

Conflict of Interest

Academics weigh in on the controversy.

BY GILLIAN McDERMOTT, EDITOR-IN-CHIEF

In an article published in late January's edition of *The Journal of the American Medical Association*, Brennan et al¹ delivered a stinging rebuke of what they view as industry's undue influence on medical care and research, and they proposed a multifaceted strategy for stringently regulating the interaction between academic medical centers and the healthcare industry. The article focused on academia—specifically, medical schools and affiliated hospitals—as leaders in US medical care through their role in both training and research.

Brennan et al stated that research in the social sciences has shown that even small gifts elicit reciprocity of some kind, and they asserted that disclosure (even if complete) is unverified and does not in itself eliminate a conflict of interest. In brief, the article's recommendations included but were not limited to the following:

- all gifts (eg, free meals, travel reimbursement) should be banned;
- pharmaceutical samples should not be given directly to doctors;
- industry should be able to support CME activities only by making contributions to a centralized body that disburses the funds;
- academics should neither serve on manufacturers' speakers' bureaus nor publish articles or editorials that are written by those companies' employees;
- any consulting agreements or speaking honoraria should be accompanied by a contract that specifies the "deliverables," which must be scientific rather than commercial in nature; and
- academic medical centers should accept general research grants only.

Brennan et al were by no means the first to voice objections to the influence of industry on medical practice and research, but their article sparked concerned discussions in the medical community and, possibly, action. In early May, the Hospital of the University of Pennsylvania in Philadelphia announced that it will

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begin requiring sales representatives to make appointments in order to see physicians, and the facility banned all gifts during office hours starting in July 2006.² Grants now must be unrestricted and given to chairs or department heads, who will determine how the funds are spent. A new Center for Evidence-Based Practice will be industry's main contact. The aim is reportedly to expand the program throughout the university health system.

In response to the growing din surrounding industry's role in medicine, *Glaucoma Today* asked several members of academic institutions in the US to assess conflict of interest in the field of glaucoma.

INDUSTRY AND ACADEMIC INSTITUTIONS

Evidence of corporate sponsorship is visible at academic medical centers nationwide. The manufacturers of pharmaceuticals and medical devices may support research, activities for residents, and courses and symposia. A major issue is one of financial constraint, as acknowledged by Eve J. Higginbotham, MD, formerly Professor and Chair of the Department of Ophthalmology and Visual Sciences at the University of Maryland School of Medicine and now Dean of the Morehouse School of Medicine in Atlanta.

"Given the current reimbursement levels in ophthalmology, marked declines in state and federal support for higher education, and the flattening of the NIH budget, it is unlikely that many institutions will be able to continue to conduct innovative research and build

robust educational programs without the support of industry," she commented.

Such is the case at the Medical College of Wisconsin in Milwaukee, according to Dale K. Heuer, MD, who is Professor and Chair of Ophthalmology. "Manufacturers support specific studies, some resident resources (eg, books and computer programs) and activities (eg, some journal clubs), and various CME courses and symposia for the department," he said. "We receive insufficient institutional support to even cover the time commitment of our Residency Program Director and other faculty involved in nonfaculty clinic supervision of the residents. Consequently, funds for the activities listed [earlier] would (and do) otherwise come primarily from faculty clinical practice dollars."

Robert J. Noecker, MD, MBA, Director of the Glaucoma Service and Associate Professor/Vice Chair at the Department of Ophthalmology at the University of Pittsburgh, echoed these remarks. "While we do have significant support from other sources, many smaller projects and activities would not occur without industry support," he acknowledged.

The question is whether such involvement gives industry too much influence at academic medical centers. Dr. Higginbotham commented, "These days industry's support is a welcome addition to the diverse portfolio of external support which is needed for academic activities. Whether or not that support translates into influence is largely dependent upon how the relationship is structured and the character of the individuals involved in the relationship."

L. Jay Katz, MD, is Co-Director of the Glaucoma Service at Wills Eye Hospital and Professor of Ophthalmology at Jefferson Medical College. Although industry provides support for educational activities at these institutions, Dr. Katz stated that steps have been taken to limit commercial influence. For example, visiting sponsored speakers in certain forums are asked to refrain from discussions that relate directly to the manufacturers' products. At ACCME-accredited activities at the university, the ground rules of the ACCME must be followed.

Dr. Heuer likewise has not considered industry's influence to be substantial at his college, but he noted, "To the extent that [the sponsorship] creates a passive acceptance of (or even an expectation of) such support, it can be problematic (particularly among the residents who may view the behavior of the department and/or individual faculty members as justification for being co-opted by industry themselves)."

Dr. Noecker has found that there is a fine line between accepting industry's support and compromising

an academic center's integrity and that of its staff and students. "[Companies] provide us an opportunity to participate in cutting-edge research and help to guide thought on future directions of ophthalmic therapy," he pointed out. "On the other hand, they can also affect balance in some educational activities, both at the resident and attending levels."

When asked about the picture at ophthalmology departments in the US overall, Dr. Noecker said, "I believe that industry, on the whole, in ophthalmology does not have an excessive role in the research being performed—although in a small field like ophthalmology, relationships do seem to influence the postmarketing research that comes out of some institutions, at least at a product [level]." He added that industry generally collaborates with individuals and institutions that hold similar research interests and that companies usually work with those with whom they have relationships. He did not think that these tendencies necessarily implied undue influence, however.

Similarly, Dr. Higginbotham stated, "Overall, the penetration of research funds from industry into academic departments is not significant. There may be three to five departments of the more than 100 academic departments which may be receiving significant industry funding (ie, more than \$50,000 per year). However, in most small departments like the University of Maryland, the funding was a mere fraction of these large amounts. In my opinion, funding from pharmaceutical companies appears to be shifting from academia into the private sector to some extent."

IS CONFLICT UNAVOIDABLE?

Many ophthalmologists and academic medical centers receive research grants from the manufacturers of drugs and medical devices. Does their involvement present an unavoidable and detrimental conflict of interest for the investigators? The answer seems to be that the relationship can but does not have to be problematic.

Dr. Noecker stipulated that the active management of studies is essential. Dr. Higginbotham expanded on this point to say that all academic medical centers have policies on conflict of interest but that their structure³ and implementation⁴ differ across institutions.

For his part, Dr. Heuer focused on who "owns" the data. "Much of industry-sponsored research represents a 'win-win' situation, in which the academic interests of faculty members are aligned with industry, such as in a study designed to elucidate the efficacy and safety of a new medication or treatment for our patients compared to another medication or treatment," he said. "To whatever extent only research funded by industry is

performed (by virtue of time, space, and other resource limitations), the cause of advancing our understanding (and thereby our potential to effectively treat) is compromised.”

Dr. Katz acknowledged that some feeling of indebtedness is inevitable among researchers who receive financial support, but he does not believe that such gratitude generally results in intellectual dishonesty or favoritism. The key, he said, may be for ophthalmologists to ensure that they or their institutions receive unrestricted grants from multiple sources in order to promote a sort of balance. “Placing all of the funds in a ‘general fund pool’ within institutional scrutiny and accountability also guards against favoritism,” he added.

OPHTHALMIC MEETINGS

When surgeons attend one of the various ophthalmic conferences held during the year, they are sure to notice manufacturers’ financial support of everything from the registration fees and speakers’ honoraria to a large number of receptions with wine and hors d’oeuvres. What impact do these expenditures have on academic ophthalmology? According to Dr. Katz, industry’s support helps to get information to doctors quickly. He noted that many practitioners use these meetings as a way to get up to date on the current thinking in the field and that general presentations—for example, on why it is important to examine the optic nerve or how to establish the goals of therapy based on clinical trials—are of real benefit.

To Dr. Noecker, manufacturers’ support of ophthalmic meetings is necessary, because physicians seem unwilling to face the alternative—paying more themselves. That reluctance can kill the efforts of medical centers to host their own events, however, noted Dr. Heuer.

“Academic departments are under considerable pressure to provide comparable no- or low-cost events,” he said. “That expectation, plus the surfeit of available CME offerings, makes it very difficult for academic departments to attract even their local ophthalmic community to their CME events.”

JUDGING A PRESENTATION

Are the presentations of consultants suspect? Not necessarily, said the physicians interviewed for this article. Many consulting ophthalmologists “maintain their intellectual independence and moral integrity,” according to Dr. Heuer. Moreover, Dr. Noecker pointed out that these speakers are often the most knowledgeable about the products on which they consult. When they extend their discussion to other products, however, he said that “the message can become skewed.”

Financial disclosures can help, but they are not always sufficient to reveal bias. Dr. Heuer commented that even stating the exact amount of money received would not necessarily demonstrate prejudice, because there is not always a correlation between bias and dollars. He nevertheless suggested the creation of a Web site on which all consulting relationships, including dollar amounts, are listed.

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According to Dr. Higginbotham, not every academic center meticulously monitors the “significant relationships” of its faculty. The bottom line, therefore, is that the audience must examine the results of a study critically. “The listener will never know how well the disclosed relationship has been managed by the institution,” she said. “Also, given the number of individuals who are involved in clinical research from the private sector, the listener has little recourse but to rely on his or her own analytical skills.”

Judging the independence of presented material can be difficult. The presentation of research funded by a single company merits scrutiny, Dr. Katz remarked. Unfortunately, he noted, sometimes the requirements for disclosure result in a laundry list of the presenter’s financial ties that obscures the fact that the study in question was funded by a single company. The most accurate assessments of presentations, he said, require listeners to pay attention to (1) the study’s design, including how subjects were recruited and what the investigators actually examined (eg, an IOP reduction from what baseline?) and (2) statistical analysis (eg, how the complications were weighted). A good sign is the inclusion of material that is not entirely favorable to the industry sponsor, remarked Dr. Katz, who thinks that blatant favoritism at the podium is the exception rather than the rule. Having other speakers or a moderator discuss the presentation and point out controversial issues is often helpful, he added.

GHOSTWRITING

Interestingly, the physicians disagreed somewhat in their views about ghostwriting. Dr. Higginbotham firmly stated that “scholarly writing should be undertaken by

ISTALOL® (timolol maleate ophthalmic solution) 0.5%

Brief Summary of Prescribing Information

Warnings

INDICATIONS AND USAGE

ISTALOL ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

ISTALOL is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Symptomatic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, ISTALOL should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (i.e., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma) or a history of bronchial asthma, in which ISTALOL is contraindicated (see CONTRAINDICATIONS), should, in general, not receive beta-blockers, including ISTALOL.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced prolonged severe hypotension during anesthesia. Difficulty in restoring and maintaining the heart rate has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetic Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients especially with latent diabetes who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyroidosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cardiovascular insufficiency if signs or symptoms suggesting reduced central blood flow develop following initiation of therapy with ISTALOL. Alternative therapy should be considered. There have been reports of tachycardia associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see PRECAUTIONS, Information for Patients).

Information for Patients

Corneal detachment after intraocular procedures has been reported with the administration of aqueous suppressant therapy (e.g., timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reduce the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. ISTALOL should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenges with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

(see PRECAUTIONS, General)

Patients should also be advised that if they have ocular surgery or develop an intermittent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidosage container.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product (see CONTRAINDICATIONS).

Patients should be advised that ISTALOL contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following ISTALOL administration.

Drug Interactions

Although ISTALOL used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with ISTALOL and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and ISTALOL should be observed for potential additive effects of beta blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the combination of beta-adrenergic blocking agents, such as ISTALOL, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension, in patients with impaired cardiac function, combination should be avoided.

Calciochannel-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving calciochannel-depleting drugs such as verapamil, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6. Caution: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine (see PRECAUTIONS, General, Anaphylaxis)

Pregnancy

Reproductive Effects — Pregnancy Category C. Teratogenicity studies with timolol in

mic, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose. In this case without apparent maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. ISTALOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from ISTALOL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon installation in 38% of patients treated with ISTALOL. Additional events reported with ISTALOL at a frequency of 4 to 13% include: blurred vision, catarrh, conjunctival edema, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE

Asthenia/tiredness and chest pain.

CARDIOVASCULAR

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

RESPIRATORY

Nausea, diarrhea, dyspnea, asthenia, and dry mouth.

IMMUNOLOGIC

Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC

Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN

Alpecia and pruritus/rash or exacerbation of psoriasis.

HYPERSENSITIVITY

Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash.

RESPIRATORY

Bronchospasm predominantly in patients with pre-existing bronchospastic disease, respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE

Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES

Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting, foreign body sensation, itching and tearing, and dry eyes); photic; decreased corneal sensitivity; cyclical corneal edema; visual disturbances including refractive changes and diplopia; pseudotumor/choroidal detachment following filtration surgery (see PRECAUTIONS, General); and keratitis.

UROGENITAL

Interperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with oral, timolol maleate or other oral beta blocking agents and may be considered potential effects of ophthalmic timolol maleate: ALLERGIC: Erythematous rash, hives, combined with itching and sore throat, laryngospasm with respiratory distress, BODY AS A WHOLE: Extremity pain, decreased exercise tolerance, weight loss; CARDIOVASCULAR: Worsening of arterial insufficiency, vasodilatation; DIGESTIVE: Gastrointestinal pain, hepatomegaly, vomiting, invertebral arterial thrombosis, ischemic colitis; HEMATOLOGIC: Neutrophilic leukocytosis, purpura, thrombocytopenic purpura, agranulocytosis; ENDOCRINE: Hypoglycemia, hypoparathyroidism; SKIN: Pruritus, skin infection, increased pigmentation, sweating; MUSCULOSKELETAL: Arthralgia; NERVOUS SYSTEM/PSYCHIATRIC: Vertigo, focal weakness, diminished concentration, irreversible mental depression progressing to catatonia, an acute irreversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometric tests; RESPIRATORY: Rales, bronchial obstruction; UROGENITAL: Urinary difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with ISTALOL ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see ALSO ADVERSE REACTIONS). An in vitro hemolysis study, using 0.5% timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSE AND ADMINISTRATION

ISTALOL ophthalmic solution is available in a concentration of 0.5 percent. The starting dose is one drop of 0.5 percent ISTALOL in the affected eye(s) once a day in the AM. If the patient's intraocular pressure is not at a satisfactory level on this regimen, concomitant therapy with other agents for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

(see PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents)

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Storage

Store at 15-25°C (59-77°F)

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References

1. Murdoch T, Ogawa T, Nakai H, Nishida G, Crockett R. A 12-month, multicenter, randomized, double-masked, parallel-group comparison of timolol-A once daily and timolol maleate ophthalmic solution twice daily in the treatment of adults with glaucoma or ocular hypertension. Clin Ther. 2004;26(4):541-551.
2. Higashiyama M, Inada K, Ohtori A, Tojo K. Improvement of the ocular bioavailability of timolol by sorbic acid. Int J Pharm. 2004;272(1-2):91-96.



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the clinician scientists involved in the study using raw data." In contrast, Dr. Noecker noted that there are strict criteria for authorship and that a ghostwritten first draft can save a lot of time. In such cases, he stated, the authors are responsible for rigorous editing and review, however.

Dr. Heuer also stipulated that the lead author is responsible for an article's content, no matter how much of it is ghostwritten. "Peer-reviewed journals should require [the] disclosure of 'editorial assistance' in manuscript preparation, including by whom any such assistance was paid," he said. "Editorial assistance can be helpful with respect to the timely dissemination of new information; however, all listed authors should personally review the primary data themselves rather than relying on a sponsor's data digest and should draw their own conclusions of the data's implications and limitations, which must be reflected in the final manuscript."

The option of ghostwriting can be seriously abused, asserted Dr. Katz, who cited the example of a multicenter trial of a pharmaceutical agent. "If it's a large study, it's very tempting to have a ghostwriter write the paper to save time and effort," he said. "On the other hand, ... [ghostwriters] working for industry are going to have a serious bias. That can be dangerous."

Although Dr. Katz does not oppose researchers' getting help with aspects of a report, he specified that they should firmly understand all aspects of the study and what should be in the article. He emphasized that the lead author should control the piece's content and should have access to all of the data. On a personal level, Dr. Katz noted, "physicians should decline to participate in an uncomfortable situation or ask that their names be removed from a paper that they feel is biased."

HOW TO PROCEED

Institutionally, Dr. Higginbotham proposed a five-step approach. First, a faculty committee and university officials should annually review the conflict-of-interest policy to certify that it is clearly presented, complies with federal and state regulations, and is accessible to the faculty. Second, a conflict-of-interest committee for the school of medicine should be established, the members of which are involved in human-subjects research and have experience with industry. Third, faculty should annually disclose their activity and involvement with industry, and the chairs should summarize these statements in their annual reports to the dean. Fourth, the institutional review committee should periodically audit randomly selected investigators to ensure that the reports to the dean are accurate. Fifth, institutions within the same system of medical schools should standardize their conflict-of-interest process across campuses.

Within the field of glaucoma, Dr. Noecker recommended limiting industry's role in determining the content of educational activities. Dr. Higginbotham suggested that the glaucoma community hold a roundtable discussion to "develop its own policies to ensure that the integrity of clinical research is maintained regardless of whether or not the research is conducted in either academia or the private sector."

Eliminating manufacturers' involvement in research and education would be neither reasonable nor possible, according to Dr. Heuer, however. He commented that capitalizing on industry's resources is appropriate in so far as its aims coincide with physicians' interests on behalf of their patients. "Given the incestuous current relationship between academia (and our professional organizations) and industry, the extreme/purist approaches will undoubtedly be met with an anaphylactic reaction," he said. "Until all physicians are willing to underwrite a larger portion of their own CME and annual association meeting expenses (admittedly difficult in the current environment of decreasing reimbursements), achieving even incremental changes toward the ideal will be difficult."

Dr. Katz noted that increasing criticism from respected leaders might cause "a swing of the pendulum to an extreme level by governing bodies at individual institutions." He cited recent steps at the Yale School of Medicine to reduce conflict of interest, legal exposure, and the dissemination of biased information.⁵ "In contrast to four existing national guidelines concerning doctors and industry (AMA's Code of Medical Ethics, ACP-ASIM [Center for Ethics and Professionalism], Office of Inspector General, and PhRMA [Pharmaceutical Research and Manufacturers of America] Code⁶), they

suggest banning faculty from receiving any gifts or free drug samples for personal use." Dr. Katz felt that such measures might quickly spread to other universities. He said, therefore, that "physicians should be prepared to have a meaningful, well-prepared discussion on [the] incorporation of ethical and practical considerations in establishing acceptable guidelines for the complex relationship between physicians and industry."

CONCLUSION

How academic medical centers and researchers will react to the spotlight on their interaction with industry remains to be seen. The stricter rules enacted at the Hospital of the University of Pennsylvania may be a clue to the future. Another unknown is how the manufacturers of pharmaceuticals and medical devices will respond if their access to physicians and residents is greatly limited. □

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1. Brennan TA, Rothman DJ, Blank L, et al. Health industry practices that create conflicts of interest. A policy proposal for academic medical centers. *JAMA*. 2006;295:429-433.

2. Fallik D. Penn bans gifts from drug reps. *The Philadelphia Inquirer*. May 3, 2006. Available at: <http://www.philly.com/mld/inquirer/2/14485248.htm%20>. Accessed May 8, 2006.

3. Lo B, Wolf LE, Berkeley A. Conflict-of-interest policies for investigators in clinical trials. *N Engl J Med*. 2000;343:1616-1620.

4. Boyd EA, Cho MK, Bero LA. Financial conflict-of-interest policies in clinical research: issues for clinical investigators. *Acad Med*. 2003;78:769-774.

5. Coleman DL, Kazdin AE, Miller LA, et al. Guidelines for interactions between clinical faculty and the pharmaceutical industry: one medical school's approach. *Acad Med*. 2006;81:154-160.

6. The Pharmaceutical Research and Manufacturers of America. Code on interactions with healthcare professionals. Available at: http://www.phrma.org/code_on_interactions_with_healthcare_professionals. Accessed May 8, 2006.

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