

Expectations For Artificial Disc Trials Challenge Market Hopefuls

Completing a pivotal trial may be the biggest challenge developers of artificial discs face as the market for the devices gets more crowded, say consultants.

"The true competitive edge after approval is the data [companies have] actually collected, the choice of control, and the endpoints they've chosen to use, such that they can differentiate themselves from the competition and say, 'Hey, we're better in this or this area,'" Glenn Stiegman, Musculoskeletal Clinical Regulatory Advisers' VP-regulatory affairs, said in an interview. "All of those things take additional money to run."

According to new FDA guidance released in April, the recommended pivotal trial design for total artificial discs is a multi-center, randomized controlled study, similar to those performed for products already on the market ("The Gray Sheet" April 28, 2008, p. 6).

Approved total disc replacements for treating degenerative disc disease include Johnson & Johnson/DePuy Spine's *Charité* and Synthes/Spine Solutions' *ProDisc* lumbar discs, and cervical discs *ProDisc-C* and Medtronic's *Prestige*.

MCRA's Director of Clinical Affairs Teresa Schroeder said the guidance's discussion of post-approval studies changed how MCRA advises firms writing investigational device exemption (IDE) study protocols.

Although FDA says two years of follow-up are usually sufficient for approval, the agency suggests IDE studies obtain patient consent for five to 10 years of follow-up to ensure their participation in post-approval data collection.

Schroeder said enrolling enough patients to have a statistically significant number at 10 years, taking into account patient attrition, will likely expand a trial's enrollment period from six months to two years and will significantly increase the cost of running the study.

A trial that might have enrolled 460 patients to randomize them 2:1 to an artificial disc for two-year follow-up may now need to enroll 600 patients so that at 10 years there will still be 150 patients participating, she said.

Finding patients willing to be randomized in a trial has also become more difficult as more patients

learn about treatment alternatives, including spinal fusion and discs already on the market.

Spinal fusion was the control therapy in most artificial disc trials in the past, but some sponsors, including Aesculap Implant Systems (*Activ-L*) and SpinalMotion (*Kineflex*) are comparing their lumbar disc devices to *Charité* or *ProDisc*.

Some payers have also suggested three-arm studies that include conservative care, including physical therapy and medical management, as another control, according to MCRA's VP-Reimbursement Charles Schneider.

Payers Take Close Look At Pivotal Trial Design

MCRA works with more than 70 orthopedics companies, including those in the portfolio of venture capital firm Viscogliosi Bros., which also owns the consulting group. MCRA says its largest niche of clients is in the spine space.

The consultants stress the importance of considering the future reimbursement strategy in the design of pivotal trials primarily intended to earn device approval. MCRA says the added investment will pay off in the long-run ("The Gray Sheet" March 3, 2008, p. 22).

The market has been reluctant to adopt *Charité* and other first generation discs as many payers refuse to cover the devices without better long-term data.

"It's a misconception to think that payers don't take a strong look at the control, the statistical plan, and other key aspects within the trial," Schneider said. "I think what the new entrants into the game are trying to do is design their trials better and anticipate some of these payer objections they've seen with the earlier discs."

In addition to long-term outcomes, functional and economic endpoints in pivotal trials can help sponsors persuade payers to cover their devices, Schneider explained. For example, payers may be more likely to pay for a disc if the trial shows the new device allows a patient to return to work faster, requires fewer concomitant medications, improves mental health, or patients with the device use fewer total health care resources than patients treated with the alternative.

Since *Charité* was approved in 2004 and *ProDisc* in 2006, certain major payers including Aetna have

decided to cover artificial discs. Cigna started covering lumbar discs a year ago but does not cover cervical discs, while UnitedHealthcare and Humana still consider all discs investigational.

CMS does not cover lumbar discs for patients over age 60, but decisions for younger patients are left up to local contractors ("The Gray Sheet" Aug. 20, 2007, p. 7). There is no national Medicare policy for cervical discs.

Schneider said cervical discs are expected to gain payer acceptance more quickly than lumbar discs have. Cervical disc replacement is considered simpler, the patient selection criteria are clearer and fewer patients need the procedure, he said.

Medtronic's Prestige cervical disc was approved in July 2007, the same month its *Bryan* cervical disc received an FDA advisory panel endorsement ("The Gray Sheet" Aug. 27, 2007, p. 4). ProDisc-C was approved in January 2008.

Firms with other discs in development include Stryker (*FlexiCore* and *CerviCore*), DePuy Spine (*Discover*), Orthofix (*Advent*), NuVasive

(*NeoDisc*), SpinalMotion (Kineflex and *Kineflex-C*), AxioMed (*Freedom*), Globus Medical (*Secure-C*), LDR Spine (*Mobidisc* and *Mobi-C*), and Cervitech (*PCM*).

Coming Long-Term Data Could Ease Burden

MCRA's Stiegman, a former chief of CDRH's orthopedic devices review branch, predicts the large volume of data on artificial discs that will become available in the next five years may provide definitive answers about the devices' safety and effectiveness.

He predicts that some firms just starting their IDE studies may deviate from FDA's guidance by conducting a single-arm study with a historical control in order to speed up their trials and reduce costs.

"[FDA is] going to advise against it and say this is going to be a panel issue, and a lot of companies will fold and do a randomized study," he said. "But there will be companies that take that risk, and then we'll have to see what FDA really says."

— *Chloe Taft* (c.taft@elsevier.com)