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Abstract:

Response to the Editorial and Points of View
Regarding the IDE Study of the CHARITÉ™ Artificial Disc

We read with interest the two Point of View commentaries[1,2] and the Editorial[3] published with the two-part paper[4] reporting the results of the IDE study of the CHARITÉ™ Artificial Disc, in *Spine*. We thank the Editor for giving us the opportunity to respond. We certainly agree with the contention that no study is perfect, and that some criticisms of both study design and the results of a study describing a new technique, or a new way of thinking about the treatment a disease state, is inevitable. It is human nature to find reasons, valid or invalid, to resist change and/or alter our current thinking in the treatment of our patients. We suspect for example, that Charnley[5] faced the same criticisms when introducing the mobile hip replacement as an alternative to joint fusion; though Charnley did so without the benefit of a randomized multi-center trial, or nearly two decades of experience with total joint arthroplasty outside the United States. However, there is a difference between valid criticism and opinions formed from incomplete information taken out of context, or the plain distortion of facts.

Many of the criticisms in the published commentary are not new. Several of the same criticisms were leveled by Burkus et al[6] in response to the paper by Geisler et al[7] describing the neurological complications in the IDE study and a meta-analysis of clinical results for lumbar fusion in the literature. A response to those criticisms was published,[8] which we invite the reader to review. We find it strange that neither Point of View commentary nor the Editorial discussed our already published response to these criticisms. Nevertheless, we feel compelled to once again set the record straight on several important points.

A comparison of two Level I studies may be used as the basis for an additional study, but it in no way "proves" that one treatment is superior to the other. The study groups, inclusion criteria, surgeons, institutions, follow-up details, and validation and analysis are different for each study, and there is no randomization step between the treatment groups. These parameters must be homogenous, and the two treatments randomized against each other, in order to statistically compare the two treatments.

The comparison of two studies, even Level I studies, is at best only Level III evidence, such as the statistical comparison of the CHARITÉ Artificial Disc group in our study with the INFUSE® Bone Graft/LT-Cage™ group from another study. For example, the INFUSE/LT-Cage IDE study[9] excluded tobacco users; included patients with facet degeneration and/or arthrosis; did not use discography as a diagnostic tool to confirm degenerative disc disease (DDD); and had no upper limit on the age of the enrolled patients. The CHARITÉ Artificial Disc IDE study did not exclude tobacco users; did exclude patients with facet arthrosis; required positive discography as a diagnostic tool to confirm DDD; and excluded patients over the age of 60. These are two different patient populations. The treatment groups are not comparable statistically across the two studies. The only valid statistical comparison that can be made between these two treatments is a prospective randomized study of lumbar fusion with INFUSE Bone Graft/LT Cages vs. total disc replacement with the CHARITÉ Artificial Disc.

All three commentaries urged caution in adopting artificial disc technology for the treatment of lumbar DDD. We wholeheartedly agree with this. We do not want to see a repeat of the "cage rage" of the late 1990's following the FDA-approval, and subsequent publication of the results of

the IDE study,[10] of the BAK® cage for interbody fusion. What is often forgotten in the historical review of that period in spine surgery is that Kuslich et al listed 11 caveats to using the BAK cage for interbody fusion. Most if not all of them were ignored, resulting in failed surgeries caused largely by poor patient selection and/or misuse of the device.

This new technology, and specifically, the CHARITÉ Artificial Disc, at this point in time is indicated for a narrow group of patients who would otherwise undergo a lumbar fusion. Unlike some of our surgeon colleagues who have advocated expanded indications for total disc replacement in the lumbar spine,[11-13] no Investigator involved with the IDE study of the CHARITÉ Artificial Disc has done so. We refer the reader specifically to the concluding statement in Part I of the paper,[4]

> "Prior reports of good clinical outcomes from TDR with the CHARITÉ Artificial Disc have been confirmed. Based on the results of this prospective, randomized, multi-center study, TDR with the CHARITÉ Artificial Disc is clinically equivalent to lumbar fusion and a safe and effective surgical treatment of symptomatic degenerative disc disease from L4-S1 in properly indicated patients."

Perhaps "properly indicated patients" should have been italicized for greater effect. But the exact same sentiment was previously expressed in the aforementioned paper by Geisler et al[7], as well as the paper by Geisler[14] describing the surgical technique for implanting the CHARITÉ Artificial Disc. There may be expanded indications for total disc replacement in the future, but

only after performing studies that support those indications. Many of these studies are currently ongoing.

Two of the commentaries cite the series published by Dr. van Ooij[15] describing complications and revisions in patients implanted with the CHARITÉ Artificial Disc. For whatever reason, this seems to be the paper most-often cited as the rationale for not performing a lumbar total disc replacement with the CHARITÉ Artificial Disc. While it is relatively easy to drop this reference into an Editorial, it should be just as easy to review the commentary by McAfee[16] which described these complications in context. These complications came from a series of 500 patients at one center, yielding a known complication rate of 5.4%. The large majority of the complications reported by Dr. van Ooij are attributed to poor patient selection (which would be off-label in the United States), inadequate sizing of the device, and the use of basic, first-generation instrumentation.

Zindrick et al noted the recent presentation by Phillips et al[17] regarding the fate of the facet joints following lumbar total disc replacement. We agree that the fate of the facet joints is an important question that needs to be answered. However, the context of the presentation was not described. The study, using MRI instead of CT scans, was performed in 16 patients, only half of whom would have qualified for the IDE study. Yet, at the same meeting, Elders et al[18] presented a paper on facet joint degeneration using CT scans in 82 patients following lumbar total disc replacement with either the CHARITÉ Artificial Disc or the ProDisc® device as part of the respective IDE studies. They demonstrated that clinical outcome was not statistically different in patients with mild preoperative facet joint degeneration compared to patients with no facet

degeneration preoperatively. This is a topic of both ongoing and future studies, in particular with respect to patients with moderate or severe facet changes preoperatively.

As Dr. Mirza noted, it is true that "few surgeons now perform anterior lumbar interbody fusions with stand-alone cages." The reasoning for the choice of this device and this particular fusion technique for the control group was described in great detail in Part I of the paper. However, we wish to note that the study design employed for the IDE study of INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN) also used a stand-alone anterior interbody fusion technique with threaded fusion cages for *both* the treatment and the control groups. The outcomes were equivalent. It seems odd that in retrospect that study was not, and has not been equally maligned. Should the INFUSE Bone Graft IDE study be repeated and compared to a contemporary control group? If so, what should it be? Critics of the study design desire both a contemporary control group, and long-term follow-up; criticisms which are in conflict with each other. Commenting that the study should have been designed in some other way that was not suggested or reasonable on a contemporaneous basis is not a reasonable criticism.

Dr. Mirza's commentary uses the words "complications" and "adverse events" interchangeably but without the proper definition of either. In an IDE study, an adverse event is *any* event which occurs that may or may not be related to the device and/or the surgical procedure under study. For example, a dog bite requiring a patient to receive a tetanus shot is an adverse event. Is that also a complication?

In his commentary, Dr. Mirza presented adverse event data and claimed "…the overall complication rate was 75.6% (155 events in 205 patients) in the CHARITÉ disc group…" based on the number of reported *adverse events* in the study. Since the paper by Burkus et al[19] describing the results of the INFUSE Bone Graft/LT-Cage IDE study also reported complications instead of adverse events, the reader may not know that the rate of adverse events in the investigational group in that study was 74.0%.[9] Is this the complication rate for lumbar fusion with INFUSE and LT-Cages? No. Table 9 (sic Table 10?) contains the adverse events which are most likely to be classified as "complications" in any spine surgery practice in the world. The one death that occurred in the study (treatment group) was determined by autopsy to be an accidental overdose of narcotic medication and cocaine, three days following surgery, and unrelated to the patient's surgical procedure, or the device.

The concept of approach-related vs. device-related complications is not new, nor is it difficult to comprehend. Brau et al[20] have previously defined and reported the rate of approach-related complications for anterior lumbar interbody fusion in 686 procedures. In reporting the results of the IDE study, the same nomenclature was used to report approach-related complications in both groups. This does not alter the safety profile of the device. The analysis of complications encountered in this study will be discussed in greater detail in a forthcoming manuscript.

The rate of clinical success in the treatment group, defined by four criteria, was criticized by Dr. Mirza. He asked the question, "how many patients will accept a chance of improvement no better than a coin toss?." Dr. Mirza may have failed to note the highly significant ($p<0.0001$) and easily visualized (see Figure 1) improvement in both the VAS and Oswestry scores from

baseline to 24 month follow-up for both the BAK and CHARITÉ groups (Wilcoxon Signed Rank Test, StatXact, Cytel Software Corp., Cambridge, MA, USA) and also the significant difference in recovery favoring the CHARITÉ group ($p<0.05$, Wilcoxon/Kruskal-Wallis Tests, JMP 5.0.1a, SAS Institute Inc., Cary, NC, USA) for all time points of VAS and Oswestry measurements in the study including the 24 month follow-up. Because this was a non-inferiority study, that "claim" can't be made by the sponsor of the study. This regulatory restraint however, does not make the analysis less statistically viable.

With respect to clinical outcome, 63.9% of CHARITÉ Artificial Disc patients achieved ≥25% improvement in ODI scores at 24 months compared to baseline, while only 50.5% achieved this level of improvement in the control group. Again, this difference was statistically significant in favor of the CHARITÉ Artificial Disc group ($p=0.0038$). Therefore it is difficult to understand Dr. Mirza's contention that, in *properly indicated patients*, the chance of improvement for patients receiving total disc replacement vs. fusion is equivalent (to a coin toss). That is not what the data shows us. To further illustrate this point, a plot of the ODI vs. VAS scores for both groups at baseline and at 24 months is shown in Figure 1, demonstrating a greater concentration of patients in the CHARITÉ Artificial Disc group with both very low ODI scores and very low VAS scores at 24 months compared to the control group.

With respect to preservation of motion, we do recognize the FDA definition of fusion. Recognizing it and agreeing with it are two different things. The FDA set their standard definition of lumbar fusion based on criteria established in the early 1990's as part of the BAK IDE study design. Today, most clinicians and study Investigators would consider this a standard

for motion rather than fusion. Neither a patient with a lumbar artificial disc, nor a patient having had a lumbar fusion procedure; and having less than 5º of motion but greater than 0 degrees of motion, is fused, despite what the FDA definition may be (Figure 2).

The contention that longer follow-up is necessary to properly address issues of safety and efficacy is somewhat flawed given the extensive experience with lumbar total disc replacement outside of the United States. Though *Spine* is an International journal, these commentaries were written through a United States prism, as if the rest of the world's experience with the CHARITÉ Artificial Disc[21-24] never existed. We assure our surgeon colleagues outside of the United States that we do not share this narrow view.

Concerning the potential for wear and osteolysis, Zindrick et al once again referenced papers and society meeting presentations without context, and without balance. They neglected to inform the readers of *Spine* that wear testing of the CHARITÉ Artificial Disc was performed to 10 million cycles, which is equivalent to 80 years of significant bending,[25] in accordance with the ASTM draft standard.[26] This testing demonstrated an extremely low rate of polyethylene wear (0.11mg/Mc). The results of this testing, combined with the 18-year clinical experience outside the United States, confirms the long-term durability of the CHARITÉ Artificial Disc.

As the meta-analysis performed by Geisler et al[7] shows, lumbar fusion is an imperfect operation with widely variable rates of technical and clinical success. The authors of the commentaries ignored this point while attempting to show that total disc replacement is not a "perfect"

operation. We agree that it is not a "perfect" operation, but as the literature shows, lumbar fusion for the treatment of painful degenerative disc disease is not a "perfect" operation either.

Finally, we find it objectionable that industry was taken to task in two of these commentaries. It was noted by Zindrick et al that the study was industry supported. It would in fact be a rare occurrence for a device to gain approval by the FDA through the IDE process and subsequently brought to market without industry support. But more to the point, none of us in our collective memories have ever seen a company's marketing slogan or marketing program for a device criticized in *Spine,* or any-other spine-related peer-reviewed journal. A company certainly has the first amendment right to market the device for the FDA-approved indications. In our experience, DePuy Spine has done this responsibly, pairing their marketing of the device with a world-class training program at the Center for Spine Arthroplasty Institute in Cincinnati. With our assistance as consultants, we believe they will continue to do so in the future. There is no gain for anyone, most of all our patients, but also not for industry, if this technology is used inappropriately.

Some of the criticisms put forth in the commentaries were valid. Longer follow-up to answer the questions related to adjacent-level disease, the fate of the facet joints, and other potential indications is required. We are committed to answering these questions and others related to lumbar total disc replacement. We will continue to disseminate the results of these studies through published manuscripts in *Spine* and other peer-reviewed venues.

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References

1. Sengupta DK. Point of View. Spine 2005;30:Article Plus online.

2. Mirza SK. Point of View. Spine 2005;30:xx-xx.

3. Zindrick MR, Lorenz MA, Bunch WH. Editorial. Spine 2005;30:Article Plus online.

4. Blumenthal SL, McAfee PC, Guyer RD, et al. A Prospective, Randomized, Multi-Center FDA IDE Study of Lumbar Total Disc Replacement with the CHARITÉ™ Artificial Disc vs. Lumbar Fusion: Part I - Evaluation of Clinical Outcomes. Spine 2005;30:xx-xx.

5. Charnley J. Surgery of the hip-joint: present and future developments. Br Med J 1960;5176:821-6.

6. Burkus JK, Polly DW, Jr., Gornet M. Artificial disc. J Neurosurg Spine 2005;2:395-7.

7. Geisler FH, Blumenthal SL, Guyer RD, et al. 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 of Charite intervertebral disc. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine 2004;1:143-54.

8. Geisler FH, Blumenthal SL, Guyer RD, et al. Response to: Artificial Disc. J Neurosurg Spine 2005;2:397-8.

9. FDA. INFUSE Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device Summary of Safety and Effectiveness Data. http://www.fda.gov/cdrh/pdf/P000058b.pdf 2002:Accessed June 2, 2005.

10. Kuslich SD, Ulstrom CL, Griffith SL, et al. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine 1998;23:1267-79.

11. Marnay T. Is there a place for Disc Replacement and isthmic repair in case of isthmics spondylolisthesis. SA5: Global Symposium on Motion Preservation Technology. Ney York, NY, 2005.

12. Marnay T. 3 Levels Lumbar Total Disc Replacement and Sagittal - Pelvic Blance. A Study about 30 Cases. SA5: Global Symposium on Motion Preservation Technology. Ney York, NY, 2005.

13. Bertagnoli R. The Treatment of Disabling Lumbar Discogenic Low Back Pain with Total Disc Arthroplasty Utilizing the PRODISC Prosthesis in Patients of the "Expanded Indications Group. SA5: Global Symposium on Motion Preservation Technology. New York, NY, 2005.

14. Geisler FH. Surgical Technique of Lumbar Artificial Disc Replacement with the CHARITE™ Artificial Disc. Neurosurgery 2005;56:ONS46-57.

15. van Ooij A, Oner FC, Verbout AJ. Complications of artificial disc replacement: a report of 27 patients with the SB Charite disc. J Spinal Disord Tech 2003;16:369-83.

16. McAfee PC. Comments on the van Ooij article. J Spinal Disord Tech 2005;18:116-7.

17. Phillips F, Diaz R, Pimenta L. The Fate of the Facet Joints After Lumbar Total Disc Replacement: A Two-Year Clinical and MRI Study. SA5: Global Symposium on Motion Preservation Technology. New York, NY, 2005.

18. Elders G, Blumenthal SL, Guyer RD, et al. Effect of Facet Joint Arthrosis on Outcome After Artificial Disc Replacement. SA5: Global Symposium on Motion Preservation Technology. New York, NY, 2005.

19. Burkus JK, Gornet MF, Dickman CA, et al. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech 2002;15:337-49.

20. Brau SA. Mini-open approach to the spine for anterior lumbar interbody fusion: description of the procedure, results and complications. Spine J 2002;2:216-23.

21. David T. Lumbar Disc Prosthesis: An Analysis of Long-Term Complications for 272 CHARITÉ Artificial Disc Prostheses with Minimum 10 Year Follow-up. Spine J 2004;4:S50-1.

22. Lemaire JP. SB Charité III intervertebral disc prosthesis: biomechanical, clinical, and radiological correlations with a series of 100 cases over a follow-up of more than 10 years. Rachis [Fr] 2002;14:271-85.

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

24. Scott-Young M. Revision Strategies for Lumbar Disc Replacement. Spine J 2004;4:115S.

25. Hedman TP, Kostuik JP, Fernie GR, et al. Design of an intervertebral disc prosthesis. Spine 1991;16:S256-60.

26. Serhan H, Dooris A, Ares P, et al. Wear Characterization of the CHARITÉ Artificial Disc Using ASTM Guidelines. SA5: Global Symposium on Motion Preservation Technology. New York, NY, 2005.

Figure Legends:

Figure 1) Nonparametric Density Estimations and data points (JMP 5.0.1a, SAS Institute Inc., Cary, NC, USA) of the CHARITÉ Artificial Disc (IDE & Training cases) and the fusion with BAK cages control group at both baseline and 24 month follow up. This Bivariate density models a smooth surface that describes how dense the data points are at each point in that surface. The plot adds a set of contour lines showing the density at each 5% quantile interval. Note at baseline the patients in the BAK control group and the CHARITÉ (IDE & Training cases) group are approximately equivalent and match the entrance criteria of the study. However, at 24 months there is a notable difference in the postoperative recovery in the two treatment groups. Although both groups have a peak near the origin (little pain and little disability), the BAK control group has a second peak near the entrance criteria values (little to no improvement in either clinical measurement) which is absent in the CHARITÉ (IDE & Training cases) group. In fact if one defines a poor outcome as having either a VAS>40 or an Oswestry Disability Index>40, then the BAK control group has a significantly greater number of poor outcomes (P=0.0165, Fisher's Exact Test).

Figure 2) Top: Lateral flexion/extension radiographs at 24 months following surgery of a patient enrolled in the CHARITÉ Artificial Disc group. The range of motion is 4.3º, in-line with the FDA criteria for "fusion". Bottom: The same radiographs with superimposed red lines showing the change in angulation.

Figure 1

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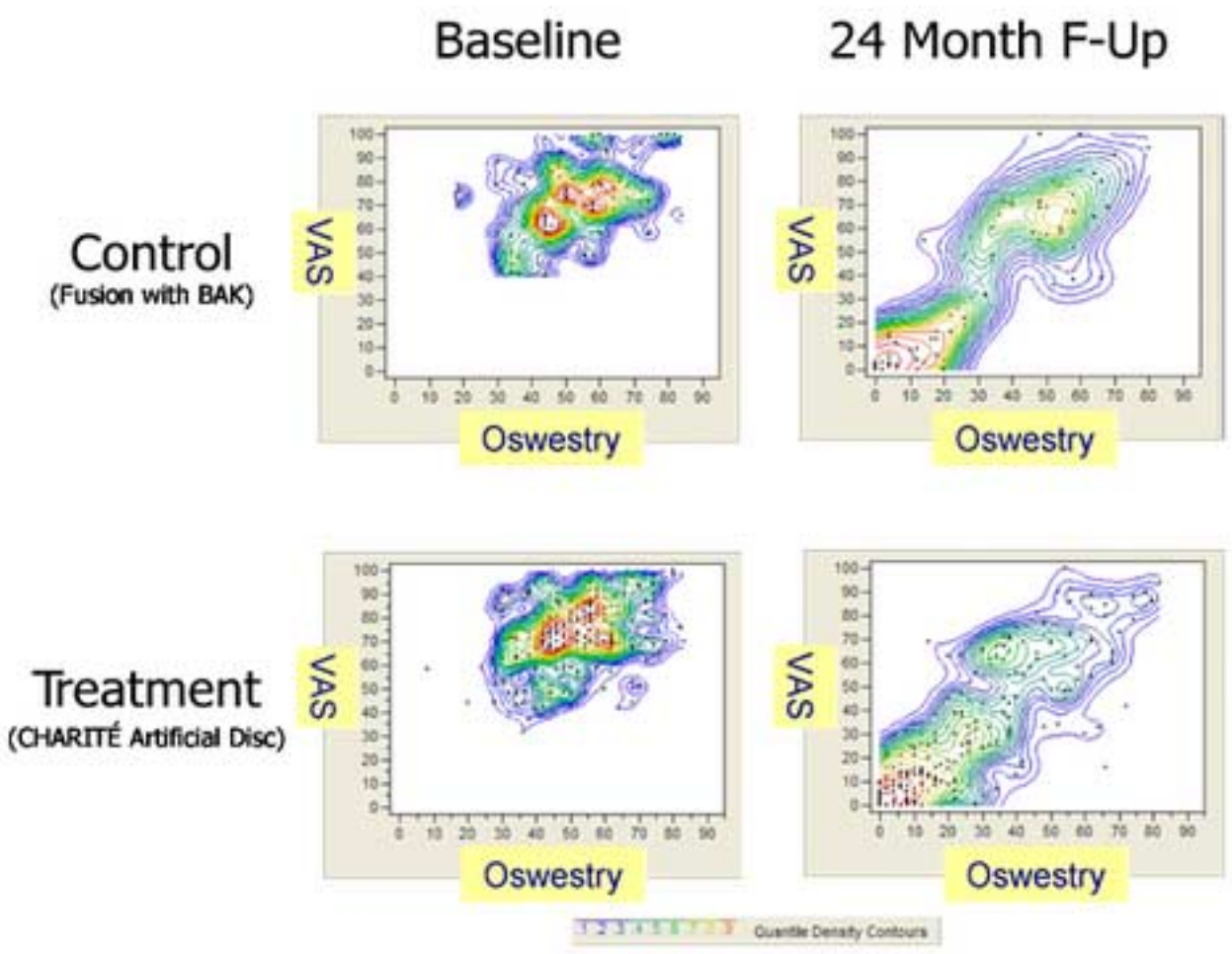

Figure 2

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