Orthopaedic surgeons in the pocket of the industry

The development of new orthopaedic products depends on a close cooperation between orthopaedic surgeons and the industry. However, in recent years a number of cases of financial collusion between the industry and parts of the professional orthopaedic environment in the US have been exposed. This has highlighted the question of the extent to which orthopaedic-related research and development may have been influenced by inappropriate financial incentives.

Robin Holtedahl
robi-hol@online.no
Department of Physical Medicine and Rehabilitation
Buskerud Hospital
and
Doctor Holtedahl's specialist practice

Conflicts of interest arise when the orthopaedic surgeon, or the department in which she/he works, gains financial benefits by promoting or using a particular product. At its most extreme, this may involve receiving a fee for consultant assignments, sales commission for a product which she/he has helped to develop (royalties), and shares or options in the company. In recent years a number of examples of such financial ties have been revealed, first and foremost among orthopaedic surgeons in the US. While cooperation with the industry is of decisive importance for the development, clinical implementation and evaluation of orthopaedic implants, possible conflicts of interests in the case of cooperating orthopaedic surgeons can lead to a weakening of quality assurance at one or more levels. If so, there is a danger that this will lead to a greater risk of unfavourable treatment outcomes, also for Norwegian patients undergoing operations with these implants.

Is the result of the operation dependent on the funding source?

To the extent that orthopaedic implants are the object of clinical studies, these studies are typically small and with a short follow-up period. In contrast to studies of pharmaceutical products, randomized clinical studies constitute between 6 % and 21 % of all articles published in orthopaedic journals (1, 2). US orthopaedic research depends to a growing extent on private funding. 75 % of clinical studies of hip joint prostheses are financed by industry (3). The ratio between public and private funding of orthopaedic research changed from 73 : 27 in 1999 to 57 : 43 in 2002, and the proportion of industry-related conflicts of interest among American orthopaedic surgeons rose from 3 % in 1985 to 39 % in 2002 (4).

In randomized surgical studies commissioned by the industry, significant positive outcomes are reported eight times more frequently than in studies financed by the public sector (5). Articles dealing with spinal surgery in the journal *Spine* reported a corresponding odds ratio of 4.5 (6). The discrepancy was partly explained by a bias in the design of the study and interpretation of the results, as well as delay or lack of publication.

The differences are perhaps even greater in joint surgery studies. Ezzet found that 96 % of industry-financed studies reported a good result following hip alloplasty as against 41 % of studies without such funding, while a poor outcome was reported in 2 % and 59 %, respectively, of the studies (3). In knee joint prosthesis studies, there was a good outcome in 72 % and 18 %, respectively, of the studies, and an unsuccessful outcome in 16 % and 83 %, respectively, of the studies. Such differences were particularly pronounced in US studies, but the majority of the other studies showed the same tendency. There is much to indicate that surgical journals, particularly those that have a high impact factor, are reluctant to publish studies with negative or inconclusive results, with a resulting publication bias (2).

Bribes from the «big five»

In 2005, the US Department of Justice initiated an inquiry into the financial ties between orthopaedic surgeons and the five largest manufacturers of orthopaedic devices, together representing 90 % of the hip and knee prostheses produced in the US (Zimmer, Biomet, DePuy, Smith & Nephew and Stryker). The aim of the inquiry was to detect whether unlawful commissions (kickbacks) had been paid for orthopaedic operations covered by public health budgets (Medicare covers approximately two-thirds of the expenses of hip and knee prostheses in the US). Agreements were revealed between companies and a number of orthopaedic surgeons who had received substantial sums of money and gifts between 2002 and 2006 if they chose the products of these firms. It also emerged that orthopaedic surgeons often failed to inform both their employers and the patients they were treating about their financial interests (7). So as to avoid legal proceedings and further investigation, the five manufacturers reached a settlement with the district attorney in the autumn of 2007. They were fined altogether $310 million and were under surveillance by representatives of the federal health authorities for a trial period of 18 months. They also had to disclose all payments to cooperating orthopaedic surgeons. In March 2009, the Justice Department announced that the trial period was «successfully completed», and the criminal proceedings were dropped.

On the basis of the lists of payments made to doctors by the five companies who were ordered to disclose these, Chimonas et al. investigated the extent to which such payments were mentioned in published articles dealing with the products of these firms. Out of 41 orthopaedic surgeons who had received more than $1 million in the course of 2007, a total of 32 had published articles during 2008 (8). The extent to which conflicts of interest were stated in the 95 articles included varied considerably, but in 54 % of the articles the author had failed to provide information about financial remuneration. None of the journals reported the size of the contribution but one (*Journal of Joint and Bone Surgery*: seven articles) stated whether the amount exceeded $10,000. There was no correlation between the official guidelines of the journals regarding disclosure of conflicts of interest and the conflicts of interest actually stated. The first authors reported conflicts of interest more frequently than other authors (54 % versus 32 %).

Okike et al. (9) collated information about payments with the proportion of orthopaedic surgeons who gave details about financial remuneration in connection

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with presentations or participation on boards at the annual national meeting of American orthopaedic surgeons. Approximately 21 % of them failed to report payments for products that were directly linked to the presentation, correspondingly 50 % where the product was only indirectly associated.

Conflicts of interest in spinal surgery

Medtronic is one of the world's largest manufacturers of technical medical devices and the largest supplier of spinal implants. In 2006, two former employees informed the federal authorities about extensive covert financial contributions to a number of orthopaedic surgeons from and including 1998 with the aim of influencing them to use the firm's implants (10). The department found documentation of extensive financial irregularities, including fictitious, but well-paid consultant contracts that the company had entered into with a number of orthopaedic surgeons. Medtronic reached a settlement with the Justice Department in 2006 whereby the company was fined $40 million, although there was no admission on the part of the company that the payments had been in breach of the law.

Medtronic is the manufacturer of Infuse, a recombinant bone morphogenetic protein-2, which is used together with an implant (LT-cage) in lumbar single-level instrumented fusions. This substance converts connective tissue to bony tissue, so that the surgeon does not have to harvest bone from the illiac crest. The US Food and Drug Administration (FDA) approved the product in 2002 for use in anterior lumbar interbody fusions, on the basis of a random study (11). The article does not mention that the authors received royalties for other products made by the firm. Later it emerged that 25 % of the patients in the study had been operated upon by orthopaedic surgeons with financial ties to Medtronic. These reported a success rate of 80 % as against a 63 % success rate where the surgeon had no such ties (12).

In 2004, a further randomized multicentre trial on Infuse used as a supplement to the titanium cage was published (13). The study had to be abandoned prematurely because of a surprisingly high prevalence of post-operative bone formation intraspinally. Significant efficacy was found on only one of the defined end-points. Despite this, the technique was described as «promising». Lists released later by Medtronic show that three of the four authors received royalties of almost $4 million from the company for other Medtronic products (14). The FDA has later admitted that the agency knew of the conflicts of interest involving the orthopaedic surgeons in question prior to approval being granted, but so far it has failed to make the information public (12). Thirteen published industry-funded Infuse studies with altogether 780 patients did not report any complications, but a group of independent researchers who collected data from the same material from the FDA and others demonstrated a complication rate of up 50 % (15).

Lumbar disc prostheses

Lumbar disc prostheses were developed as an alternative to conventional fusion with the aim of retaining mobility at the operated disc level. One of these is the Prodisc prosthesis, which was implanted in the US for the first time by Jack E. Zigler of the Texas Back Institute in 2001. The following year he invested at least $25,000 in a subsidiary company that financed the product development of the prosthesis. Other cooperating orthopaedic surgeons also invested large sums of money in the company at the same time as they were implanting Prodisc prostheses (16). In 2003 the American Prodisc manufacturer was bought by the Swiss

company Synthes for $175 million with a pledge that the amount would be doubled if the FDA approved the prosthesis.

In 2001 Synthes initiated a randomized multi-centre study of the Prodisc prosthesis in which the Texas Back Institute together with 18 other orthopaedic centres participated. On the basis of preliminary data from the study, the FDA approved the prosthesis in 2006. In 2007 the study was published in the journal *Spine* (17). Investigations and later hearings held by the district attorney in New Jersey in 2009 revealed that approximately half of the orthopaedic surgeons who had participated in the study had investments in the company while the study was ongoing, and this had not been declared in the application for approval submitted to the FDA (18). In the settlement, Medtronic was ordered to publish all future payments to cooperating doctors and to refrain from distributing shares and options. The district attorney criticised the FDA for its failure to attempt to identify conflicts of interest prior to approval, and recommended that there be stricter control measures.

A man with several hats

One of the orthopaedic surgeons involved in the well-known Medtronic judgment of 2006 was Thomas Zdeblick of the University of Wisconsin. In 1998 he signed a 10-year contract with Medtronic to work as a consultant eight days a year in return for an annual fee of $400,000. The patients at the university clinic were not informed that he was receiving payment from the company (19). He reported to his employer that he had received between $20,000 and $40,000 annually from Medtronic. When Medtronic was ordered to submit lists of payments to doctors, it emerged that in the period 2003–2007, Zdeblick had received over $19 million in royalties in connection with Medtronic products, including the LT cage.

In 2002 Zdeblick became the editor-in-chief of the *Journal of Spinal Disorders and Techniques,* and according to the journal he still holds this position (20). The journal gives no information about the editor's links to Medtronic. During Zdeblick's editorial reign each issue of the journal has contained at least one article about Medtronic products (21). Two of the six articles which Zdeblick co-authored are about Infuse. Financial conflicts of interest are not declared in any of the articles.

A Pubmed author search for Thomas Zdeblick for the period from 1 January 2002 to 8 May 2011 shows that he has been the (co-) author of 16 articles in peer-reviewed journals. Althogether 13 of these describe Medtronic products (table 1). In six articles there was no mention of conflicts of interest in Zdeblick's case, and in one article such conflicts of interest were denied. In the remaining six, conflicts of interest were mentioned cryptically, with no information about specific amounts and little information about the kind of remuneration.

Will the balloon burst?

In this article I have cited a number of examples of lack of transparency and ethically dubious financial collusion in parts of the American orthopaedic environment and among manufacturers of orthopaedic devices. The choice and use of implants in clinical activities are to a large extent based on results produced by industry-funded research. We cannot necessarily take it for granted that such studies describe the qualities of the product or the procedure in an objective and unbiased manner. Even though it is difficult to document any direct connection between financial conflicts of interests and unfortunate treatment outcomes, confidence in the reliability of the product will decline if doubt can be shed on the integrity of the researcher or the surgeon. Such problems are exacerbated when the supervisory authorities are more interested in a swift approval process than a thorough evaluation.

Recently, constructive suggestions have been put forward for measures that are

Table 1 Articles in peer-reviewed journals where Thomas Zdeblick is the first or co-author about clinical trials in which Medtronic products have been used. The articles were identified through an author search in PubMed for the period from 1 January 2002 to 8 May 2011

Journal	Yr	First author	Product described	Medtronic product	Conflict of interests stated	Information about payment from Medtronic
J Spin Dis Tech	2002	Burkus	Yes	Rht-bmp2	No	–
J Spin Dis Tech	2003	Burkus	Yes	Infuse	No	–
J Spin Dis Tech	2005	Schuler	Yes	LT-cage	No	–
J Spin Dis Tech	2006	Ragab	Yes	Cervical plate	No	–
J Spin Dis Tech	2009	Jensen	Yes	Cervical plate	No	–
Eur Spine J	2005	Le Huec	Yes	Maverick disc prosthesis	No	–
Orthopedics	2004	Burkus	Yes	Rht-bmp2	Yes	Has financial interests in Medtronic
Spine	2003	Zdeblick	Yes	LT-cage, Infuse	Yes	One or more of the author(s) has/have received or will receive benefits, (e.g., royalties, stocks, stock options, decision making position) for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript.
J Bone Joint Surg Am	2009	Burkus	Yes	Rht-bmp2	Yes	In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of $10 000 from Medtronic
J Bone Joint Surg Am	2008	Riew	Yes	Prestige disc prosthesis	Yes	In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of $10 000 from Medtronic
J Neurosurg Spine	2007	Mummaneni	Yes	Prestige disc prosthesis	Yes	The authors have received or will receive benefits for personal and/or professional use from Medtronic in relation to products named in this article.
Orthop Clin N Am	2004	Burkus	Yes	Interfix cage	Yes	Two of the authors are consultants to Medtronic, and Dr Zdeblick receives royalties from Medtronic
Spine J	2004	Mathews	Yes	Maverick disc prosthesis	No	Nothing of value has been received from a commercial entity related to this research

regarded as absolutely essential to improve the reputation of the industry and the surgical community (22, 23). American orthopaedic surgeons have proposed that all orthopaedic products be taxed and that the surplus be deposited in a fund to support manufacturer-independent research. In 2008, the American Orthopaedic Association (AOA) established such an independent fund – OmeGA – and so far four manufacturers have contributed with funding (Zimmer, Smith & Nephew, Synthes and Integra). Keeping in mind the danger of publication bias, proposals have also been launched to require obligatory registration of all clinical trials with implants, in line with the procedure for pharmacological products (24).

The Physician Payment Sunshine Act was adopted by the American Congress in March 2010. The Act requires producers to report most types of payment to doctors. In addition, doctors' co-ownership in companies and financial support for product-related research must be reported. The authorities now demand annual reporting of payments to doctors in excess of $100 from and including March 2011. Federal legislation will require full disclosure of financial transfers to doctors and research institutions by 2013. The FDA is now in the process of tightening up approval procedures for medical technical devices. In the EEA, directives on the reporting of irregularities have also been reinforced and further quality assurance requirements were introduced from March 2010.

If manufacturer-independent research environments are successfully created, there is hope that this will generate trustworthy research results. This will in turn promote the quality assurance of orthopaedic implants.

Robin Holtedahl (born 1948)
Specialist in physical medicine and rehabilitation, and a practicing specialist.
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