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Did Medtronic sell an unsafe product?

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For Dr. Harlan Krumholz, numbers tell stories.

The pioneering Yale University cardiologist's medical sleuthing -- called "outcomes research" -- involves studying how sick people are treated, then analyzing the results for clues on how to better care for them, often in a more-efficient and cheaper way.

His methods have attracted wide attention. Forbes magazine called him "the most powerful doctor you never heard of."

The latest challenge for Krumholz involves applying his techniques to a signature product from Medtronic Inc., the world's largest medical-device company. The back surgery product, Infuse, has long been a top seller, reaping $700 million a year for the Fridley-based company.

But that success has been marred by allegations that Medtronic paid illegal kickbacks and sham royalties to doctors to entice them to use Infuse in ways regulators hadn't approved, possibly putting patients at risk. Some critics say researchers with financial ties to the company have understated serious complications with Infuse, including cancer.

Krumholz and his team at Yale will address fundamental questions: Does Infuse work? Is it safe?

"I'm not seeking to address how the product was marketed," Krumholz says. "I'm just sticking to the science. I'm trying to set in place a new way of doing business."

His ultimate aim: To bring a new level of transparency to the way clinical studies sponsored by drug and medical-device companies are conducted, a process that is little understood by the public.

The stakes are high for Medtronic, whose reputation has been nicked by repeated revelations, some tawdry, about questionable marketing practices, some of which are being investigated by Congress and the U.S. Department of Justice.

Collins Stewart analyst Tao Levy said Medtronic had to take action, given the "negative press."

"Whatever results come out, the Yale group's credibility will help with the nervousness surrounding Infuse now, and the data will be viewed as more credible," Stewart said. "But even if the findings are positive, the product will still be pretty tarnished."

The Star Tribune calculated that during the company's 2011 fiscal year it paid $61 million to doctors for royalties, consulting services, educational talks and training. Of that amount, $46 million was paid out in royalties, about three-

quarters of which went to spine specialists.

Medtronic, one of few medical-device companies that publicly reports such financial relationships, has steadfastly maintained that collaboration with physicians ensures that medical devices are safe, and that doctors who invent new products or techniques should be fairly compensated.

Now the company is funding Krumholz with a $2.5 million grant to provide the sort of tough-minded analysis that it hopes can't be disputed, and it will provide him with all available patient data on Infuse. Beyond the money, the company says it won't be involved in any way.

"We knew we had to take the high road and seek out a third party, a completely unbiased and independent organization," CEO Omar Ishrak said in an interview. "We want to take transparency of clinical data to a whole new level. What we're doing is pretty unprecedented."

Focus on safety

Enter Krumholz, an unassuming Midwesterner with Ivy League cachet.

He became involved after a series of articles appeared in a medical journal last summer suggesting that researchers with financial ties to Medtronic understated serious complications associated with Infuse. Doctors rarely dress down one another publicly, and the Spine Journal publication caused a firestorm in the field of back surgery.

"I think that for many people at Medtronic, these episodes are a great source of embarrassment," Krumholz said. "I want to liberate the data, and let the science speak for itself."

Medtronic has promised to give Krumholz and his team all the available medical records of patients who have been treated with Infuse for further study by two independent research organizations chosen by his team. The probe will assess Infuse's safety performance, including side effects such as cancer, excessive bone growth, male sterility and "retrograde ejaculation." Currently, most of this information is privy only to the companies paying for the research, regulators and the researchers themselves.

Yet several of Krumholz's colleagues in medicine -- while praising the unique scope and potential of his project -- are skeptical.

"I think it's ridiculous that the company is saying it's now going to complete an independent study [on Infuse]," said Dr. Charles Rosen, a California spine surgeon and founder of the Association for Medical Ethics. "That implies the previous studies weren't independent."

A blockbuster product

The scientific name for Infuse is recombinant bone morphogenetic protein-2 (or BMP-2), and it's used in a kind of surgery called spine fusion, where

vertebrae in the back are permanently joined together to eliminate pain or correct a deformity.

After the Food and Drug Administration (FDA) approved Infuse in 2002 for use in the lower back, the number of fusion surgeries surged. Today, about 550,000 spine fusions are performed in the United States annually, according to the Millennium Research Group, though not all involve Infuse.

While Wall Street cheered Infuse's spectacular growth, allegations surfaced that Medtronic was using its financial largesse to coax doctors to use it in ways regulators hadn't approved. Industry analysts have speculated that roughly 80 percent of Infuse use is "off-label."

Some doctors, for example, used it in neck surgery -- a practice that prompted an FDA warning in 2008 after reports of excessive bone growth surfaced. It isn't illegal for doctors to use devices as they see fit, although companies cannot market use of their products off-label.

At least four whistleblower lawsuits have been filed by former Medtronic employees -- including the spine business' onetime general counsel -- alleging that the company courted doctors' brand loyalty with lavish perks, including trips to exotic locales for "training," lucrative consulting pacts and trumped-up royalty agreements that paid some surgeons millions.

In 2006, Medtronic paid a $40 million fine to settle with the Justice Department, but admitted no wrongdoing.

Questions arise

The latest wrinkle in the Infuse debate erupted last summer when a blue-ribbon panel of spine experts reviewed the 13 original studies of Infuse paid for by Medtronic. The panel found that authors with financial ties to the company reported 10 to 50 times fewer complications with Infuse than were found in FDA reports and in other documents. Complications include different types of cancer, male sterility, infection and inappropriate bone growth.

The results were published in the Spine Journal, which is read by doctors who specialize in the field. But outrage spread beyond the spine community -- and Congress promptly launched an investigation on whether Infuse's side effects have been underreported.

The editor of the Spine Journal, Stanford University's Dr. Eugene Carragee, said questions about money's influence on research have "been a big problem in the orthopedic and spine worlds." A new device c omes out, "it's met with a great deal of enthusiasm, but as the controlled trials come in, it's not as good as previously thought, and it falls from favor. But, in the interim, it has been enormously profitable."

Some doctors took issue with the Spine Journal's conclusions. In a letter to the editor, University of Wisconsin spine surgeon Dr. Thomas Zdeblick called the articles "naive and short-sighted at best

and at worst inappropriate and irresponsible." He called the Spine Journal research flawed, and said "a single publication in the medical literature does not constitute a 'truth.'"

A Medtronic consultant and co-author of some of the disputed Infuse studies, Zdeblick has reportedly received $23 million in royalties from the company since 2002.

Seeking transparency

Around the same time as the Spine Journal brouhaha broke, Krumholz was nosing about for a new project.

His previous work is notable. He's studied how heart attack patients are treated in emergency rooms, resulting in new ways to treat them quicker. He's partnered with Medicare to develop national measures for public reporting of hospital performance.

He also testified on behalf of aggrieved patients who had taken the pain drug Vioxx in a court case charging that drugmaker Merck & Co. hid heart attack risks.

"Once I got into [the Merck case], I saw there was a truth that needed to be told," Krumholz said. He discovered that Merck had a plethora of safety data in-house about Vioxx that was not public. This convinced him that clinical data from drug and medical device companies should indeed be made public.

But how? Part of the challenge is that companies are skittish about releasing patient information for competitive, legal and ethical reasons.

Krumholz saw an opportunity last summer when the Infuse story broke. He phoned Dr. Rick Kuntz, Medtronic's chief scientific officer, whom he knew.

"I said, 'If you hire someone to look at your data and they find something that's favorable for you, it's not going to be credible. People will say you paid them,'" Krumholz recalls.

Medtronic was well aware of Krumholz's reputation. Christopher O'Connell, president of the company's Restorative Therapies Group, which includes the spine business, said he "has high credibility. He's a researcher of the highest caliber."

Beyond the initial studies of Infuse, Medtronic said it will make the data available to other researchers who could access it through a website. "Because there are so many questions about Infuse, we think that's a good standard for transparency," O'Connell said.

The results of the Yale project will be released by mid-2012.

Strategic challenges

As Krumholz and his team probe Infuse, more immediate challenges face Medtronic's spine business. In a tough economy, patients facing higher out-of-pocket health care costs have

delayed back surgery. Insurance companies have pushed back on paying for the expensive procedures. And more broadly, there's "a dearth of significant technological advancement across the industry," said Wells Fargo Securities analyst Larry Biegelsen.

Some analysts have suggested a once-unthinkable option for Medtronic -- spinning off its spine b usiness entirely, a notion CEO Ishrak dismisses.

In addition, the newest iteration of Infuse, a product called Amplify for other types of spine surgery, failed to gain FDA approval in March after concerns were raised about possible cancer risks. Medtronic is appealing the decision.

Earlier this month, even more questions surfaced about Amplify. At a convention of spine surgeons in Chicago this month, Carragee released findings that indicated the cancer risk is more serious than originally thought.

Carragee said many surgeons are still shocked at his revelations about Infuse. "There's a lot of bitterness out there," he said. "People used this product in good faith. They thought it was the right thing to do."

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