neurologic deterioration	88% (160/182)	87% (74/85)	0.844
Other Outcomes, ITT Population			
Pain Visual Analog Scale Significant improvement	74% (128/182)	62% (49/85)	0.076
SF-36			
Physical component, >15% improved	73%	66%	0.348
Mental component, >15% improved	50%	55%	0.496
Patient satisfaction, % satisfied	73%	55%	0.009

* Not statistically significant by traditional "superiority" p-value, significant p-value to rule out greater than 15% inferior success rate with Charite disc.

Table 5 Results of Clinical Trial, Adverse Events (Randomized Population)

	Charite Disc	BAK Cage
Patients with severe or life-threatening adverse events	15% (30/205)	9% (9/99)
Device-related adverse events	7.3% (15/205)	4% (4/99)
Device failures	4.9% (10/205)	8.1% (8/99)

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether the artificial disc for treatment of degenerative disc disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental bodies.

In October 2004, the U.S. Food and Drug Administration (FDA) granted Premarket Application (PMA) approval for the Charite Artificial Disc, stating that the device is indicated for spinal arthroplasty in skeletally mature patients with DDD at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. As a condition of approval, the manufacturer has agreed to conduct a postapproval study, using a maximum of 366 patients (201 randomized investigational subjects, 67 training

investigational subjects, and 98 control subjects). Postapproval study patients will be evaluated for a period of 5 years post-implantation.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Current evidence supporting the effectiveness of artificial vertebral disc is insufficient. Case series evidence is inadequate to establish efficacy. There is only one completed randomized, clinical trial that evaluates the Charite artificial disc compared to BAK fusion cage. No other disc replacements have better or more rigorous evidence of efficacy.

The only randomized, controlled trial has several methodologic issues that make it difficult to interpret the results. The Charite artificial disc had a success rate of 63%, compared to a success rate of 53% for BAK fusion, using a composite measure of outcome that incorporated improvement of symptoms and absence or complications. The first concern is that the analysis showed noninferiority compared to BAK fusion using the composite measure of success, but did not show statistically significant superiority in most outcome measures. A noninferiority trial design implies that there is a trade-off between efficacy outcomes and some other advantage of a new technology, for example, morbidity or invasiveness, such that a less-stringent threshold for efficacy is acceptable. However, at this time, no such advantage has been demonstrated for the Charite artificial disc. So the reported success rate shows that the artificial disc is not inferior to the BAK procedure, not that it is better.

The second concern is that the lack of a pre-specified analysis plan, unexplained closure of the database before all patients reached completion, and lack of intent-to-treat analysis may cast some doubt on the analysis. Although the sponsor provided TEC with additional analysis that included patients that were excluded from the analysis presented to the FDA, it was unclear how many additional patients actually provided 24-month outcome data and what imputation was performed for missing or discontinued data.

Finally, although fusion is considered a standard surgical treatment for back pain due to DDD, doubts remain about its effectiveness, as clinical trials comparing fusion to nonsurgical alternatives show conflicting results. Moreover, substantial variation in frequency, success, reoperations, and complications has recently been reported for spinal fusion procedures. The use of the BAK procedure as a comparator to the Charite disc highlights the problem, as no randomized, controlled trials exist comparing the BAK to other spinal fusion techniques or to conservative management. Given the broader clinical context, and the concerns with the sole randomized, controlled trial, the evidence is not sufficient to conclude that the use of artificial vertebral disc improves health outcomes. Low back pain is a common condition. Given the population affected, additional and more rigorous trials of the outcomes of the use of artificial disc in the treatment of DOD are needed.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The evidence is insufficient to determine whether the use of artificial vertebral discs improves the net health outcome or whether they are as beneficial as any established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether the use of artificial vertebral discs improves health outcomes has not been established in the investigational settings.

Therefore, the use of artificial vertebral discs for degenerative disc disease does not meet the TEC criteria.

References

Cherkin DC, Sherman KJ, Deyo RA. et al. (2003). A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med,138:898-906.*

Cinotti G, David T, Postacchini F. (1996).Results of disc prosthesis after a minimum follow-up period or 2 years. *Spine,* 21:995- 1000.

de Kleuver M, Oner FC, Jacobs VVC. (2005). Total disc replacement for chronic low back pain: background and a systematic review of the literature. E*ur Spine J, 12:108-16.*

David T. (1993). Lumbar disc prosthesis: surgical technique, indications and clinical results in 22 patients with a minimum of 12 months follow-up. E*ur Spine J.* 1:254-259.

Deyo RA, Tsui-Wu YJ. (1987). Descriptive epidemiology of low-back pain and its related medical care in the United Stales. *Spine, 12:264-268.*

Deyo RA, Nachemson A. Mirza SK. (2004). Spinal-fusion surgery - the case for restraint. *N. Engl J Med, 350:722-6.*

Fritzell P, Hagg O, Wessberg P et al. (2001). Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine, 26:2521-32.*

Geisler FH, Blumenthal SL, Guyer RD et al. (2004). Neurological complications of lumbar artificial disc replacement and comparison of clinical results with those related to lumbar arthrodesis in the literature: results of a multicenter, prospective, randomized investigational device exemption study or Charite intervertebral disc. Invited submission from the Joint Section Meeting on Disorders or the Spine and Peripheral Nerves, March 2004. *J Neurosurg Spine.* 1: 143-54.

Gibson JN, Grant IC, Waddell G. (1999). The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine, 24:1820-32.*

Griffith SL, Shelokov AP, Buttner-Janz K et al. (1994). A multicenter retrospective study of the clinical results of the LINK SB Charite intervertebral prosthesis. The initial European experience. *Spine, 19:1842-9.*

Grigg P, Schaible HG, Schmidt RF. (1986). Mechanical sensitivity of group III and IV afferents from posterior articular nerve in normal and inflamed cat knee. *J Neuphysiol, 55:635-643.*

Haldeman S. (1999). Low back pain: current physiologic concepts. *Neurol Clin, 17(1):1-15.*

Hirsch C, Ingelmark BE, Miller M. (1963). The anatomical basis for low back pain. A*cta Orthop* Scand, 33:1-17.

Huang RC, Sandhu, HS. (2004). The current status of lumbar total disc replacement. *Orthop Clin North am,* 35(1):33-42.

Ivar Brox J, Sorensen R, Friis A et al. (2003). Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine, 28:1913-21.*

Kuslich DS, Ahern, JW. (1994). What tissues are responsible for low back pain and sciatica: an investigation or tissue sensitivity in humans. In: *Proceedings of the Orthopedic Research Society,* 40th Annual Meeting, New Orleans, LA, p. 110.

Lemaire JP, Skalli W, Lavaste F et al. (1997). Intervertebral disc prosthesis. Results and prospects for the year 2000. *Clin Orthop,* (337): 64-76.

Meade T, Brown W, Mellows S et al. (1986). Comparison of chiropractic and outpatient management of low back pain: a feasibility study. *J Epidemiol Commun Health, 40:12-17.*

Pope MH, DeVocht JW. (1999). The clinical relevance of biomechanics. *Neural Clinics North Am, 17:17-41.*

Roland M, Fairbank J. (2000). The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine. *25:3115-24.*

Smyth MJ, Wright V. (1958). Sciatica and the intervertebral disc. .*J Bone Joint Surg Am, 40:1401-1418.*

Sott AB, Harrison DJ. (2000). Increasing age does not affect good outcome after lumbar disc replacement. *lnt Orthop, 24:50-3.*

Swenson R. (1999). Differential diagnosis: a reasonable c1inical approach. *Neurol Clinics North Am,* 17:43-63.

Turner JA, Ersek M, Herron L et al. (1992). Patient outcomes after lumbar spinal fusions. *JAMA, 268:907-11.*

U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. (2004a). DePuy Spine Charite"' Artificial Disc (P040006) clinical review. Available online at: http://www.fda.gov/ohrms/dockets/ac/04/briefing/4049bl_03_Clinical%20Review%20Memo%20MAY.pdf Last accessed January 2005.

U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. (2004b). In-depth statistical review for expedited PMA (P010006) ChariteM Artificial Disc, DePuy Spine, Inc. (dated Feb. 23, 2004). Available online at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4049b1-04_Statistical%20Review%20Memo%20JCC.pdf. Last accessed January 2005.

U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. (2004c). Premarket application approval letter from Director, Office of Device Evaluation (Tillman DB) to Vice President, Clinical and Regulatory Affairs, DePuy Spine. Inc. (Christianson W), dated October 26, 2004. Available online at: http://www.fda.gov/cdrh/pdf4/p040006a.pdf Last accessed February 2005.

U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health. (2005). Summary of safety and effectiveness: Charite artificial disc. Available online at http://www.fda.gov/ohrms/dockets/dockets/05m0092/05-0092-aav0001-03-SSED-vol1.pdf

Weinstein J, Claverie W, Gibson S. (1988). The pain of discography. *Spine. 13:1344-1348.*

Yoshizawa II, O'Brien JP, Smith WT et al. (1980). The neuropathology of intervertebral discs removed for low back pain. *J Pathol, 132:95-104.*

Zeegers WS, Bohnen LM. Laaper M et al. (1999). Artificial disc replacement with the modular type SB Charite III: 2-year results in 50 prospectively studied patients. *Eur Spine J. 8:210-7.*

Technology Evaluation Center
Blue Cross and Blue Shield Association
225 North Michigan Avenue
Chicago, Illinois 60601-7680
www.bcbs.com/tec

@ Registered marks of the Blue Cross and Blue Shield Association, an Association of Independent Blue Cross and Blue Shield Plans
@' Registered trademark of Kaiser Permanente
© 2005 Blue Cross and Blue Shield Association. Reproduced without prior authorization is prohibited.

DePuy Spine
a Johnson & Johnson company

DuPuy Spine, Inc,
325 Paramount Drive
Raynham, MA 02767-0350 USA

Toll Free Customer Service: +1(800) 227-6633
Toll Free Receptionist: +1(800) 365-6633
Direct Receptionist: +1(508) 880-8100
Fax: +1(508) 828-8122

December 27, 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: NCA Reconsideration 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 CHARITE™ Artificial Disc, manufactured by DePuy Spine. The current decision is specific to the CHARITE Artificial Disc for the Medicare population over sixty years of age. 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 Memorandum for Lumbar Artificial Disc Replacement (CAG-00292R).

CMS is now opening this NCO 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 fol1owing:

- 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 in the Oswestry Disability Index (001) and the Visual Analog Scale (VAS) for pain outcomes.
- Provide coverage to both the CHARITE Artificial Disc and ProDisc-L Total Disc Replacement, recognizing that they both meet the standard of "reasonable and necessary".
- Apply the same evidentiary standards for review of the ProDisc-L data as were applied to the CHARITE data.

MEDICARE COVERAGE ADVISORY COMMITTEE

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 addressing the question of the treatment effect in chronic low back pain, two instruments validated for measurement of chronic low back pain from degenerative disc disease are commonly used (Hagg, et. al[1]).

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. 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 CHARITE Artificial Disc and the ProDisc-L Total Artificial Disc IDE studies, all devices exceed Hagg'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 Hagg 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 [2]	CHARITE	50.6	26.3	24.3	48.0%
Blumenthal [2]	BAK	52.1	30.5	21.6	41.4%

ODI	Treatment	Mean at Baseline	Mean at 24 Months	Mean Point Reduction	Mean % Reduction
Synthes [3]	PRODISC	63.4	34.2	29.2	46.1%
Synthes [3]	360	62.9	39.1	23.8	37.8%

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 [2]	CHARITE	72.0	31.2	40.8	56.7%
Blumenthal [2]	BAK	71.8	37.5	34.3	47.8%

VAS	Treatment	Mean at Baseline	Mean at 24 Months	Mean Point Reduction	Mean % Reduction
Synthes [3]	PRODISC	75.1	36.1	39.0	51.9%
Synthes [3]	360	73.2	41.2	32.0	43.7%

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

Since a randomized controlled trial has not been conducted comparing CHARITE 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 and the published literature that support our request:

- Non-inferiority studies
- Age 18-60 years old
- 24 month duration
- FDA requires five-year follow-up as a condition of approval
- Limited evidence for the elderly population and
- European case series for long-term data.

The control arms differ: the CHARITE Artificial Disc study control is a BAK cage and the ProDisc-L Total Disc Replacement control is a 3600 fusion (anterior/posterior incisions), yet both trials compared a motion device to fusion.

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 CHARITE Artificial Disc and ProDisc-L Total Disc Replacement can be 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 I862(a)(l)(A) of the Social Security Act. The CHARITE 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 CHARITE Artificial Disc.

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

Sincerely,

Richard M. Toselli, MD, MBA
Worldwide Vice President, Clinical Evidence and External Relations
DePuy Spine, Inc.

REFERENCES

1. Hagg 0, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J 2003 Feb;12 (l):12-20.
2. Blumenthal SL, 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 CHARITE™ Artificial Disc Versus Lumbar Fusion Part I: Evaluation of Clinical Outcomes. Spine 2005; 30: 1565-75.
3. Data obtained from Synthes ProDisc™-L Total Disc Replacement, IDE Clinical Study Brochure (differs from Summary of Safety and Effectiveness that has been pulled on the FDA website after error was identified).