Trends-in-Medicine

February 2003
By Lynne Peterson

SUMMARY

It may not be the best of times, but it is still very good times for the orthopedic field. The number of patients needing – and getting – hip and knee replacements and spinal fusions continues to grow, and the outlook is for all of these procedures to continue to increase as Baby Boomers age. In addition, manufacturers have been able to steadily raise prices each year, and they are optimistic that this will continue at least for another year or two. There are no signs that CMS is about to trim reimbursement.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

American Academy of Orthopedic Surgeons
New Orleans
February 5-9, 2003

Minimally invasive surgery probably was the hottest topic at the meeting, but it was not without controversy. Even the definition was debated. Some experts called minimally invasive surgery (MIS) a bit of a misnomer, referring to it instead as less invasive surgery (LIS) or mini-incision surgery (mini), but regardless of the name, knee and hip replacement incisions are getting smaller, down to 7-10 cm from the traditional 20 cm.

Overview of MIS

Contraindications	Potential benefits	Disadvantages
Joint-specific contraindications	Less pain	Steep learning curve
Significant deformity	Quicker recovery	Infection
Previous total joint surgery	Outpatient procedure	Skin necrosis
Revision	Less complication	Malapposition
Significant deformity	Earlier return to work	Technical error
Subcutaneous tissue >5 cm (Obesity by weight is not an absolute contraindication.)	Superior outcomes	Limited exposure
		Wear and fixation failure
		Fracture
		Cement technique compromised

Doctors and company officials took some rather strong stands on the topic of MIS. Their comments included:

- A Texas doctor called MIS "hip hype," saying, "It is advocated by those trying to get a commercial advantage…My biggest office problem is fixing problems and I don't want more of those…I've never heard patients complain they are unhappy with (hip) surgery because they were in the hospital too long. In Texas, we are ***not*** under pressure to do minimally-invasive hip surgery."

- A surgeon who uses mostly Biomet said, "We're in an MIS craze. I'm enthusiastic, but I have a large dose of skepticism. MIS is not new, but it's been thrust on the orthopedic community in the past few years. We are all a little intrigued with it. No one knows how to define MIS in hip. Is MIS the answer? The data is simply not in…I favor the posterior mini-hip approach, with a 10 cm incision…MIS advocates say payors and employers will favor this, but my duty is to do the best for the patient, not the payers or the employers. My biggest worry is implant recalls and diminished outcomes, so I think we should proceed cautiously…20%-30% of hip cases might possibly qualify for MIS, but knee MIS is totally experimental."

➢ The chairman of orthopedics at Lenox Hill Hospital in New York, Dr. Chitranjan Ranawaat, said, "MIS remains a marketing tool for individual surgeons, companies and hospitals…Minimally invasive does ***not*** mean a small incision. It really means reduced trauma to the skin, subcutaneous tissues, muscles, and ligaments -- but not the bone…The aim of MIDCAB (minimally invasive bypass surgery) was to reduce morbidity in CABG without deviating for safety and efficacy...but after 10 years, acceptance among heart surgeons is about 25% because the complications are similar (to traditional bypass), and there are no appropriately-done prospective, randomized studies…I raise a challenge -- demonstrate that MIS is safe, effective, reproducible and provides as good an operation as conventional surgery and define the precise indications… Proponents have gone public without peer review and publication…The concept is good…but we should do what is good for the patient and not for personal gain or the company."

➢ A Stryker official said, "MIS is the big buzz here. We've been active in that for some time...many of our surgeons have been using 3-4 inch incisions for a while now. (One of our surgeons) had the only peer-reviewed article on minimally invasive hip surgery, which appeared in the October 2002 issue of *Orthopedics*. Our approach is different – a mini-incision approach…We have more experience with less-invasive knees than anyone else in the marketplace."

➢ A Zimmer official said, "MIS is not about cutting small (incisions), it's about living life big (patient quality of life)."

➢ A Smith & Nephew official said, "We only have one minimally-invasive business which is endoscopy. That really is minimally invasive; all the rest is less-invasive but not minimally invasive…We have been working with a team of surgeons in hip and knee on development of small incision surgery (SIS)…We think our competitive advantage in SIS will be marrying our efforts with the modification of instruments and technique and the advantages of using our computer-assisted systems to provide visualization…We also are building relationships with hospital CEOs and purchasing agents."

TOTAL HIP REPLACEMENT

Zimmer is aggressively pushing the MIS concept and actually trying to appropriate the term MIS for itself, suggesting that MIS hip surgery means a specific procedure – the two incision Berger procedure developed by Dr. Richard Berger of Rush-Presbyterian-St. Luke's Medical Center in Chicago. Dr. Berger estimated that 80% of hip arthroplasties could be done this way, and with improved implementation, 90%-95% could utilize this approach, "We are in the process now of re-designing and refining the instruments; they are still too big… We are thinking about designing some implants which are specifically designed around small incision surgery, which will not only make this but also small incision surgery easier."

Comparison of Hip Replacement Procedures

	Traditional THR	Berger procedure
Operative time	3.5-4 hours	80-120 minutes
Length of hospitality	3 days	Home same day

Zimmer is investing $20 million in the Zimmer Institute, a program to train hip surgeons in the Berger procedure at a specialty-outfitted surgical suite in the Zimmer headquarters building, but it is also to beam the course to other countries and is outfitting an 18-wheel mobile training center. Starting March 31, 2003, Zimmer plans to train up to 500 surgeons a year, starting with its key customers first but expanding to other doctors soon. A Zimmer official said, "Right now, there are 220 surgeons on the waiting list. We've already trained 50 surgeons. We know we can't train to level of demand, and not everyone wants to come to us…So, we are partnering on a satellite uplink basis. It will look and feel and act like our operation, but it can be in their language." A Zimmer user who has taken the course said, "I do mini-incisions. They take a little longer, but the pain is less for the patient, and the patient can go home sooner. I've done 30-40 mini-incisions and a couple of two-incision operations. However, a guy doing one or two total hip replacements a month shouldn't be doing any two-incision surgery."

To complement the training, Zimmer has prepared a direct-to-consumer advertising program for participating doctors. There is a slick kit with patient, ad slicks and radio ad copy. A Zimmer official said, "We think patients will drive change (to MIS)…There is a fine line between marketing hype and showing results of people…We want to be sure we don't cross that line, but we want to show the potential and capabilities of what we can do… Small incision (is) not what the battlefield will be about…The battle will be over teaching, education, computer assistance, delivery of patient quality of life and outcomes. Zimmer has been a superb educator for years and years. This is going to be about education, first-mover advantage, and direct to consumer advertising…This is about strategy, execution and education."

Zimmer officials also claimed to have a long-term, exclusive agreement with Medtronic that restricts use of Medtronic's Stealth navigation technology (which currently has an installed base of about 1,000) so that no one else can use Stealth for "minimally-invasive surgery." A Zimmer official said, "We will have software to match up with Stealth, which has 50% market share -- and with our other partnerships we have 67% share (in navigation)." Another Zimmer official said, "No one else can have an MIS relationship with Medtronic except us. It is a two-way exclusive deal on MIS procedures."

This appears to be a bit misleading. A Medtronic official insisted Stealth is an open platform, available for anyone to use. He said the exclusive arrangement is only for the Berger

procedure; that is, Stealth cannot be used to perform the Berger procedure except with Zimmer implants. The agreement, he insisted, does not prevent doctors from using Stealth to perform any other type of minimally-invasive, less-invasive or mini-surgery of the hip.

There also is a catch to Zimmer's free training – doctors who are not currently Zimmer customers will be asked to sign both an intellectual property agreement and a contract that they will buy Zimmer hip implants in the future. This angered some doctors. A North Carolina doctor said, "A contract? That's wrong. I did a hip last week without MIS training, and the incision was 4.5 inches – and it wasn't that hard to do." A Florida doctor said, "I can't see how Zimmer can legally have us sign that. I wouldn't sign it." A Louisiana doctor said, "Although I use mostly Biomet hip implants, I would look at another brand if it looked interesting, but I would not sign the Zimmer contract."

However, not every source rejected Zimmer's contract approach. An Arizona doctor said, "MIS is a scam, but the Zimmer contract is okay. If I did MIS, I would want a big company behind me." Another doctor said, "I would consider the Zimmer course, and the contract wouldn't put me off." A source who took the Zimmer course said, "There was some contractual agreement. Zimmer is the only company with instrumentation for one- or two-incision hip surgery…Zimmer won't let you use its instruments unless you are using Zimmer implants."

Thus, many sources believe Zimmer already has crossed the line with its promotion of the Berger procedure. Competitors, speakers, and most of the doctors interviewed at the meeting were critical of Zimmer's approach, and many were critical of the Berger procedure itself. Among their concerns are:

➢ **Promotion.** Zimmer is over-promoting the Berger procedure, many complained. A Texas doctor said, "The two-incision approach is intriguing, but there is no literature to support it, just massive hype, and no peer review…The only literature on two-incision hip surgery (the Berger procedure) is on websites...The true complication rate has yet to be determined, but it will be higher than traditional surgery because of the diminished visualization. And it is technically difficult." Another doctor said, "It took me six months to learn to do a mini-incision, and I do a lot. If you do a couple of cases a month, you will never get beyond the learning curve." A Biomet official said, "We did surveys, and the doctors said patient information is fine, but we don't want you hyping patients." A Stryker official said, "We are very cautious to make sure new procedures and instruments are carefully quantified so that more than one surgeon can deliver the results. When we promote something, we want to be able to demonstrate that a wide range of surgeons across a wide range of patients can get the same benefits, that we can quantify the risks – dislocation, infection, nerve damage, femoral fracture, etc. (One of our doctors did) a prospective study. That is responsible science. To promote expectations in the minds of patients beyond what is validated scientifically is not what I would see us doing."

➢ **Patents.** Zimmer and/or Berger are trying to patent a surgical procedure, and many sources had ethical problems with this.

➢ **Technical skill.** The Berger procedure is very technically difficult. Sources predicted it would be restricted to high volume surgeons and it inappropriate for most community doctors who do fewer than 50 hip replacements a year. Dr. Berger said, "My learning curve was 12-13 cases because of changes in technique and instruments. Now, it is good and written. I think it will be 1, 2 or 3 cases for others." Even sources who have taken the Zimmer course disagreed, saying it takes more cases than that to be competent in the Berger procedure.

➢ **Contracts.** Even Zimmer users complained that it is heavy-handed and perhaps unethical if not illegal to make doctors sign an agreement to purchase Zimmer implants in order to get trained in the Berger procedure. A Kentucky doctor who uses Zimmer implants was interested in the MIS training – until he found out about the contract. He said, "I would not want to sign a contract, so I might not take a course as a result." Another Zimmer user said, "MIS is the future, and I would like to learn it, but I wouldn't sign any contract…The technology will be very similar (from company to company), so it doesn't matter which implant you use. One course is not enough to do MIS, and I wouldn't use a product based on a course."

➢ **Eligible patients.** Berger said that he currently is going MIS on 25% of his patients, and that is the most that his hospital would permit because of logistics constraints. These also are smaller, younger patients since (1) the maximum cup size that can be used is 46 and (2) Medicare reimbursement is not sufficient to pay for this procedure.

➢ **Potential complications.** An expert who is trained in the Berger procedure said, "The risk is intraoperative fracture, but the mini-incision will be the standard of the future."

➢ **Training location.** Several competitors insisted that doctors will not want to travel to Zimmer's headquarters for their training, and they plan to offer more geographically dispersed training centers. For instance, a Stryker official said, "Our philosophy is a little different. Zimmer set up central training facilities. Our approach is a satellite center at various sites. We have three sites now -- Philadelphia, Johns, Hopkins, and the University of Georgia at Athens – and that will expand as demand for more training comes up. On the MIS knee side, we have five sites identified and involved in a clinical study or doing initial evaluation work, and we'll gauge training requirements and add sites as needed…but our philosophy is to do it regionally."

Medicare does not pay for the Berger procedures when done in the hospital if the patient stays less than 23 hours, so it is being reserved for younger (under age 65) patients or those with private insurance. Dr. Berger said it is unlikely that doctors will get paid more to do this cementless procedure, "It would be great to think I'm going to get paid for it…That probably is not going to happen, but it will get me more business and keep my business going because if I don't do it, I'm out of business…Today, I could take almost all of these patients to an outpatient surgery center, and that would increase my income because I am a part owner in the outpatient center...but there is no outpatient code for arthroplasty, so the facility fee is almost non-existent. Obviously, that will change. As insurance companies realize they can pay an outpatient center less than a hospital, then more procedures will move to outpatient. Only revision surgeries that are far too complex will remain in the hospital."

If Zimmer works with CMS and private payors to get new coding for outpatient total hip replacement (THR), that raises the possibility that CMS could take a look at overall implant reimbursement. Furthermore, if the procedure is identified as an outpatient procedure but a doctor keeps a patient in the hospital longer in order to quality for Medicare reimbursement, CMS could consider that Medicare fraud. So, there are two cans of worms that Zimmer could be opening with its outpatient effort.

On the other hand, Zimmer's MIS effort could bring new patients into doctors' offices and expand the U.S. market. Source doubt that Zimmer will be successful in shifting market share because of the procedure or its implants, but they admitted Zimmer could pick up market share if more new patients go to Zimmer doctors as a result of the advertising.

In Europe, the Berger procedure may do even better. A German hip surgeon said, "Mini-incisions have been standard in Europe. The Berger procedure is easy for European doctors to learn, and they will do more of it to get patients out of the hospital sooner, which will be important under our new DRG-type system that goes into effect in April. The Berger procedure will capture a lot of the German market initially, and that will help Zimmer there."

Yet, sources estimated that a only a small number of THR procedures will be done in the U.S. by minimally invasive surgery, with only a share of these patients going to Zimmer. A Midwest surgeon said, "Two-incision hip surgery (the Berger procedures) won't take over. A maximum of 20% of procedures will be done that way." A California surgeon said, "About 15% of hips are done at academic centers, and only 20% of those hips will be done with MIS. The other 80% of procedures are done by community doctors, and less than 20% of their procedures will be MIS, though they are most susceptible to the competitive environment. So, about 19% of all hips might be done with MIS…It will be a niche market."

The Implants

Each of the major orthopedic companies had one or more new products to show at the meeting, but despite all these new products, sources doubted there would be any significant market share shifts in the near future. In fact, none of the doctors questioned at the meeting plans to change total joint implant vendors, and none even plan to try the new products to get a feel for them. Rather, sources insisted that they will continue to use the implant on which they were trained and currently use. Unlike interventional cardiologists who are quick to try the newest stent and huge market share swings can occur just 30 days after a new stent hits the market, orthopedic surgeons are intensely loyal to their implant sales rep and their current vendor and rarely experiment or switch. Thus, the new implants seem mostly a way for companies to keep their current customers happy, to justify price increases, and to market to consumers, but they are not really a way to gain market share.

European Market

In Europe, there continues to be a waiting list for hip implants.

Sweden. A Swedish doctor said the list there has shortened recently from 10 months to seven. However, a Germany doctor who recently studied hospital management in Europe said this is misleading. He explained, "The government health insurance waiting list is three to four years. Doctors like that because it increases their private procedure business. It's the private wait list that has gone down, and that is more like four months."

Germany. A German doctor said the waiting list in that country has been holding steady at about six to eight months, but he warned to expect a slowdown in implants in the future that would lengthen the waiting list. Another German doctor said his hip waiting list is about two months, and he expects that to hold steady, but he pointed out that the new DRG-type reimbursement system goes into effect in April, and that could slow procedures.

U.K. A doctor said the waiting list is long, and no improvement is likely in the near future.

TOTAL KNEE REPLACEMENT

Minimally invasive surgery is not limited to the hip; it is also being perfected for knee replacements. While hip and knee surgery has an extremely high success rate, even the best surgeons have outliers – less than perfect outcomes. A speaker said, "Mechanical alignment guides have improved the success (of knee surgery), but errors in alignment still occur, with errors of more than three degrees occurring in at least 10% of TKR (total knee replacement) – by experienced surgeons."

Another speaker compared his MIS knee patients with traditional and knee replacements and found:

- MIS patients required 20% less post-op pain medication
- Shorter hospital stays with MIS
- Surgical time was similar
- Less post-op blood loss with MIS
- Faster and greater range of motion with MIS
- More success in obese patients with MIS, but not in patients with big muscles.

Three types of minimally invasive knee surgery are possible:

1. Image-free navigation systems, which a speaker said, "This is getting the most knee attention…In the knee, image-free systems are probably going to be the standard."
2. Image-guided alignment systems. A speaker said, "In (non-TKR) procedures currently using fluoroscopy, image-guided alignment systems are more likely to be used."
3. Robot-assisted TKR instruments (e.g., Integrated Surgical Systems' Robodoc, which several speakers indicated has generally been mothballed.)

Next year, Zimmer also plans to introduce its own minimally-invasive knee surgery, developed by Dr. Alfred Tria of the Robert Wood Johnson Medical School in New Jersey. A Zimmer official said, "We've done 100, and like what we see. We've also done some very early work on knee revisions. We are not happy with the results, but we think we can fix that." Zimmer also reportedly is developing implants that can be assembled in the knee, kind of a "boat in the bottle" approach, to facilitate smaller incisions.

Dr. Tria presented data on the first 90 knees done with MIS TKR. Only two had to be stopped – one because the patient was too obese and another because of bleeding. Range of motion improved rapidly with MIS, and there were no infections and no skin compromise.

Comparison of Total Knee Replacement Procedures

Post-operative measure	Tria Procedure	Traditional TKR
Pain score	5.4	7.0
Length of hospital stay	2 days	5 days

MINIMALLY INVASIVE SPINE SURGERY

There did not appear to be much enthusiasm for minimally-invasive spins surgery systems at the meeting. A Biomet official said, "Of systems for minimally-invasive spine, none are terrifically popular or being done at a fast pace. There are a number of shortcomings."

Among the spine systems that attracted attention at the meeting were:

- Endius' Atavi. The company claims 100 surgeons at 70 sites are trained. The system adds $1,000-$1,500 to procedure cost, but there is no added reimbursement. A source said, "This is a good approach, but has to be done with a scope, has a long-learning curve, and the fixation instrumentation is not optimized for easy use."
- Medtronic's CD Horizon Sextant percutaneous rod system. A source said, "It uses a small incision, but it is complicated, it has a long learning curve, the instrument is not optimal, and it is expensive."
- Biomet's EBI Acumen Surgical Navigation System, which is a low cost, disposable system costing about $500 per case. It reported has a short learning curve because it utilizes existing surgical techniques, and it allows for posterolateral fusion, if desired.
- CBYON. This privately-held company claims 75 of these 3-D visualization systems are installed world-wide, with about 40 in the U.S., with 30% used for spine, 40% for neuro and 30% for ENT. A fully-loaded system costs $300,00-$350,000, but most buyers reportedly are opting for just one or two modules at a system cost of $200,000-$250,000. However, hospitals can obtain the system for free if they guarantee a certain number of procedures. The system is very, very slick, but none of the spine surgeons who were questioned expressed any interest in it.

COMPUTER-ASSISTED SURGERY (NAVIGATION)

Combining MIS and computer imaging -- computer assisted surgery (CAS) or computer navigation – also was a hot topic at the meeting. Computer-assisted surgery is likely to be more useful in TKRs than THRs, sources said. A New York knee surgeon said, "CAS is the wave of the future." A Zimmer official said, "Orthopedic surgeons hate being hot, and they have to wear lead for fluoroscopy. Fluoro is relatively crude, makes it hard to see the lateral plane, plus a (computer) navigation system doesn't need to be operated by an x-ray tech (as with fluoro) – and orthopedic surgeons hate to use fluoro techs."

Speakers generally agreed CAS is not a marketing ploy, but they also predicted it will be five to 10 years before it becomes commonplace – if it doesn't remain a niche product. A speaker said, "We don't know whether MIS or CAS will improve clinical outcomes. I say, at least at the moment, MIS has more data than CAS-devices." An expert discussed a study of 550 cases comparing CAS to non-CAS TKR which found that the CAS group had fewer outliers ($p<.05$) and a greater percent of patients in which all portions of the surgery were accurate. There also was an unproven suggestion that

CAS may reduce fat embolization. Another speaker predicted that navigation systems, which typically cost $100,000-$150,000 today would catch on when the price comes down, "Navigation systems are mostly software…I guarantee the cost will come down." Still another expert said, "Five years is a good number…At the end of their training, residents will want to go out and do it, and then things will change. As soon as the first generation of residents are out there, we will all be doing it."

GROWTH FACTORS

Growth factors also got a lot of attention at the meeting. A speaker said, "We've clearly entered the biologic age of orthopedic surgery."

Currently two growth factors are FDA-approved. Speakers pointed out that they are different and not equally interchangeable, but both work. A speaker commented, "I can't say one is better than the other."

Medtronic/Sofamor Danek's InFuse (rhBMP-2) for anterior spinal fusion in combination with the company's LT-Cage. A researcher said 100% fusion is achieved with an open approach cage, 97.6% with a laparascopic approach cage, and 95.65 with autograft in the cage but he said 31% of patient reported some pain at two years. A California doctor said, "BMP is used now for anterior procedures, but off-label posterior use will give it even bigger market share…I would guess that 50% of InFuse is off-label use." He cited several risks to InFuse: (1) artificial disks, (2) cost, which averages $4500 per procedure, and (3) clinical efficacy has not been proven.

Stryker's OP-1 (BMP-7) for the treatment of long bone non-unions in patients where alternative treatments are not feasible or have failed. A BMP researcher said data that is not yet published shows that OP-1 achieves successful fusion in the posterolateral spine in 55%-77% of cases. A Stryker official claimed 250 U.S. institutions have IRB approval to use OP-1 in spine. Several trials are ongoing, including:

- A Phase III spine fusion trial was half-way enrolled at the end of 2002, with 116 patients. That trial is expected to be completed by the fourth quarter of 2003.
- A Phase II Japanese posterolateral fusion studied began at the end of 2002.
- A pilot study is underway of OP-1 with an allograft bone dowel.
- A pilot IDE study of the Ray cage with OP-1 putty is due to start in 3Q03.

In 2001, Centerpulse (formerly Sulzer) shut down its development program for ne-Osteo, a multiple extracted mix of bovine BMPs. However, a BMP researcher said ne-Osteo has shown 100% success in rabbits and monkeys, 83% when delivered with DBM and up to 100% with a different carrier.

Johnson & Johnson/DePuy/Acromed also has gotten into the BMP arena. It has a license from Biopharm for a broad BMP technology portfolio, and it got the Healos bone graft substitute with the recent acquisition of Orquest. A Louisiana doctor said, "I'm using Healos in lieu of BMP, but only anterior until it is approved for posterior. Reimbursement is an issue, but I'm getting paid $350-$500 per procedure." A California doctor said, "We're using Healos instead of BMP because it costs $600 instead of $4,500."

J&J also has a new Symphony device which recently got FDA 510K clearance for use in creating a bone graft substitute out of a patient's own blood. The Symphony technology was licensed from the Cleveland Clinic. A patient's blood is taken by needle aspiration from the iliac crest, then put into the device which pulls out bone stem cells and concentrates them into a domino-shaped wedge which can then be removed from the device. The preparation takes about 10 minutes and can be done in the OR without adding to the procedure time. A source said, "This will compete with BMP. It's osteogenic and has the consistency of autograft bone. It has the consistency of sauerkraut." A J&J official said the company will start marketing this device in 2Q03, "We intend to use Healos in this, but not initially."

Several speakers discussed the issues revolving around growth factors, particularly the carriers, timing of the dose, and cost. And they suggested that the BMPs available today are less than ideal.

➢ **BMP.** One speaker said, "InFuse may not be the be-all, end-all."

➢ **Carrier.** An expert said, "The selection of carrier is critical to the success of tissue engineering strategies." Another expert said, "With BMP-2 (InFuse) on a collagen sponge in a rabbit, there was 100% consistent success, but the same carrier in the rhesus monkey did not lead to spine fusion. That was the first clue the carrier was important."

➢ **Delivery.** A speaker said, "I think binding growth factors to sutures is the way to deliver them to ligaments or tendons."

➢ **Dose.** A BMP expert said, "At the Orthopedic Research Society meeting this week…(there were) slides suggesting that BMPs are not working well or are difficult…There is a dose threshold…and that is the greatest reason for the variability in preclinical and clinical studies. Our observation is that there is threshold."

➢ **Timing.** A New England doctor said, "For a long time I thought the major limitation was a lack of sophistication of the delivery vehicles, but I'm starting to think it may be delivery time. I've seen a number of studies that show that if you wait to introduce a growth factor, you get a better response, and that could have to do with local conditions or because it takes times for cells or blood vessels to get there…if you introduce the growth factor right away, its activity may be gone by the time other things get there, so timing may be an issue."

Medtronic may be picking up some market share in the spinal cage area with the introduction of InFuse, but numerous doctors questioned about BMP use said the cost is holding them back. A speaker said, "These are very expensive, which is another reason why it is important to pay attention to the FDA guidelines. If you do a cost analysis on re-treatment of non-unions, putting in a $5,000 growth factor is not expensive…but if you use it in every case because you feel better, that is probably too expensive." Another expert said, "You don't need a $5,000 agent for every non-union. You need to be careful in selection...and you have to hold patients back because they always want to know if this is the best you can do. And HMOs are particularly concerned (about growth factor use). We need to take the lead with patients.

Doctors were warned not to use BMPs off-label for indications for which they are not approved. One speaker said, "I would caution clinicians…to be careful of off-label use...Each BMP is different…BMP-7 (OP-1) has systemic activity if injected…BMP-2 (InFuse) has no known systemic toxicity or effect, but the profile for BMP-2 (InFuse) suggests that in more than 52 cell lines in every case it either slows growth or has no effect…On average it is about a 30% slowing of cell division. That is not enough to make it an anti-cancer effect, so I am not worried about it causing alterations in cell division and causing cancer." Another expert said, "You need to pay attention to regulatory agencies and what these BMPs are approved for. Regulatory agencies are not the bad guys...they are tying to help us understand the best way to use these materials. I changed my view on this. Right now…you have to stick to what is approved." A third expert said, "With off-label use of BMP, the risk is no bone formation – a lack of fusion, etc. -- but not harm…The collagen sponge for InFuse is challenging and not forgiving."

Gene therapy – and the combination of gene therapy and growth factors -- also holds promise. A speaker reported that RBM-Ad-BMP-2 creates more dense, coarse trabecular bone, compared to the lace-like bone created with InFuse and OP-1. He said, "We have a long way to go before gene therapy hits the clinics, but it has real potential…We need to find the appropriate uses. It won't be for all cases…And we need to be careful of off-label usage…Gene therapy is exciting, but there's been one death…and we have a way to go. We don't know the side effects of some of these growth factors." Another speaker said, "Gene therapy needs to be viewed as a delivery system. Very early data we have in animals suggests it is quite effective. One of the things I like about it is offers ability to control the activity of the gene with extracorporeal methods (e.g., use of tetracycline)…It also gives us the opportunity to combine different growth factors and express their activity at different times, which is too expensive with proteins."

The issues for gene therapy include:

- Safety has to be established. An expert said, "This is not cancer. We can't afford any morbidity or mortality."
- Duration of protein expression is unknown.
- Clinical problems need to be identified.
- More needs to be known about the biology.
- Immunogenic response has to be tested.
- Carriers need to be optimized.

Other approaches to bone, cartilage and tendons stimulation also are being explored, including:

- Prostaglandin compounds.
- PTH. A speaker said, "We and other investigators are reporting that PTH can speed healing. We are ..working with the company (NOTE: I assume this means Lilly) to see if the low dose that is approved is osteogenic, and we didn't find an effect...but a slightly higher dose does appear promising…so we might find that subcutaneous PTH has a systemic effect."
- Growth hormone.
- Insulin-like growth factor.
- Amgen's Kinetra (IL-1ra). A speaker said, "We are looking at ex vivo gene transfer ways of delivering this…A Phase I trial of 9 patients found it safe and the gene transfer successful. I understand a Phase II trial is well underway."
- Intra-articular administration of TGF-β. A speaker said, "This has been problematic…It's not ready for clinical use, but progress is being made." Another speaker said, "We are a little behind bone in cartilage use of growth factors."

ARTIFICIAL DISKS

Several artificial disks are in development, but sources remain dubious about their outlook. An expert said, "If I were a patient, I'd opt for minimally-invasive spine fusion instead. There is a lot of interest in artificial disks, but they are still untested." Another surgeon said, "The question is how long these devices will take, and how well they will hold up because these are younger patients, and revisions will be very tough. I'll sit on the sidelines for now." A California doctor said, "I think nuclear replacement will be better than disk replacement, but that won't come for two years after artificial disks…We are working on a Gortex mesh with a hydrogel interior, but there is no commercial company involved yet, and there are two problems: (1) the material can escape from the annulus, which we are working to fix, and (2) fixation is a problem."

Artificial disks in development include:

- Link's SB Charite
- Spine Solutions' ProDisc

- Medtronic's Maverick. A source said this is delayed because of an FDA issue, putting it at least two years away and in No. 3 position.

- Biomet's EBI Restore Artificial Disc. Animal trials are underway, with human clinical trials due to start later this year.

- RayMedica's PDN. The company reportedly has an IDE.

KYPHOPLASTY

Kyphoplasty appears to be catching on, and the popularity of vertebroplasty appears to be waning, at least among spine surgeons. The outlook is for kyphoplasty use to continue to increase. Kyphon has FDA approval for its KyphX system, which doctors use to perform kyphoplasty to treat vertebral body compression fractures. These fractures are a common osteoporosis-related injury and result in the dowager's hump that deforms some older women. KyphX uses a proprietary, inflatable balloon bone tamp to create a space in the vertebra, and then doctors insert a bone cement (filler), polymethylmethacrylate.

The major competition for kyphoplasty is an alternative procedure, vertebroplasty, in which a bone cement – again, polymethylmethacrylate -- is injected directly into the disk space without first inflating it with a balloon. Spine surgeons said they do kyphoplasty under general anesthesia, but vertebroplasty generally is done by radiologists under local anesthesia – making vertebroplasty easier, quicker and cheaper. Several companies are involved in vertebroplasty including Biomet and I-Flow, which has the re-usable OsteoJect Bone Cement Delivery System.

Physician Perspective of Kyphoplasty

Positives	Negatives
1. Effective procedure with good patient results.	1. Reimbursement risk to the hospital.
2. Doctors paid more for kyphoplasty than vertebroplasty.	2. Reimbursement poor for doctors compared to other procedures.
3. Referral patterns increasing.	3. FDA warning letter on cement.
4. May help with other fractures (distal, radial, etc.).	4. Risk of adjacent segment stress.

Fifteen spine surgeons were asked for their opinions of kyphoplasty and vertebroplasty.

- Nine of the 15 are either doing kyphoplasty, are in a group or are at a hospital where at lest one spine surgeon is doing it.
- Six spine surgeons are already doing kyphoplasty themselves, and one plans to start. Generally, one or two doctors in a spine group are doing kyphoplasty, and the others refer those patients to them. A Texas doctor said, "I was the only one in our 15-person group doing kyphoplasty, but now three of us do it."

- Three said one or more partners in the group or at the same hospital is doing kyphoplasty. A Connecticut doctor said, "Both the spine surgeons in are group are doing it. The goal is, first and foremost, to relieve pain and then to decrease further neurological compromise in older, frail people."

- Neurosurgeons are doing kyphoplasty at one hospital, and the spine surgeons refer to them. A Georgia spine surgeon said, "I don't see our spine doctors doing it because reimbursement is low, the risk is high and it is time intensive, but we are referred patients to our neurosurgeons to have it done."

- Four are not doing kyphoplasty and have no interest in it. A Pennsylvania doctor said, "We definitely won't start doing kyphoplasty, and we will probably stop doing vertebroplasties…There have been some experiences where the results were not good, and I heard the insurance companies would stop paying for these procedures." An Oregon doctor said, "I did a few during my fellowship, but I don't do them now, and I don't plan to start. There is a liability issue, and I need to limit the number different procedures I do." An Alabama doctor said, "We're too busy to do it, and the cement burns bridges for the future."

Kyphoplasty is not a money-making procedure for spine surgeons or their hospitals, but many doctors said "it is the right thing to do." A California surgeon said, "It is a money loser, but patients do great." A Texas doctor commented, "This is not an income generator." A Missouri doctor said, "It is very, very helpful for patients." A Connecticut doctor said, "The disposables are expensive, and in some cases, reimbursement doesn't even cover the hospitals' costs. There is no pass-through (on cost). At one point, we halted the procedures because our institution was concerned with funding, but we analyzed the situation and made some changes, and resumed doing them again." An Arkansas doctor said his partner does kyphoplasty, "There are a lot of logistics involved. For instance, it's hard to get OR time for small cases, but the procedure has value. It is a good procedure in selected patients, and we have an aging population." A New York surgeon said, "Every time I think the procedure is technically demanding, and poorly reimbursed and more trouble that I want to get involved with, I see one of the dramatic responses, so I keep doing it." A Midwest doctor said, "Kyphoplasty is here to stay. It is very helpful in reducing pain and morbidity."

Many of these spine surgeons and their colleagues have been doing vertebroplasty either in addition to or in lieu of

kyphoplasty, but vertebroplasty appears to be losing ground to kyphoplasty.

- Three doctors are performing vertebroplasty as well as kyphoplasty, but the mix is shifting or has shifted in favor of kyphoplasty. A California doctor said, "I do both, but 99.9% of the time I do kyphoplasty. It's a low pressure system, so there is less chance of extravasations into the great vessels or the spinal cord. Vertebroplasty is cheaper, but the high pressure makes it more risky." A Texas doctor said, "I choose between these two procedures based on the age of the fracture. The Kyphon folks say you can use kyphoplasty any time, even several months after a fracture, but after the first couple of weeks, it becomes more difficult. So, I use vertebroplasty on fracture that have been there more than six weeks…I used to do 70% vertebroplasty because it started first, is quicker and is less expensive, but now I'm doing more kyphoplasties…Ultimately, kyphoplasty will take over." A Missouri doctor said, "I do kyphoplasty in younger, healthier senior citizens, and vertebroplasty in the frail elderly."

- Three doctors said a partner or another spine surgeon in his group or his hospital is doing vertebroplasty, but, again, kyphoplasty tends to be more commonly performed. A New England doctor said, "Our spine surgeons do kyphoplasty mostly because it has better outcomes than vertebroplasty."

- Four sources said radiologists in their hospital are doing vertebroplasty, and one said pain management doctors have started doing vertebroplasty. These doctors cannot perform kyphoplasty. (NOTE: At the Mayo Clinic, spine surgeons taught the interventional radiologists to do vertebroplasty, and that's whose doing it now, but due to "political reasons" spine surgeons are not doing any kyphoplasty.) An Oregon doctor said, "Pain management specialists are getting into vertebroplasty, and I think that is overstepping their bounds."

- Five doctors/groups have no interest in vertebroplasty, and only two are not doing kyphoplasty either.

Eleven of these 15 doctors predicted that kyphoplasty procedures would increase, but none predicted vertebroplasty would increase as patients and other doctors, particularly primary care physicians, become aware of it. A Texas spine surgeon said, "Kyphon has a bigger PR program, so new folks are going mostly kyphoplasty…Usage will be related to education of the primary care doctors." A New England doctor said, "Kyphoplasty use will go up, driven by patient and physician interest, referrals and institution-related support." An Arkansas spine surgeon said, "Kyphoplasty will be done more in the future as people learn more about it." A Missouri doctor said, "Procedures have mushroomed in my community because of primary care physician referrals." A Louisiana doctor who has done 35-40 kyphoplasties in the past year said, "The volume will increase as more primary care doctors become aware of it." A California doctor said, "Referrals have gone up dramatically in the last year, mainly from primary care doctors, but less than expected from oncologists…Future growth will be from more procedures per surgeon more than new surgeons getting trained."

The FDA recently warned doctors that the poly-methylmethacrylate bone cement used in both kyphoplasty and vertebroplasty has been associated with complications from leakage of the cement, such as soft tissue damage, nerve root pain and compression, and even pulmonary embolism, respiratory and cardiac failure and death. The FDA advised doctors to "be aware of considerations and recommendations regarding patient selection, vertebroplasty and kyphoplasty techniques, complications, and patient monitoring…when considering these procedures to treat osteoporotic compression fractures of the spine."

However, no doctors interviewed have stopped doing either procedure as a result of the warning. With one exception, doctors just were not worried about this issue, and none expect it to have an impact on future procedures. Several noted that the cement does leak, but they said this occurs to a lesser degree with kyphoplasty than with vertebroplasty and blamed some of it on poor technique. Several sources acknowledged that polymethylmethacrylate is not the ideal cement, but they anticipate new products coming along that will be much better.

Key Products by Selected Companies

	Biomet	Stryker	Wright	Zimmer	Johnson & Johnson	Smith & Nephew
MIS approach	Mini-hip approach	Mini-incision	N/A	MIS (Berger procedure)	N/A	Small-incision
Hip implant	Metal-on-metal	Ceramic-on-ceramic with titanium rim	Ceramic-on-ceramic hip	Trabecular metal acetabular cups	N/A	Highly cross-linked poly
Key new items	Unicompart-mental knee	◊ T2 nailing system ◊ S2 stainless steel nailing system ◊ Trauma navigation	NA	Zimmer Institute	Symphony device and Healos	Oxinium hip just launched, Oxinium knee later this year

Following is a look at some specific companies:

BIOMET

Marketing. A Biomet official said, "What sets Biomet apart is service…We do ethical marketing." (This was an obvious dig at Zimmer.)

Metal-on-metal hip. A Biomet official said, "The unique advantage of our metal-on-metal hip is that it is self-polishing. Small scratches heal themselves with time." Asked about metal ion release, a doctor said, "There have been no sarcomas and no statistically significant increase in leukemia…They are indicated for patients with a life expectancy greater than 10 years and a high activity expectation, but probably not for a lifetime…Almost half my patients are under age 65, and almost all get metal-on-metal, so I do metal-on-metal in half my practice." Another doctor said, "Metal-on-metal are about 30%-40% of our hips now." Asked if metal-on-metal can compete with ceramic-on-ceramic, an official said, "I'm not aware of any metal femoral head that fractured, but ceramic has fractured."

Unicompartmental knee. A Biomet official said, "Our **u**nicompartmental knee has moderate consumer interest and high patient satisfaction in my hands…and I think this will be an important product line in select patients…this is a good pre-total knee option and lends itself to mini-techniques."

Navigation. Biomet's navigation system is the Z-kat system.

DMB. The company plans to introduce its own Ostestim DBM putty this year. This is already FDA-approved and will launch at the end of this quarter.

Electrical stimulation. "The outlook is for 7% growth in electrical stimulation (to $160 million). BMPs have had no impact on our electrical stimulation sales."

New spine products, including the SpF PLUS, Ionic inter-body spacer system, the EBI VuePASS Portal Access Surgical system (an MIS system), and EBI Acumen Surgical Navigation System.

JOHNSON & JOHNSON

This company was not studied for this report, but some positives came up, including:

- The Isola system for deformity, which got some rave reviews.
- Osteobiologics, where J&J was described by one source as a leader. The company reportedly is working on BMP-14, which may be as effective as BMP-2 or BMP-7.
- Regeneration research appears promising and could make the company a real leader in that area.

KINETIC CONCEPTS

KCI has a vacuum-assisted wound closure system to promote wound healing. A Zimmer official had high praise for this competitor, "KCI did something quite astonishing. This is a vacuum assisted wound closure process…run on a rental, not a sales, basis, and now they have grown from nowhere to the No. 3 player. Next year, we predict they will be No. 2. It is a dramatic product. It is a privately-owned company...with many products in patient services (such as specialized beds), and they use that to grow their wound technique. They are the fastest growing business in the marketplace, and we are No. 2…We (Zimmer) are pursuing different approaches to theirs...but both share one commons success factor – introduction of high tech treatments that are physician-selected and that are being accepted by reimbursement systems in the U.S. and the world…It is clear that Smith & Nephew and KCI will be the drivers of this market going forward."

SMITH & NEPHEW

Key 2002 launches included additional Oxinium knee lines, the Exogen 3000 bone healing device, Accuris uni knee instrumentation, Jet-X unilateral fixator platform for trauma, and the Achieve computer-assisted trauma software and instruments.

Outlook in knees is for:

- Continued rollout of Oxinium. An official said, "We are taking this to a different level – going with direct-to-customer and direct-to-consumer campaigns. We are going to get the word out in a considerably louder fashion."
- Launch of Oxinium Uni-Knee, which an official described as "the ultimate Uni knee for younger, active patients."
- Introduction of the Achieve CAS total knee application.
- Expansion of the mini-incision knee technique. An official said that 12 surgeons in the U.S. and Europe currently are doing this procedure.
- FastFix AB meniscal knee repair system expected to have 50% market share by the end of 2004.
- Introduction in 2Q03 of a biosorbable version of the company's meniscal knee.

In hips, the company just got approval and will launch this month its Oxinium femoral heads. An official said, "We expect this to account for 25% of sales in a year—and to carry a premium over ceramic."

On MIS, an official said, "We will train surgeons locally...The old model was to build a large center and fly people there to learn...but surgeons don't want to be out of the OR…so we want to build sites around the world for surgical training…The size of the skin incision is not so important. It is the lack of damage to muscles and tendons which gives real benefit…There clearly is a limit to how small you can get given the size of the implants.

An official outlined a three-pronged strategic approach:

1. Focused growth – divisionalization, sales for specialization, geographic market targets (U.S., Germany, Japan), speed of innovation, specialized service for customers.
2. Technology – active acquisition search underway.
3. Superior financials -- sales growth expected by company to outpace market.

STRYKER

Interesting comments from Stryker officials include:

- **Spine.** "I see a growing trend to posterior (spine) systems."

- **Ceramic-on-ceramic hips.** "We are not losing unit share (just dollars)…We probably lost a bit in hips…We built our strategy around ceramics, and the delay took a bit of the wind out of our sails, and we lost share, but I think it will come back strong with ceramics in 2003…Ceramics are key to our growth. We have patients lined up waiting for ceramic-on-ceramic (hip) inserts…This will be a massive launch in late March or early April."

- **MIS.** "I think we have a responsible position on less-invasive surgery. You will see us on the marketplace by the end of the year with less invasive knees."

- **Sales.** Asked what's driving the company's turnaround, an official said, "A handful of new products that are 'on the mark' and a greatly improved sales organization." Another commented, "The Pacific was the top performing division in 2002: 54% of sales were in Europe, 29% in Japan and 17% in the Pacific…In Europe, the U.K. has been strongest, and France has been a challenging market. We have a new French strategy. We are increasing our sales force there by 50%. We also purchased an Italian distributor in 2002, doubled the sales force (there)…and we are poised to attack the Italian market in 2003…and we consolidated distribution in Germany."

Planned product areas for 2003:

- Expand T2 nailing system – including reconstructive and proximal humerus nails).
- Launch S2 stainless steel nailing system – addressing more price sensitive markets, especially China, but also price conscious teaching institutions in the U.S.
- Gamma 3 – improving and innovating. (1 millionth nail will be implanted in 2003.).
- Lag Fix – a hydroxyapatite screw augmentation system that is expected to be a smaller, niche product for Japan, but it also could be a delivery vehicle for OP-1.
- Trauma navigation – to help with procedures in trauma and pelvic surgery.
- Titanium (foam metal) –evaluation of this will start in late 2003.
- Ceramic-on-ceramic hip implant. An official said, "We had hoped to have this two years ago, but there were issues at our manufacturing plant about quality, and the FDA wanted to hold them to a significantly higher standard. Finally, we met the FDA standards, and we now have approval for our second generation design…We also have a titanium sleeve which eliminates chipping, which was 3%-4% in our first generation product." Another official said the market opportunity for these is "100% of patients under 50 and discretionary up to age 65, but not over 65 because of Medicare reimbursement. Over 60% of total patients are Medicare patients, and we will not see a lot of usage in this age group. The target over the next couple of years is 15%-20% penetration."
- Trauma navigation – to help with procedures in trauma and pelvic surgery.
- Titanium (foam metal) –evaluation of this will start in late 2003.
- Modular revision hip system – probably will launch in 2Q03.
- GMRS – an oncology system to launch this year.
- Stryker knee navigation system -- second generation software.
- Stryker hip navigation program – to launch in 2Q03.
- Distribution agreement with RTI (Regeneration Technology) on allograft tissue for sports medicine

Among the company's hottest products in 2002 were: Accolade C and TMZF (which accounted for about 20% of total cementless hip stems); the premium-priced Scorpio Flex which did well in Japan and has now been introduced in U.S.; Eius UniKnee; the Xia upgraded screw; the Ray cage; the T2 nail, Matta Pelvic system, and Zoom stretcher.

ZIMMER

Among the areas on which Zimmer is focusing are minimally invasive surgery (*discussed above*), revisions, and trabecular metal. A Zimmer official said, "We were not seriously in revisions until recently…and especially not in hips…but it is an opportunity…Revisions are now 10%-13% of unit procedures and growing faster than primaries."

Some interesting points Zimmer officials made about the company's recon business:

- **Market share growth.** An official thought MIS could help Zimmer capture 30%-40% market share. "We have such a lousy economy that 10%-13% growth feels good…but that is irrelevant in the U.S…If you are not growing in the Americas at 16% or more in the recon business you are losing market share…We are confident that it will be a slam dunk in knees. Hips are harder. We are confident, but there is a more favorable mix factors in knees. I don't think our mix gains are any different than others. I am confident we are getting market share gains, but we are all benefiting from mix."

- **Sales terms.** "Our terms are 30 days. All sales reps work on straight commissions. We collect in 31 days in the U.S., compared to 80 days for Biomet and Stryker and 91-92 days for the industry, so we are much faster than the industry in collections."

- **Outpatient surgery.** "I think business will shift away from the big rehab business toward surgeons participating in outpatient clinics without hospitals…I think insurance companies and workers comp will love this stuff…but the rehab business won't like us." Even Zimmer sources noted that this cannot occur until and unless carriers (and CMS) issue new codes for outpatient hip surgery, and nearly everyone agreed that this is unlikely to occur in the next year or two. However, a California doctor said, "Payor pushback will come within the next five years."

One Surgeon's Perspective of Zimmer

Positives
1. Most advanced MIS hip and knee, with good outcomes data and possibly bone-preserving 2. Trabecular metal, which may be good for cages or pedicle screws in the future but is not strong enough to be a complete hip. 3. Hybrid hip is close to normal bone.
Negatives
1. MIS results only great with a few surgeons, significant learning curve and potential complications. 2. Cost of navigation will be an issue for low volume doctors.