EDITORIAL

Potential problems with industry-supported clinical research

Robert B. Rutherford and K. Wayne Johnston, *Silverthorne, Colo, and Toronto, Ontario*

Device manufacturers and pharmaceutical companies are a significant source of research funding for clinicians in all specialties. Industry-clinician relationships may provide important professional and financial opportunities, but they may also jeopardize not only the investigators' scientific integrity, but also their primary responsibility to patient rights and safety.

In this editorial, we review some important issues raised by industry-supported clinical research, including the control by industry of the clinical trial and the data; discuss problems that may arise in the relationship between clinicians and industry; illustrate some of the dilemmas with some recent examples; and make suggestions that may avert potential problems. Our suggestions appear in italic type.

Most young clinicians consider themselves fortunate when they obtain funding from industry to carry out research to support their academic development. They recognize that such corporate-funded clinical research is generally less demanding than peer-reviewed funding because the company usually supplies the research protocols, prototype institutional review board (IRB) applications, and patient consent forms. Funding allows the investigator to hire research associates to collect and report the patient data. In many multicenter trials, the company analyzes the data centrally. Despite these and other advantages from industry-supported research, there are also some risks, and not all are obvious to the potential investigator—particularly, the control of scientific data by the industry sponsor.

In a research study, both the investigator and the company share the objective that the new technology (typically a device or drug) will significantly improve our ability to diagnose disease or treat patients. Both hope and expect that the joint venture will reflect well on themselves and their institutions. However, the company and the investigator have additional, but differing, objectives in the same research project, and these may come into conflict.

In funding the research, the company also has the underlying objective to maintain or increase profit for shareholders and employees. In return for their investment in a research project, the company can reasonably expect protection of its commercially valuable intellectual property, and, not unsurprisingly, contractual agreements will reflect this. Because profit will, in part, depend on a short time-to-market, the company will be eager to obtain regulatory approval and publish positive results as quickly as possible. The investigator may be concerned that steps in the usual scientific process are being circumvented.

Physicians have a primary duty to ensure ethical patient care and patient safety.[1] While performing research, their primary goal should be the acquisition of knowledge for the general good of patients. *In pursuing these particular goals, the researcher must have ready access to the data, verify the results and their analysis, and report those results in a timely and accurate fashion*. The company also has responsibilities in regard to patient safety, but in the analysis and reporting of results, a conflict with the company's financial, marketing, and proprietary interests may arise.

From the University of Colorado School of Medicine and Toronto General Hospital and the University of Toronto.

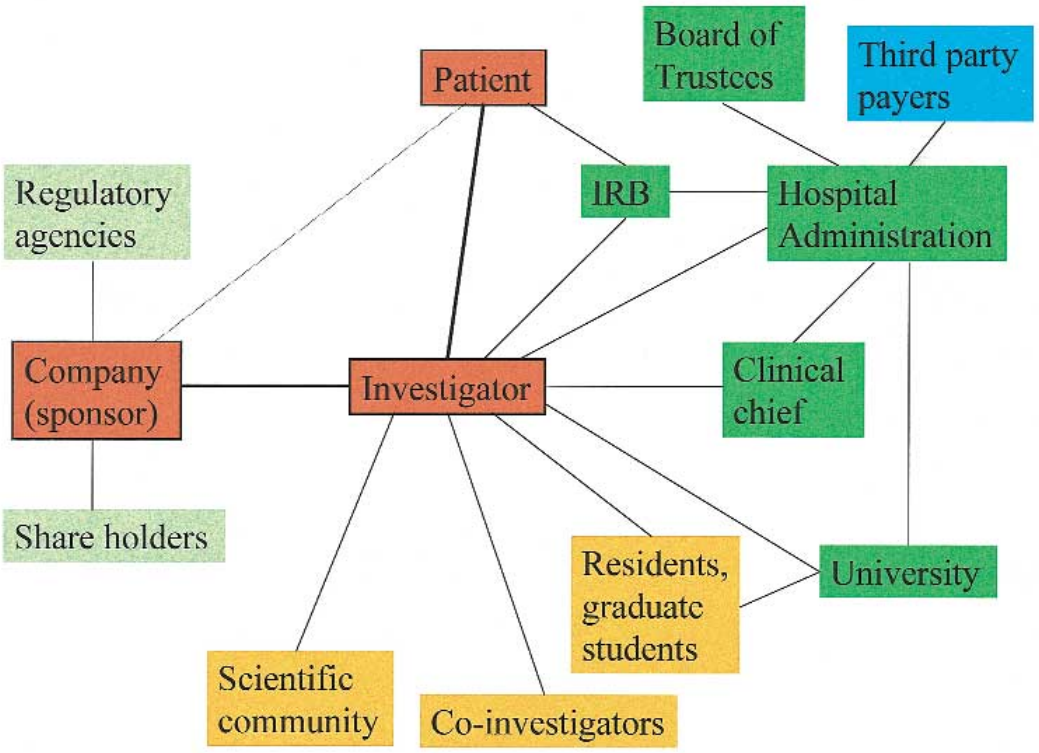
Competition of interest: currently none. Recent past: co-chair of a transatlantic intersocietal consensus on peripheral arterial occlusive disease (TASC) supported by an unrestricted educational grant from Schering AG, Berlin, Co-principal investigator of a completed trial of oral Iloprost in chronic critical limb ischemia, supported by Berlex, consultant on the design of clinical trials of the evaluation of thrombolytic agents (Abbott, Amigen); PI and member of the Scientific Advisory Board of EVT during the phase I trials (R.B.R.).

Competition of interest: nil (K.W.J.).

Reprint requests: Dr K. Wayne Johnston, Editorial Office, Toronto General Hospital, 5 Eaton Room 312, 200 Elizabeth St, Toronto, Ontario, M5G 2C4, Canada.

J Vasc Surg 2000;31:1066-76.

0741-5214/2000/$12.00 + 0 24/39/106031
doi:10.1067/mva.2000.106031



Complex interactions in relationship between industry and an investigator.

Although a research agreement between a company and an individual investigator may appear straightforward, it is nevertheless part of a complex interaction that also involves patients, IRBs, coinvestigators, the university, the clinical division / department chiefs, the hospital administration, the scientific community, and the regulatory body to which the company is responsible (Figure). With submission of the results of a trial for publication, this interaction also involves scientific journals, their editors and reviewers, and finally, the readers.

Consideration of patient rights and safety is dominant. Approval of the contract between a company and an individual investigator requires adherence to the policies of the hospital and university and their approval of the content of the contract. The institution will want assurance that the investigator does not enter into a contract that raises a significant conflict of interest or conflict of commitment with the investigator's hospital or university activities. The IRB must approve the ethics of the study and monitor it. *During the study, the investigator should reassure the IRB, the clinical division/department chief, and the hospital administration and university of the continued safety of the study.* This requires reassurance by an independent data-monitoring committee that the results support the continuation of the study. However, problems may arise if the data-monitoring committee is inappropriately constituted and ineffective or if the company analyzes the data and determines what is released to the investigators.

POTENTIAL PROBLEMS

The following discussion presents some of the problems that may arise in corporate-sponsored clinical investigations. It is organized in order of the chronology of events that occur during the course of a study, not in order of perceived importance.

Financial conflict of interest

After publication of the first study of the efficacy of tissue-type plasminogen activator, it was reported that several of the investigators owned stock in the sponsoring company.[2] Concerning this, the following is recommended by the American Medical Association: "in order to avoid criticism that the decisions an investigator makes during the study might have been biased by financial conflict of interest and the concern that the validity of the scientific data may have been jeopardized, the investigator should not hold stock or stock options in the spon-

soring company or be an officer of the company."[3] Investments in mutual funds that are managed by others may be overlooked, but all known holdings in the company, including those by close family members or practice partners, should be declared to alert the readers of potential competition of interest.

Although the above recommendation warns against stockholding by the investigator, a company may offer stock after completion of the research, in recognition of contributions to the development or testing of a device or drug. This is not wrong, as long as it is not by prior tacit agreement, but failure to disclose this when research is presented or published is inappropriate and has led to increasing public criticism, as exemplified by the recent media coverage of the Heart Port device and coronary stents.[4,5]

Nondisclosure agreements

Nondisclosure agreements protect the company against the investigators divulging proprietary information and thereby devaluing the product. Investigators appreciate the need of the company to protect proprietary information, but they may not fully comprehend the legal verbiage or the legal implications in the nondisclosure agreements that they are asked to sign. Such agreements are usually drawn up by the company's lawyers to protect their client's proprietary interests, and only occasionally are the investigators' rights addressed as well. In addition, the agreement may not give the consultant or the investigator appropriate credit or reward for innovative ideas or constructive advice, which may have significantly improved the ultimate design of a device or determined the success of a trial.

The research contract

The contract to perform a research study in collaboration with industry may be complex. Few investigators ask a lawyer to review the contract the company asks them to sign. They do not want to appear to be looking a gift horse in the mouth; however, knowing that it may be a one-sided agreement, *one should read over all contracts and pay particular attention to certain details (eg, be sure that the investigator has access to the data and that the right to publish important aspects [with co-investigators] is not inappropriately restricted by the agreement). Clauses in the contract dealing with publication rights, confidentiality, intellectual property, access to data, and conflict resolution, in particular, should be carefully reviewed by the institution as well as by the investigator, to ensure patient safety through prompt access to data and to guard the scientific freedom of the investigator.*

The Olivieri case at the Hospital for Sick Children in Toronto illustrates the complexity of this problem. The following paragraph was included in the contract of a drug study[6]:

> Contract provides that all information whether written or not, obtained or generated by you during the term of the LA-02 Contract and for a period of three years hereafter, shall be and remain secret and confidential and shall not be disclosed in any manner to any third party except with the prior written consent of Apotex. Please be aware that Apotex will take all possible steps to ensure that these obligations of confidentiality are met and will vigorously pursue all legal remedies in the event that there is any breach of these obligations.
>
> —Excerpt from a letter dated May 24, 1996, from Dr Michael Spino, vice president of Scientific Affairs, Apotex Research Inc, to Dr Nancy Olivieri.

During the study of the drug deferiprone for the treatment of iron overload in patients with thalassemia major, Dr Olivieri became concerned that the drug lost effectiveness with long-term use and suspected that it might worsen hepatic fibrosis. When these safety concerns were reported to the hospital's research ethics board, she was instructed to change the wording of the informed consent. When informed of the change, Apotex terminated the drug trial in Toronto. When it was determined that the data of others reflected similar observations, Dr Olivieri and her colleagues, in the face of threatened legal action from Apotex, published the controversial findings in the *New England Journal of Medicine*.[7] Although not a vascular example, this study is cited because it raised important issues within the scientific community related to contracts with companies that are signed by an individual researcher, and the researcher's hospital research institute, hospital administration, hospital institution review boards, and university. It also illustrates the importance of institutional policies and procedures that define the responsibilities for scrutinizing a contract.

Ideally, individual researchers should seek expert advice before making a commitment that may be inappropriate. *It would be of great help if societies collaborated to obtain legal advice in drawing up a generic confidentiality document and contract. In doing so, it would be valuable to identify the items that should be included in research contracts—items that would be viewed as fair and standard practice and would protect*

the rights of scientific investigators, patients, and institutions, as well as the sponsoring company. In particular, it is important to define the right to have access to data and present and publish the data in a timely fashion, regardless of the results of the study.

An exemplary relationship between industry and investigators is illustrated in a recent publication on the economic analysis of low-dose heparin versus the low-molecular-weight heparin enoxaparin.[8] Under the heading of "funding" the following statement was made:

> Unrestricted funding for this analysis was provided in part by Rhone-Poulenc-Rorer (Quebec, Quebec), the manufacturer of enoxaparin. The terms of the contract with the company were determined at the outset after we proposed the study design and methods, including measurement, modeling, and analytical strategies. We retained the rights to control entirely the methods and conclusions throughout the study and to publish or otherwise disseminate the results of the study and their conclusions regardless of outcome. The company received a copy of the report and manuscript before publication but was specifically precluded from influencing us at any stage after the contract was signed.

As will be seen below, the ability of investigators to make statements such as this, according to their research contract, is far too uncommon.

Addressing these issues at the outset and having them addressed in the contract in a manner that is fair to both the company and the investigator can avert significant problems later.

Development of research protocols

In carrying out a clinical trial, the investigator has the ethical responsibility to ensure that the design and execution of the study protect the patient's rights. The investigator has a responsibility as a scientist to see that it is properly designed so as to produce meaningful data to answer the question posed by the trial. Having a research protocol already drawn up by the sponsoring company is convenient and can serve as a useful starting place for discussions between the sponsor and the potential collaborating investigators; however, *investigators should not simply accept the drafted protocol. They should take an active role in improving the design of the trial.*

Conflicts may arise if the investigator recommends changes in the company's original protocol (eg, because it lacks objective enough end points, has too favorable exclusion and inclusion criteria, lacks appropriate controls or uses comparison with historical controls, does not account for treatment crossovers or does not analyze their impact on outcome judged solely on an intent to treat basis, has too short a follow up, or fails to include a cost analysis and quality-of-life assessment). The investigator should oppose any aspects of the trial that might hinder determination of conclusive and meaningful results, or might produce results that can be generalized or will be accepted by one's peers.

Conflict may also arise because the company's underlying goal may only be to prove "safety and efficacy" in the broadest terms and take the quickest route to gaining regulatory approval, rather than to compare the treatment with current competitive approaches. Depending on whether their background is primarily in marketing or in research and development, those responsible for the company's sponsorship of a clinical trial may be more comfortable with simply achieving recognition of safety and efficacy than with attempting a comparison with an alternative treatment. Once approved by the regulatory agencies, marketing strategies rather than risking scientific comparisons may be used to pursue advantages over competitive treatments. *The investigator should take the responsibility to help ensure proper stratification, comparable study groups, accurate power estimates, definitions of what constitutes a reportable complication, and gathering and analyzing the data in a format that is compatible with standardized reporting practices.* Even though some companies hire experienced trialists as consultants, investigators involved in the study are more likely to have detailed knowledge of the key clinical issues involved.

Comparative groups: inclusion and exclusion criteria. The outcome of a trial and its generalizability are greatly influenced by the inclusion and exclusion criteria. In the early studies of endografts designed for abdominal aortic aneurysm (AAA) repair, inclusion of only cases with favorable anatomy is a cautious approach and furthers one of the company's goals of demonstrating safety and successful deployment, but the results cannot be generalized to most patient with an AAA. Liberal inclusion criteria can have the same effect; examples include trials of laser and atherectomy devices, and stent studies that included patients with lesions that would have yielded good results with PTA alone, and trials of endografts for occlusive lesions for which good results have been established for PTA and stenting. *After initial studies that demonstrate safety, each new advance in technology (and cost) should be tried on the marginal lesions that the simpler technology cannot satisfactorily address.*

Blinding and randomization. Blinding and randomization in prospective trials are obviously desirable but not always possible. Blinding is not feasible when the compared treatments are perceptibly different; unfortunately, this opens the door not only to investigator bias, but also to patient bias. In some of the AAA endograft trials, patients randomized to surgery backed out and went to another participating institution for another roll of the dice. Randomization may also present a problem if the individual investigator concludes that one treatment is clearly preferable. This raises the question, should that individual participate in the trial or continue entering patients? Freedman[9] addressed this ethical challenge in clinical research by suggesting that clinical equipoise (ie, uncertainty) exists if the informed professional group (not an individual) has not reached a consensus and that it is ethical for the individual to enter patients into a trial that will give a definite answer to the question at hand. Recent debates over clinical trials on carotid angioplasty have repeatedly raised the issue of clinical equipoise.[10,11]

It is important that the mechanism for randomization be predefined and independent of investigator and sponsor input. Further, validation of the suitability of the patient for inclusion in the trial must be efficient, and not too complex or time-consuming, so that the process does not interfere with recruiting a broad spectrum of cases. In trials of thrombolytic agents for acute arterial occlusion, those with acute limb-threatening ischemia were grossly underrepresented, in part because of the complexity of the study design and the time consumed by the randomization process.[12] Another contributor to this was a natural selection bias in the group with acute ischemia because the treating physician could exclude a patient from randomization if the physician thought that patient safety was at risk.

End points. The choice of end points of a trial is critical. What end point constitutes evidence of efficacy of treatment? Under what conditions will the trial be stopped? Some end points are desirable but unrealistic. In pharmacotherapy trials for critical limb ischemia, the Food and Drug Administration (FDA) has insisted that the primary end points include salvaging limbs and saving lives rather than using the useful and potentially achievable clinical goals of relieving rest pain and healing ischemic ulcers. This may have resulted in falsely negative studies. Similarly, in the case of the thrombolytic trials, restoring graft or artery patency for a reasonable period would be a more realistic end point, considering that the treatment of the underlying lesions, not the method of clot removal, determines long-term outcome. This too has contributed to negative results of trials.

Combining end points may add strength to the statistical analysis, decrease the number of cases required, and save costs, but this approach may reduce the generalizability. In the STILE trial,[12] four clinical end points were combined into one clinical outcome, resulting in the premature stopping of the trial when two less important end points, major morbidity and ongoing ischemia, created a statistically significant difference in combined clinical outcome in favor of surgery, at a time when the more important end points of mortality and amputation were not significantly different. Again, the result was a negative trial for the tested therapy.

The appropriate selection of objective end points is essential but does not solve the problem of a trial that does not have a proper comparative control group. This is particularly true of treatments for severe limb ischemia, because patients may improve spontaneously with time rather than as the result of treatment (eg, sympathectomy, use of hyperbaric oxygen, spinal cord stimulation, and, up until now, VEGF).

Cost considerations

It is reasonable for a sponsoring company to aim to obtain scientifically valid data to support regulatory approval and the introduction of their product into the medical market place and to expect the study to be carried out in a time-efficient manner and at reasonable cost. The investigator and the host institution can reasonably expect fair compensation for their participation. Attempts to limit the expenditure on a clinical study may compromise the quality of the data. *In discussions with company representatives over the design of a research trial protocol, one should be wary if the company is unwilling to modify the protocol (eg, the number of patients recruited or the duration of follow-up) because of cost considerations.* This is a warning sign that you may be dealing with a company whose resources are too limited to support a proper study or one that places its financial interests above scientific investigation.

In being reimbursed for running a clinical trial, the investigator faces a potential conflict of interest—specifically, the conflict between (1) ensuring that the individual patient's rights to receive the most appropriate medical care are guaranteed and (2) the investigator's self-interest in obtaining reimbursement for entering patients into the study and

other benefits that might accrue to the investigator from participating in the study.[13] Clinicians should expect to be reimbursed fairly for their time spent managing the patients and the project, the salaries of study coordinators and fellows, and the overhead and miscellaneous expenses. The American Medical Association recommends that remuneration of the investigator should be commensurate with the efforts and that funds should be administered by the institution that pays the direct and indirect costs. However, it seems reasonable that unforeseen "profit" could be used to assist funding other research or educational programs or trainees. Most institutions have mechanisms to prevent faculty from personally receiving the excess money generated from a research study; however, policies on the use of the profit for academic purposes are often vague. *The IRB should be informed of funding agreements, and it should be disclosed whether the investigator has any other relationship with the sponsoring company, such as stockholder, corporate officer, or paid consultant.* However, disclosure alone is not a remedy; IRBs need to develop recommendations for understanding and managing the conflict so that patients' rights are protected.

Institutional Review Board approval

The IRB must ensure that the study design is scientifically valid; approve the ethics of the study to ensure that patients are properly enlisted, receive appropriate informed consent, have a low risk-benefit ratio if enrolled in the study, and are not subjected to unnecessary procedures; and be sure that the financial arrangements are appropriate. In addition, the IRB should be in a position to monitor the study as it progresses. *To safeguard patient care, the investigator must have reports from the data-monitoring committee to be able to communicate the results of the safety of continuing the study to the IRB on a regular basis.* To fulfill its obligations, the IRB must be independent of the sponsor, investigator, and institution.

Data collection, analysis, and control of data: data monitoring committee

If the company controls the data *and* does not provide frequent reports, including complications, the investigators may not be able to fulfill their ethical and moral obligation to the patients and their responsibilities to the IRB and institutions. Interim evaluation of the data is important to detect unexpected complication, low accrual rates, protocol violations, incomplete follow-up, and other problems to ensure safety (because analysis of a clinical trial is a dynamic process). *An appropriately constituted data-monitoring committee is the optimum method to protect the patients' interests by disclosing unexpected complications, ensuring that there are no serious methodologic deficiencies that would prevent the study from meeting the scientific objectives, and determining whether the end point of the study, be it positive or negative, has been reached. Explicit "stopping rules" should be defined.* The committee should include experienced investigators, statisticians, and company representatives. Expert statistical advice is necessary because false conclusions may be drawn from an apparent statistically significant difference early in the study, when the number of patients entered is low.

On occasion, "leaks" of results have changed the investigators' pattern of recruiting or excluding subjects for a trial and consequently affected the final outcome. For this problem to be prevented until the study is complete or stopped, the end point results must be available to the data-monitoring committee but not to the individual investigators.

Data analysis. Unfortunately, it has become increasingly apparent that some presenters and primary authors of manuscripts at our national and regional meetings have reviewed only the summarized analysis of the data that was supplied by the company. They have not reviewed the raw data or performed or checked the statistical analyses and cannot supply the additional information requested by discussants or reviewers.

For proprietary reasons, device manufacturers and pharmaceutical companies rarely release the results of their own "in-house" research; there is also a perception that they may be selective about the data from clinical studies that they choose to release to their clinical investigators to make public. Although the company and its consultants are not likely to try to hide unfavorable data, by not releasing all the data to the investigators for analysis, there is the risk that significant relationships in the data set are not analyzed. *Thus, the use of summary data provided by company officials can lead to problems.*

There are many examples of the control of trial data by industry. The often-quoted European randomized prospective trial in which the benefit of primary stenting, with Palmaz stent, was compared with iliac percutaneous transluminal balloon angioplasty (PTA) alone, completed many years ago, is one example. The results, claiming statistically significant advantages for primary stenting in both "clinical success" and secondary patency at 5 years, were presented at several meetings and in abstract form in 1993,[14] but the study has not yet been pub-

lished as a peer-reviewed article. It is regrettable that the principal authors and the company have not persisted in achieving publication by providing the necessary data to satisfy peer review. Approval by the FDA has been obtained for this indication, and it is presumed that this study was among the data presented. With regulatory approval and marketing success achieved, the scientific aim of the study seems to have taken a backseat.

Recently, summary data were the sole basis for two abstracts submitted to major vascular societies. This is a risky but not uncommon practice. One paper had to be withdrawn from the 1998 American Venous Forum meeting because the company that sponsored the study did not reply to repeated requests to supply the necessary background information (the denominators) to put the study's findings in proper perspective in sufficient time to allow presentation.[15] When the actual data were ultimately obtained, they did not match the summary data originally submitted to the investigators for preparation of the abstract. In presenting and publishing a recent analysis of the cost-effectiveness of an aortic endograft device,[16] the authors were accused of not having data to support their direct cost analysis. Although an inquiry subsequently demonstrated that a company consultant had raw data from most of the individual centers and had supplied the authors with summary data on which to base their projections, nonetheless, they were vulnerable to the criticism of using summarized data rather than analyzing the raw data themselves.

Finally when the results of a trial depend significantly on the interpretation of diagnostic studies, arrangements should be made for these studies to be independently interpreted by blinded individuals (eg, those in a core laboratory who have no vested interest in the outcome and are independent of company or investigator interference).

Interim data release. With nonrandomized studies of new devices, preliminary interval reports of the progress of the trial are possible and may even be desirable. Unfortunately, many of the early reports contain soft data and are often presented with enthusiastic bias. At the beginning of such a study, during the active patient-recruitment phase, results can often be obtained from investigators' meetings, and the participants may be allowed (if not encouraged) to present the data at meetings and symposia. In the case of the evaluation of the Endovascular Technologies (EVT) device, restrictions were subsequently placed on the presentation of data released at investigators' meetings. It was announced that, because of the need for compliance with "inside trader rules" when the company "went public," official data updates would only be released by the company. Such data disclosures took the form of periodic press releases, seemingly intended more for investors than for clinical investigators. A more appropriate reason for a company not releasing data during the course of a trial is the desire to avoid having to retract impressions from preliminary analyses, and rather wait for full analysis on completion of one of the phases of the trial. This has been the explanation given for the Gore Excluder Trial. Other companies have been willing to release their device data from the Eurostar registry, but increasingly companies are wary of releasing interim data from ongoing FDA trials and will generally designate one of the principal investigators to present updates at well-intended vascular symposia. Such updates of data are rarely critical and often present summarized data supplied by the company. This deprives the vascular surgical community, who mostly attend a limited number of meetings, of objective updates of trials that could help in patient management decisions (eg, open AAA repair vs referral to an endograft trial and, if so, which one). This dilemma could be avoided because *in a properly constructed prospective device evaluation, the data are collected in a way that will be suitable for submission to the FDA and for publication; consequently, there is no reason why interim data releases, such as presentations at symposia, should not contain objective data and be reported by using standard reporting practices. The details of the device and its use are proprietary; objective data from a clinical trial into which patients are still being actually recruited should not be.* One of the main reasons for regular objective and complete disclosure of the outcomes of new devices is the need to assess the failure rate and complications, particularly significant adverse events. Even periodic investigators' meetings may not fulfill this need when the data are prepared and presented by company officials or the investigators are instructed not to disseminate the information.

Presentation and publication of data

Adverse events. Significant delays may occur between the initial discovery of device-specific problems and their eventual dissemination at meetings or in published reports. *Reports of serious complications should be circulated immediately by the company to all investigators, who then have a responsibility to notify their patients, institution, and the IRB.* In a recent editorial, one of the authors of this editorial[17] emphasized the importance of promptly disseminating information if a problem is noted that potential-

ly reflects on the design or deployment of the device. When hook fractures occurred with the EVT device, the problem was quickly disclosed.[18] However, when fabrication flaws were detected in another commonly used device, the Min Tec Stentor graft, it was some time before there was public acknowledgment at meetings or in publications,[19] although one heard of "disappearing (breaking) sutures" from discussions at investigators' meetings. In an analysis of the Eurostar data[20] it was reported that "breakage of polypropylene sutures connecting the rings of the metal stent frame has recently been observed in one of the commercially available types of endografts," but the device was not identified by name. Several important issues are raised by these adverse events: Is it the company's or the principal investigator's responsibility to disseminate information about adverse events? Who should receive such information—only potential device implanters or the vascular community? What is the appropriate middle ground between premature allegations of device failures and delayed disclosure? And is it appropriate to accede to company requests not to identify complications by device name in registry presentations and publications? These issues have been the subject of an exchange in letters to the editors of this journal regarding the disclosures of adverse events associated with the Stentor and the Vanguard devices.[21,22]

Min Tec's Stentor device has been taken over by Boston Scientific Corporation and superceded by the redesigned and differently fabricated Vanguard device. A case report of a Vanguard graft developing fabric erosions was published in this journal in June 1999.[23] The authors quoted a November 1998 letter that Boston Scientific Corporation sent to "all its customers," noting that "late endoleaks due to holes in the fabric covering now have been reported to the manufacturer in six cases." This letter also noted that "the reported events occurred between five and twelve months post-implant" and "only one of the events described in this letter occurred within this Eurostar data set." Five of these six cases had been discussed at a breakfast session at the Montefiore Symposium in November 1998. A year later, at this same symposium, the nine cases were reported to have fabric holes, but overall data on this unique complication have yet to be published a year and a half after its first appearance. This may yet be found to be simply a new and relatively low frequency form of endoleak with this device, but this potentially important information has not been promptly and widely transmitted. How else can practicing surgeons be sure that it is safe to refer their patients with AAAs for implantation of a particular endograft or, if they have appropriate endovascular skills, begin using a device that is now being marketed? Thus, the early disclosure of possible device failures remains a nagging issue. The Vanguard device was recently withdrawn, but according to a company spokesman this was not because of concern over the increasing number of fabric holes, but because of microscopic particles separating from the sheath, although the latter have not had any known clinical consequence.

Full disclosure of adverse events has subsequently been seen with the problem of late rupture of aortic aneurysms "repaired" with the AneuRx device. Three cases were reported by Politz et al[24] in the March issue of this journal, and an analysis by Zarins, Fogarty, and White of all seven cases known to date appears in this issue.[25] Although these reports differ somewhat in their interpretation of the potential seriousness of this particular adverse event, at least the vascular community has been alerted and has the opportunity to review the details. *Journals should promptly report and fast-track articles addressing potentially important adverse events.*

Negative trials. There is a tendency not to submit negative results for publication, and it is difficult to get negative trials published. Just like surgeons with poor results, companies are not likely to want to report negative trials. However, *failure to publish negative results may result in the continuation of harmful patient treatment, unnecessary duplication of studies, and failure to release important scientific data; it also subverts the ethical principle of honesty in publishing research data.* In some instances, the contract between the investigator and the company may appear to give the company the right to block publication. Recently, an investigator was obliged to step to the podium at a major national scientific meeting and announce that he was being prevented from presenting the results of the study by the pharmaceutical company sponsor.[26] Permission was withdrawn the evening before presentation. Because of contractual agreements with the investigators, the industry-sponsor maintained a right to block public disclosure. In an editorial discussing this incident,[27] it was pointed out that the signed American Heart Association abstract submission document was also binding regarding presentation and that informed consent documents generally include such statements as "the patients and their families have agreed to participate in an activity with risk and have the right to be assured that the results of the study will be transmitted to the scientific community in a timely fashion." The authors of the editorial maintained

"that these other documents (and the informed consent in particular) may also have legal standing as contracts, and that inappropriate delays or limitations in the scope of presentations may represent breaches of these contracts." Prevention of harm to patients has ethical standing that would likely outweigh and supercede the obligations to follow the terms of a contract requiring nondisclosure.

A company may not have included a clause to prevent disclosure, but if it controls the pooled data, it can effectively prevent publication. This was observed a few years ago, when investigators from one center, who had recruited by far the most cases in a negative trial, finally decided to exercise their right to present and publish their own results[28] after it became apparent that the company was not going to have the overall trial data published. After the presentation, company officials tried unsuccessfully to undermine that publication through telephone contact with one of the former editors of this journal. When told that it was undergoing peer review and if accepted would be published, they then asked to publish a rebuttal article but declined when they found it too would have to be submitted for peer review. After the article was published, they published a letter to the editor[29]; in addition, there were two seemingly spontaneous letters published by others,[30,31] one of whom had a contract with the study sponsor, Curative Technologies, Inc. The primary author's reply[32] effectively dismissed their objections, but the company officials' response demonstrates the extent to which a study sponsor may go to prevent or oppose publication of negative trial results. To not allow publication of results interferes with the investigator's right to report scientific data from a trial in a timely fashion regardless of outcome and with the patient's right to know the outcome since this information may modify their current or subsequent management.

Hailey[33] quotes two examples where companies have used the court system to delay publication. Bristol-Myers-Squib Canada, Inc, tried unsuccessfully to have the courts block the release of a summary document on statins prepared by the Canadian Coordinating Office for Health Technology Assessment. Release of the report was delayed for almost a year. Recently, the Ontario Ministry of Health requested that a group of experts formulate guidelines on the use of drugs aimed at treating ulcers and related diseases. When the panel concluded that cheaper alternatives to Losec might be equally effective, a lawyer for Astra Zeneca wrote the chair of the committee an intimidating letter requesting that she not finalize and distribute the guidelines and stating if she persisted, legal action would be instigated. The company subsequently stated that it has never had the intention of restricting a researcher from publishing the study results.

Delays in publication. Although the company may encourage early publication of favorable results, conflict between the company and the investigator may result if the results are not favorable to the company. Last summer, it was communicated to participating investigators that enrollment had been stopped in an almost 5-year randomized trial of carotid stenting using the Schneider Wallstent (now owned by Boston Scientific Corp) versus carotid endarterectomy for carotid stenosis. More than 200 patients had been entered, and the procedural mortality and neurologic morbidity were said to be much higher for the stent group than for those undergoing carotid endarterectomy. Inquiring about possibly fast-tracking a report of this study, the senior editor of this journal was informed by a clinical research investigator coordinating the trial for the company that "enrollment was stopped in June [of 1999, but] we are continuing to follow the patients and plan to do so for an indefinite period of time. The data have not yet been presented or submitted for publication. The investigators agreed that a publication committee should be identified and that they would write the manuscript." The reply continued "the committee is just in the process of being selected" and "there is no principal investigator for the trial." The trial sponsors appeared to be in no rush to present or publish the initial outcome (ie, mortality and neurologic morbidity) of the compared procedures, as is common practice for treatment of carotid stenosis, yet it would seem that if the outcomes had been reversed and in favor of carotid stenting, their response regarding prompt presentation and publication might have been quite different.

In addition to a responsibility to inform the vascular community, patients consenting to such a randomized trial are normally assured of obtaining prompt disclosure of the results of a trial if there is a clear difference between groups. *Investigators should be certain that a publication committee is established before the start of the study and that provision for prompt publication of the results is assured in the research contract they sign. The research contract should specify that the company can only delay publication for a reasonable time to allow them to review the manuscript and complete application for patent protection or submission to a regulatory body.* Ordinarily,

90 days is sufficient for these purposes, assuming the latter contingency has been arranged for in advance.

Multiple publications. One of the problems with multiple publications of the same longitudinal data is that subsequent accounts may have different starting points, ostensibly because the device itself has undergone redesign. However, this practice hides "learning curve" data that may be important information for others who are going to start to use the technique. Although it is reasonable to show the impact that improvements in the device or the skills of those implanting it have on the results, it is more appropriate to present the entire experience and then carry out subgroup analysis to provide the reader with the full perspective. Detailed publications covering results, complications, and special aspects of a device are clearly justified, but others, in which essentially the same data are revisited with a somewhat different discussion, are clearly examples of "salami slicing," which prevents the reader from getting a broad perspective on the reported results. To avoid this problem, *a publications committee should decide ahead of time how to fairly present the data to avoid multiple publications and should resist company pressures to broadly publish similar data.*

As pointed out by Rennie,[34] multiple publications from the same data set, along with the tendency to publish only positive results, bias the opinion in the literature in favor of a device or a drug. A proposed solution is to register trials before they are carried out and to ensure publication of all results.[35]

Publication committees. The early establishment of a publications committee from among the principal investigators, a committee chaired by one of them, is the optimum way to fairly divide up the data emanating from a trial for publication. It should be constituted at the outset of the study and be made up of selected investigators, members of the data-monitoring committee, and a representative or two of the company. In May 1998, a paper presented at the Eastern Vascular Society concerning "the origin of perigraft flow after endograft aneurysm repair," based on an analysis of core laboratory data from phase II of the EVT trial, was withdrawn from submission for publication at the time of the meeting at the insistence of a representative of EVT who did not approve the release of the information at that particular time, even though the submitted abstract and final manuscript had been reviewed and approved earlier. The purported reason for this action was to allow prior publication of the "official" results of the second phase of this trial being presented at the joint vascular meetings a month later. This short delay in submission may seem innocuous (even though it was in violation of the society's rules for submission of abstracts, namely, that if accepted for presentation, a manuscript will be submitted for publication at the meeting); however, it demonstrates that company representatives are making decisions on submitted abstracts and manuscript submissions that should be the purview of the entire publication committee. Ironically, the major paper on the phase II results was presented and submitted for publication, but after peer review it was never resubmitted.

CONCLUSIONS

Editorials of this nature run the risk of seeming hypercritical or "holier than thou." We realize that most research and development personnel in industry are scientists, too, and understand and respect the investigator's position in these research collaborations. This editorial is not primarily based on personal negative experiences that may have given us a biased view of this scene. However, the corroborated examples given have all been reported by colleagues, witnessed at national or regional meetings, or have come to our attention while pursuing our editorial duties.

We have identified some of the problems that can occur in the complex relationship in clinical research studies between clinical investigators and industry representatives. Industry seems to be exerting more control over the design, conduct, and data analysis in trials, and the busy clinical investigator is less able to defend his or her rights as a research scientist. Because the aim of collaborative clinical research with industrial sponsorship is to develop safe and effective methods for diagnosing and managing diseases, clinical investigators should recognize their primary responsibility. It may well be time to collectively look the gift horse in the mouth and take a stand against inappropriate control of clinical trials and their data by industry.

The opinions expressed are those of the authors, but they acknowledge the helpful discussions with Drs V. M. Bernhard, J. L. Cronenwett, C. B. Ernst, R. T. Gregory, N. R. Hertzter, W. C. Krupski, J. Matsamura, M. F. McKneally, J. M. Porter, F. J. Veith, and Mr J. Hoover during the preparation of drafts of the manuscript.

REFERENCES

1. Shimm DS, Spece RG Jr. Discovering the ethical requirements of physicians' roles in the service of conflicting interests as healers and as citizens. In: Spece RG Jr, Shimm DS, Buchanan AE, editors. Conflict of interest in clinical practice and research. New York: Oxford University Press; 1996.

2. Shimm DS, Spece RG Jr. An introduction to conflict of interest in clinical research. In: Spece RG Jr, Shimm DS, Buchanan AE, editors. Conflict of interest in clinical practice and research. New York: Oxford University Press; 1996.
3. Council on Scientific Affairs and Council on Ethical and Judicial Affairs, American Medical Association. Conflicts of interest in medical center/industry research relationships. JAMA 1990;263:2790-3.
4. King RT Jr. The doctor as a stockholder. The Wall Street Journal 1999 May 5, 1999; Sect A:1.
5. Eichenwald K, Kolata G. Hidden interest—a special report: when physicians double as entrepreneurs. New York Times 1999 Nov 30; Financial/Business sect.
6. Phillips RA, Hoey J. Constraints of interest: lessons at the Hospital for Sick Children. Can Med Assoc J 1998;159:955-7.
7. Olivieri NF, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McLelland RA, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med 1998;339:417-23.
8. Etchells E, McLeod RS, Greets W, et al. Economic analysis of low-dose heparin vs. the low-molecular–weight heparin Enoxaparin for prevention of venous thromboembolism after colorectal surgery. Arch Intern Med 1999;159:1221-8.
9. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
10. Beebe HG. Scientific evidence demonstrating the safety of carotid angioplasty and stenting: do we have enough to draw conclusions yet? J Vasc Surg 1998;27:788-90.
11. Hobson RW II. Status of carotid angioplasty and stenting trials. J Vasc Surg 1998;27:791.
12. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg 1994;220:251-6.
13. Shimm D, Spece R. Industry reimbursement for entering patients into clinical trials: legal and ethical issues. Ann Intern Med 1991;115:148-51.
14. Richter GM. Results of a randomized trial of iliac PTA vs primary stenting [abstract]. J Vasc Interv Radiol 1993;4:30.
15. Jones DN Jr, Nehler MR, Merli G, Durham JD, Hiatt WR, Whitehill TA, et al. The incidence of adequate surveillance exams in multicenter trial of deep venous thrombosis prophylaxis. Abstract submitted and accepted for the American Venous Forum 1998 meeting. Presentation withdrawn.
16. Sternburgh WC III, Money SR. Hospital cost of endovascular versus open repair of abdominal aortic aneurysms: a multicenter study. J Vasc Surg 2000;31:237-44.
17. Rutherford RB. Problems with the dissemination of up-to-date information on the results of endograft repair for abdominal aortic aneurysm. J Vasc Surg 1999;29:1167-9.
18. Bernhard VM. Development of the endovascular prosthesis. Bull Am Coll Surg 1996;81:20-1.
19. Riepe G, Heilberger P, Umscheid T, Chafke N , Raithel D, et al. Frame dislocation of body middle rings in endovascular stent tube grafts. Eur J Vasc Endovasc Surg 1999;17:28-34.
20. Buth J, Harris PL, Miahle C. Eurostar endovascular registry: success rates, complications, significance of endoleaks, and is suture breakage in stent grafts important? Montefiore Symposium on Current Critical Problems, New Horizons and Techniques in Vascular and Endovascular Surgery; 1998 Nov 19.
21. Harris PR, Buth J. Regarding "problems with the dissemination of up-to-date information on the results of endograft repair for abdominal aortic aneurysm" [letter]. J Vasc Surg 1999;30:767-8.
22. Rutherford RB. Reply to letter regarding "problems with the dissemination of up-to-date information on the results of endograft repair for abdominal aortic aneurysms." J Vasc Surg 1999;30:768-9.
23. Krohg-Sørensen K, Brekke M, Drolsum A, Kvernebo K. Periprosthetic leak and rupture after endovascular repair of abdominal aortic aneurysm: the significance of device design for long-term results. J Vasc Surg 1999;29:1152-8.
24. Politz JK, Newman VS, Stewart MT. Late abdominal aortic aneurysm rupture after AneuRx repair: a report of three cases. J Vasc Surg 2000;31:599-606.
25. Zarins CK, White RA, Fogarty TJ. Aneurysm rupture after endovascular repair using the AneuRx stent graft. J Vasc Surg 2000;31:960-70.
26. Clarke WM, Raps EC, Tong DC, Kelley RE. Cervene in acute ischemic stroke: results of a Phase III randomized efficacy study [abstract]. Stroke 1999;30:234.
27. Goldstein LB, Brott TG, Kothari RU, Smith WS. Clinical stroke trials: guarding against bias. Stroke 1999;30:1165-6.
28. Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH. A prospective randomized trial of autologous platelet derived wound healing factors for the treatment of chronic non-healing wounds: a preliminary report. J Vasc Surg 1991;14:526-32.
29. Loss LE, Deitrick GA III, Duff RG. Regarding "a prospective randomized trial of autologous platelet derived wound healing factors for the treatment of chronic non-healing wounds: a preliminary report" [letter]. J Vasc Surg 1992;16:125-6.
30. Glover JL. Regarding "A prospective randomized trial of autologous platelet derived wound healing factors for the treatment of chronic non-healing wounds: a preliminary report" [letter]. J Vasc Surg 1992;16:124-5.
31. Dosick SM. Regarding "A prospective randomized trial of autologous platelet derived wound healing factors for the treatment of chronic non-healing wounds: a preliminary report" [letter]. J Vasc Surg 1992;16:125.
32. Krupski WC. Reply to letters to the editor regarding "A prospective randomized trial of autologous platelet derived wound healing factors for the treatment of chronic non-healing wounds: a preliminary report." J Vasc Surg 1992;16:126-8.
33. Hailey D. Scientific harassment by pharmaceutical companies: time to stop. CMAJ 2000;162:212-3.
34. Rennie D. Fair conduct and fair reporting of clinical trials. JAMA 1999;282:1766-8.
35. Horton R, Smith R. Time to register randomised trials [editorial]. BMJ 1999;319:865-6.