Patient Outcomes Research Teams (PORTS): Managing Conflict of Interest

Molla S. Donaldson and Alexander M. Capron, Editors; Committee on Potential Conflicts of Interest in Patient Outcomes Research Teams, Institute of Medicine

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in Patient Outcomes Research Teams
Institute of Medicine

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This serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

COMMITTEE ON POTENTIAL CONFLICTS OF INTEREST IN PATIENT OUTCOMES RESEARCH TEAMS

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Preface

The ability to assess the probable outcomes of alternative medical responses to disease or disability is obviously a matter of great interest to patients, physicians, and payers alike. Yet surprisingly little reliable information has been available to guide choices among treatments or to determine which treatments are appropriate for health insurance coverage. The field of health services research has yet to catch up with the remarkable developments in clinical science and the changes they have wrought in health care.

In recent years, however, health services researchers have developed increasingly sophisticated means of assessing outcomes. A major means is through multidisciplinary groups known as patient outcomes research teams (PORTs) which focus their combined expertise in fields from clinical care to decision analysis on the outcomes and costs of alternative practice patterns in treating a particular medical condition. Beginning with meta-analysis of the existing literature on treatment for the condition, each PORT constructs means of measuring the connection between practice variations and a range of appropriate outcome measures that go beyond simple mortality and morbidity data. This model is then used to analyze both large data sources (from hospitals, insurance carriers, state health departments, and the like) and the results of specially conducted interviews and chart reviews. After its findings are disseminated, a PORT also evaluates their effects on the choices made by physicians and patients.

In their size and complexity as well as in their direct connection with the actual practice of medicine, PORTs differ from traditional clinical research. If well conducted, their findings are likely to have a major influence on clinicians' practice patterns and third-party payers' reimbursement policies. Even if every PORT does not become the recognized arbiter of the "best alternative" to achieve a specified outcome for its particular disease, all PORTs can reasonably be expected to wield considerable influence.

Accordingly, it is important that both the public and health professionals be able to rely on the objectivity of PORTs and the reliability of their findings. Yet, as Dr. J. Michael Fitzmaurice, then director of the agency within the Department of Health and Human Services (DHHS) responsible for funding PORTs, observed in a letter to Dr. Samuel Thier, president of the Institute of Medicine, once PORTs are perceived as ideal evaluators, "designers and manufacturers of drugs and devices as well as the developers and proponents of new diagnostic and therapeutic procedures will quickly recognize [their] potential . . . to significantly influence the adoption and dissemination of their innovations."

Should PORTs add prospective studies of such new products or procedures to their evaluations along with the retrospective data on existing alternatives? Or should they participate in separate studies of new treatments or lend their expertise in designing such studies to permit them to incorporate the PORT's latest thinking about appropriate ways to measure patient outcomes? Should a PORT supplement its governmental support with funds from insurance companies or other entities that have an interest in health care expenditures (such as patients' groups) in order to extend the reach of its studies or the vigor of its dissemination efforts? Should members of a PORT accept fees from, hold stock or officerships in, or otherwise be involved with any concern having a proprietary interest in the field under study? What about PORT members' involvement with professional groups that advocate a particular treatment for a disease or that have a financial or intellectual stake in certain treatment alternatives?

The potential for conflicts of interest—of which the foregoing are only a sample—to bias, or to be perceived as biasing, the findings of a PORT should concern anyone who hopes to see our knowledge of clinical effectiveness improve. Although it would be imprudent to dismiss out of hand all possibilities of support for PORTs from private companies or third-party payers, accepting such support could make it "problematic" for PORTs "to maintain the impartial and unbiased stance that is essential to the long term effectiveness and viability of the program," as Dr. Fitzmaurice stated in his letter requesting that the IOM undertake this study.

In response to that request, our committee has probed the concept of conflicts of interest, both financial and otherwise, as it has been used in recent years, especially as concerns biomedical researchers. Based upon our evaluation of the areas of special concern regarding the work of PORTs, we recommend not a set of rules and regulations for DHHS but points for all parties—the PORTs, the federal sponsors, the research community, the health care industry, and Congress —to consider in avoiding, ameliorating, and administering potential conflicts of interest. We expect that our suggestions will be implemented in such a way as to build upon, rather than to duplicate, existing measures that research institutions and other groups have adopted regarding conflicts of interest. We also place

primary emphasis on self-regulation, voluntary disclosure, and the responsibilities of the principal investigator for the ethical conduct of his or her PORT.

We view these suggestions as a first response to what are still largely anticipated rather than actual problems in new and rapidly evolving areas of research. We hope that by providing a structure for analyzing and perhaps overcoming problems, our suggestions will contribute to what we see as the great promise of PORTs in both improving patient well-being and satisfaction and increasing the efficiency of health care resource allocation. We are certain, however, that our suggestions will themselves need to be monitored and revised in light of experience.

Given the novelty of the subject, the committee was particularly blessed by the creative and tireless work of Molla Donaldson, ably advised and assisted by Holly Dawkins, Kathleen Lohr, and Karl Yordy of the IOM staff. Clifford Goodman, then Director of the Council for Health Care Technology, and Maria Elena Lara, also at the Council, did the initial staff work for the committee. Dr. Goodman drafted one of the scenarios. We are also grateful for the suggestions and analysis of the participants in our workshop, especially those who wrote background papers (several of which are appended to this report) and those who participated in panels.

ALEXANDER MORGAN CAPRON
COMMITTEE CHAIR

Contents

Summary

Outcomes research is the systematic assessment of clinical practice. It evaluates all (reasonably held) theories and alternative clinical practices by focusing on the treatment of clinical conditions rather than individual procedures or treatments. Outcomes include those relevant to patients—mortality, morbidity, complications, symptom reduction, and functional status improvement—as well as physiologic or biologic indicators. Outcomes research utilizes multidisciplinary assessment teams and emphasizes new strategies and methods for making inferences both from experimental and nonexperimental data.

The Omnibus Budget Reconciliation Act of 1989 (P.L. 101–239) established the Agency for Health Care Policy and Research (AHCPR) within the Department of Health and Human Services and appropriated funds for outcomes research and particularly for the establishment of the Patient Outcomes Research Teams (PORTs). Eleven PORTs have been funded as of October 1990. Each PORT focuses on a specific acute or chronic condition that occurs frequently, especially among Medicare beneficiaries, and for which risks and costs are particularly high, treatments are particularly variable, and outcomes uncertain. It identifies and analyzes the outcomes and costs of current alternative practice patterns to determine the best treatment strategy.

PORTs are large multidisciplinary, multi-institutional projects that employ larger and more diverse groups of researchers than is typical in health services research. Each PORT includes academic and practicing community-based health care providers and has expertise in pertinent clinical specialties, literature synthesis, research design, epidemiology, biostatistics, economics, decision analysis, survey research, data management, and research dissemination. PORTs conduct at least the following activities: a comprehensive literature review and synthesis on the condition or treatment being assessed; collection and analysis of data including

variations in medical practice and associated patient outcomes; dissemination of findings about effectiveness; and evaluation of the effects of dissemination.

The research being conducted by PORTs is in many ways similar to traditional clinical, health services, and epidemiological research. However, PORTs have several features that justify giving them special attention in relation to conflicts of interest. First, PORT findings will be used in the development of practice guidelines. As such, they can be expected to influence medical practice more directly than the findings of a particular clinical trial. Second, the findings of PORTs are likely to affect reimbursement decisions by third party payers and thus have significant financial implications for both manufacturers of medical devices and drugs and for practitioners who rely heavily on modalities that may be found to be relatively ineffective. Finally, some PORTs may come to have multiple sources of research funding in addition to federal funding.

INSTITUTE OF MEDICINE STUDY

Recognizing the vulnerability of PORT findings to challenges based on conflict of interest, the Institute of Medicine (IOM) was asked to convene a committee to provide points for the agency and PORTs to consider in anticipating and managing conflicts of interest. The nine-member committee, which represented expertise in medical center and research administration, health services and clinical research, law, medical sociology, ethics, pharmaceutical and device manufacturing, and regulation—commissioned background papers and convened a one-and-a-half-day workshop to discuss issues relevant to conflicts of interest in PORTs. The committee was not charged to develop formal recommendations, nor does it regard its points to consider as such.

DEFINING CONFLICT OF INTEREST

Conflict of interest arises in a situation in which (1) one is in a fiduciary relationship with certain others, and (2) one's financial or professional self-interest substantially differs from the interests of those others. The concern with conflicts of interest arises in biomedical research because of the possibility that such conflicts, both real and perceived, may erode scientific objectivity and engender the loss of public trust.

Because PORTs conduct research for the public benefit, PORT researchers have fiduciary obligations to the public. Yet their interactions with other groups, although necessary and even desirable, in some instances risk creating conflicts of interest. The committee does not, however, consider financial conflicts of interest to be the only, or even necessarily the most important, sources of bias in PORT research. For researchers, desire for public recognition, publication, grant renewal, career advancement, or tenure may exert strong inducements to produce positive results. These professional conflicts of interest need not be conscious decisions on the part of an investigator; nevertheless, intellectual attachment or commitment to a particular scientific theory pose possible conflicts.

Financial relationships that may give rise to conflicts of interest take two typical forms for clinical researchers. One type is an individual researcher's financial relationship with a company that owns a technology that the researcher is evaluating. These relationships include ownership of stock or stock options; management or executive positions with such companies; royalties from licensing of intellectual property rights, including patents on inventions, copyrights (e.g., computer software), and sale of other proprietary materials; and consultant positions and honoraria paid for lectures. A second type of financial relationship is the support a company provides to the university where researchers conduct their work; such support may come by a variety of mechanisms, including technology-transfer cooperative agreements to promote rapid commercialization of products.

In the last decade, as such university-industry relationships have increasingly included the biomedical sciences, concern has been expressed in public and professional circles about adverse effects on research and especially on the independence of researchers. However, very few comparative assessments have been published on the risks and benefits of the variety of relationships adopted by academic centers, industry, and external organizations including the federal government. Policymakers have neither rigorous data about risks and benefits nor accurate assessments of the effects of policies meant to diminish the risks and enhance the benefits.

The trend over the past 10 years has been for government agencies and academic organizations to mandate or strongly advocate full investigator disclosure of any financial interests in businesses that might profit from the products or procedures under study. The responsibility of academic institutions for oversight and management of conflicts of interest has also been increasingly stressed. Recent reports issued by the American

Association of Medical Colleges and the Association of Academic Health Centers address the management of conflicts of interest in the university and particularly in the academic health center. Although these works were helpful to the committee's deliberations, special aspects of PORTs remain to be addressed.

PORTs are a new hybrid entity which encompasses academic medical research leading to peer-reviewed scientific findings and a "quasi-regulatory" role directly related to public policy and health insurance payment questions. This hybrid responsibility confers special expectations on PORTs and argues for well-defined, irreproachable standards to address the appearance of conflict of interest as well as its actual occurrence. PORTs may require a level of scrutiny and a threshold of acceptability that are higher than those established for other research efforts—perhaps comparable to those for judges, public officials, and others with fiduciary responsibilities. Existing institutional guidelines and procedures may thus not be adequate for this kind of entity or for multi-institutional PORTs and nonuniversity clinicians.

Other concerns regarding conflict of interest in PORTs include the following: congressional expectations regarding the cost-containing effects of PORT findings may result in a powerful potential bias. A concentration of expertise in PORTs may give them a continuing advantage over other researchers in obtaining grants and contracts, disseminating findings, and influencing insurance reimbursement and other policies affecting care of the medical condition on which each PORT specializes. Their findings will not be replicable (or at least not easily) and will accordingly be difficult to challenge. Moreover, the committee noted that the use of qualitative judgments in outcome assessments, in contrast to the quantitative end points usually found in clinical research, will make subtle biases much harder to discern. PORT researchers are also vulnerable to biases arising from professional and collegial ties to the subjects and the practitioners being studied. All these issues raise concerns about the effects of conflicts of interest and make it important to provide access to valuable PORT data bases to challenge and confirm their findings and for secondary analysis. Further, evolving PORT methods, which include prospective data collection from patients and community-based clinicians, will attract outside funding, spin-off ventures, and consultancies. All these developments promise better technology, better information for medical decision making, and more rapid medical progress, but they also pose difficult questions regarding conflicts of interest. Freedom of communication among PORT investigators—a tenet of science generally—and between PORT investigators and manufacturers of technologies being evaluated pose special problems. When manufacturers provide additional funding to evaluate technological modifications and new practices, medical knowledge

may be pushed forward more rapidly, but with a potential diminution of scientific objectivity. Similar issues arise when PORT members enter into financial arrangements related to intellectual property rights and spin-off ventures. Equity interests of PORT investigators in companies whose products are being evaluated present special hazards in creating an appearance—and possibly the reality—of conflict of interest.

MODELS FOR ADDRESSING CONFLICTS OF INTEREST

Two models can be used to approach conflicts of interest. One would prohibit all relationships that might give rise to a conflict of interest unless an overriding social benefit could be established. The other would allow most relationships and rely on a strong disclosure and peer review process to protect the public interest. Although differing in their starting points and in their effect on particular research projects, each model can incorporate similar means of reducing or managing the effects of a conflict of interest: mandatory disclosure, mechanisms of financial distancing, self-regulation, defining categories of acceptable activities and implementing oversight of such activities, and defining unacceptable activities and implementing prohibitions or, when necessary, sanctions.

POINTS TO CONSIDER

This report suggests points for consideration by PORTs and their institutions, AHCPR, the health services research community, industry, and Congress regarding conflicts of interest in outcomes research. The committee believes that the primary role of AHCPR should be to insist that institutions have a method in place for acknowledging, exploring, and managing these potential conflicts. The report bases its points to consider on a number of assumptions and observations about PORTs and PORT research:

- Like other scientists, PORT researchers seek to maximize the validity of their inferences by identifying sources of bias and by minimizing the effects of those biases on their findings.
- The varieties of PORT relationships with other entities are evolving, and any pitfalls resulting from financial and professional conflicts of interest cannot yet be well delineated.
- PORTs may be exposed to accusations of conflict of interest because of connections to industry, professional associations, and the like, possibly with the intent of discrediting their findings when such results are

at odds with the interests of other parties.

- PORT investigators need guidance in recognizing a potential or real conflict of interest and knowing when to disclose it.
- Each PORT or its home institution should have in place an appropriate mechanism by which relevant conflicts of interest and biases can be revealed and addressed.
- Each prospective PORT should be required in its funding application to file copies of the conflict-of-interest policies of the home institution and of its proposed subcontractors and to describe the process it will use to manage conflicts of interest.
- Requirements regarding conflict of interest should be at least as stringent as those that apply to clinical investigators. Where institutional rules distinguish between bench and animal research on the one hand and clinical trials on the other, PORTs should be subject to the rules that apply to the latter.
- Methods of dealing with conflict of interest include disclosure, followed by assessment and management or, where essential to the integrity of the research, outright prohibition. The PORT members and their institutions are best placed to determine the process by which they will manage conflict. Important aspects of such a process include education about conflicts of interest for researchers, faculty, and students; clearly stated expectations for early and complete disclosure of relevant interests; well-formulated, well-implemented institutional process for responding to disclosures; and emphasis on the role of the principal investigator in managing conflicts.
- Collaborative research agreements with industrial entities (firms) should ensure freedom to publish the outcomes of studies, whether favorable or unfavorable, and latitude for communication among PORT investigators and industry.
- Generally, PORT researchers (and their immediate families, including minor dependents) should not be equity holders in firms that produce technologies used for the conditions being studied.
- To counteract nonfinancial sources of bias, such as those arising from professional loyalties and training and from other academic affiliations, PORTs should actively encourage internal and external scrutiny and should ensure that the team has representation from the full range of relevant clinical and scientific disciplines.
- PORTs of necessity rely heavily on observational studies, incomplete data bases, and qualitative outcomes, and their findings are no substitute for traditional clinical trials and should not be the sole basis for clinical or public policy decisions.
- Outcomes research (and PORTs in particular) has been funded for a variety of reasons including improvement in information, knowledge,

quality of care, and rationalization of the nation's allocation of health care resources. Although there is a hope, if not an expectation, that PORTs will save money for federal programs, this is unlikely in the short run. PORT teams should not be overtly or subtly required to recommend cost-saving practices as a basis for renewed funding.

- Since AHCPR cannot assume the role of sole supporter of patient outcomes research, PORTs may need, or even require, other sources of funding, much of which may come from industry. The manner in which such funds are juxtaposed with agency support, however, needs serious consideration in each case and careful management to safeguard the conclusions of PORTs from the appearance or reality of a conflict of interest.
- Uniform standards for conflict of interest and self-dealing in PORTs are not needed at this time. If AHCPR does establish minimum agency standards, it should do so in collaboration with the National Institutes of Health.
- Grant specifications should include a requirement that both internal and bona fide external investigators and analysts may have reasonable and timely access to PORT data.

Outcomes research as exemplified by PORTs holds out the promise of greatly improving the value and effectiveness of the health care system. The fear of unresolvable conflict of interest should not inhibit commitment to outcomes research or the continued evolution of what must be seen as a bold new "social invention" on the part of Congress.

1

Introduction

PORTs…represent the coming of age of health services research as a useful, clinically relevant discipline, whereby the evaluative sciences for the first time are, with the help and support of Congress, going to become directly relevant to clinical decision making in a way that they haven't before. They're going to have to carry the same burdens of scrutiny that clinical trials and other kinds of clinical research have carried.

We haven't considered epidemiology to be as important to regulate in the past as randomized clinical trials. We haven't considered decision-analytic papers as important to scrutinize, largely because we didn't expect them to have as much impact. Maybe that's changing, and maybe for that reason the increased authority carries with it increased responsibilities.

—David Blumenthal, Institute of Medicine Workshop, 1990

OUTCOMES RESEARCH

The term outcomes research—sometimes called effectiveness research, evaluative clinical science, or clinical evaluation—has come into common usage in the health care community to describe an approach to clinical research that has lately received increased emphasis. Outcomes research examines the treatment of clinical conditions rather than individual procedures or treatments. It is the systematic assessment of clinical practice, encompassing both outcomes that are relevant to patients—mortality, morbidity, complications, symptom reduction, and functional status improvement—as well as physiologic or biologic indicators; it involves all reasonably held theories and alternative clinical practices. Outcomes research emphasizes multidisciplinary assessment teams and new strategies and methods for making inferences from experimental and nonexperimental

data (Wennberg, 1990a). It has been embraced by health care professionals and policymakers who are deeply concerned about (1) two decades of studies showing wide variations in the use of health services in different locales but little understanding of the effect of those variations on the health of patients served, (2) evidence of frequently inappropriate use of a number of diagnostic and surgical procedures, (3) rapidly increasing health care costs, and (4) the possible effects of changing health care reimbursement schemes on quality of care.

Outcome—the effect of an intervention on patient health and well-being—is the greatest concern of patients who seek care and the most obvious criterion for measuring the effectiveness of care. However, Congress's Office of Technology Assessment has estimated that only 10 to 20 percent of what physicians do has clearly been shown to be of value as judged by well-designed randomized clinical trials (OTA, 1983). Even these studies, regarded as the best available, are limited in generalizability because they exclude large numbers of patients, such as those with other coexisting diseases or those not within the age or gender designations of the study protocol. More fundamentally, such clinical trials typically examine only a single and usually innovative modality and do not include all alternative treatments. The end points measured have often not included patient health and functioning status.

Why has outcomes research been slow in coming? It has proved difficult for clinical researchers to design short-and long-term end points that are reliable and valid for the dimensions of health and well-being valued by patients and to measure them in such a way as to draw conclusions about the care provided. Health status is determined in large part by environmental, personal, and social factors that are not related to clinical interventions. Outcomes research has been developed as a means of responding to the need for data that are useful and reliable despite these problems. Recently, researchers have demonstrated the practicality of using large administrative data bases to assess some outcomes, and they have developed and validated instruments for accurately assessing patient health status to augment administrative data bases. Decision analysis and meta-analysis (to be described in greater detail in Chapter 2) are two other methods that are used in clinical evaluative research to augment our understanding of the clinical effectiveness of treatments despite large areas of uncertainty and a dearth of randomized controlled clinical trials.

Recognizing the potential of these methods of health services research, the Department of Health and Human Services sought and received congressional appropriations beginning in fiscal year 1989 for outcomes research and particularly for the establishment of the patient outcomes research teams (PORTs) described in this report. These are important new initiatives that recognize the potential of improved methods

of health services research to assess the effectiveness of alternative medical practices.

THE INSTITUTE OF MEDICINE STUDY

The potential importance of the findings of PORTs generates the possibility of real or apparent conflicts of interest in the interaction of PORT members with professional groups and business firms affected by those findings. Recognizing the vulnerability of PORT findings to challenges on such grounds, the National Center for Health Services Research and Health Care Technology Assessment (now subsumed in the Agency for Health Care Policy and Research—AHCPR), the Pharmaceutical Manufacturers Association, and Dartmouth Medical School (site of the first PORT to be funded) sponsored an Institute of Medicine (IOM) study to provide points for the agency and PORTs to consider in anticipating and managing conflicts of interest.

The IOM appointed a nine-member committee representing expertise in medical center and research administration, health services and clinical research, law, medical sociology, ethics, pharmaceutical and device manufacturing, and regulation. The committee met three times from April to October 1990 and commissioned six background papers on topics that covered the structure and methods of PORTs and potential sources of bias; a comparison of PORT and clinical research; a review of conflict-of-interest regulation in biomedical science; the possible impact of PORTs on health services research, technology innovation, and payment policy; and PORT research from provider and industry perspectives.

In June 1990, the committee convened a one-and-a-half-day workshop with some 60 invited participants who also brought extensive expertise and offered wide-ranging views. In addition to informative presentations and discussion, the workshop featured discussions of three scenarios written for the conference.

STRUCTURE OF THE REPORT

This report presents the results of the deliberations of the IOM study committee, augmented by the background papers, and the presentations and discussions at the June workshop. Chapter 2 describes the Medical Treatment Effectiveness Program within AHCPR and the structure and methods of PORTs and then examines the ways in which PORT research differs from other biomedical and clinical research. Chapter 3 provides the committee's working definition of conflicts of interest,

describes financial and professional conflicts of interest, and gives a brief history of recent attempts to deal with conflicts of interest on the part of universities, medical publications, certain government officials, judges, lawyers, and other individuals with fiduciary responsibility.

Chapter 4 describes special concerns about conflicts of interest in PORTs, and Chapter 5 describes two models and some general, frequently proposed approaches for dealing with conflicts of interest. Chapter 6 outlines suggestions and other points for consideration by PORTs and their home institutions, AHCPR, the health services research community, industry, and Congress. Appendices to the report include the scenarios discussed at the June workshop, the rapporteur summaries of those discussions, and several of the background papers and presentations.

2

Patient Outcomes Research Teams

THE MEDICAL TREATMENT EFFECTIVENESS PROGRAM

To support studies on the outcomes of health care services and procedures, the Omnibus Budget Reconciliation Act of 1989 (P.L. 101–239) established the Agency for Health Care Policy and Research (AHCPR), replacing the National Center for Health Services Research and Health Care Technology Assessment (NCHSR/HCTA) within the Department of Health and Human Services. Within AHCPR, the Center for Medical Effectiveness Research has primary responsibility for administering grant and contract research under the Medical Treatment Effectiveness Program (MEDTEP).

MEDTEP is charged to improve "the effectiveness and appropriateness of medical practice by developing and disseminating scientific information regarding the effects of presently used health care services and procedures on patients' survival, health status, functional capacity, and quality of life" (AHCPR, 1990:1). To fulfill this charge MEDTEP supports multidisciplinary research groups called PORTs—patient outcomes research teams.[1] In fiscal year 1990, AHCPR received $100 million, $38 million of which was allocated to MEDTEP, including the PORTs.

Table 2.1 lists the 11 PORTs that had been funded as of October 1990. With one exception, they result from investigator-initiated grant applications.[2] These applications are peer reviewed for scientific merit.

[1] The present program succeeds the Patient Outcome Assessment Research Program (POARP) initiated by NCHSR/HCTA, which made the initial grants to research teams in 1989.

[2] One PORT at the RAND Corporation has been funded as a competitive contract to study the appropriateness of cesarean sections and other obstetrical procedures in labor and delivery.

Afterward they are periodically reviewed by the agency study section that first awarded the grant.

PORT RESEARCH TOPICS

Each PORT focuses on a specific acute or chronic condition "to identify and analyze the outcomes and costs of current alternative practice patterns in order to determine the best treatment strategy and to develop and test methods for reducing inappropriate variations" (AHCPR, 1990:2). In selecting conditions to study, MEDTEP has given priority to conditions occurring frequently, especially among Medicare beneficiaries, conditions and interventions for which risks and costs are particularly high, treatments are particularly variable, and outcomes uncertain. PORTs also evaluate the effects of their findings and recommendations on practice patterns.

PORT STRUCTURE

PORTs are large multidisciplinary projects that employ larger and more diverse groups of researchers than is typical in health services research. MEDTEP requires that each PORT include academic and practicing community-based health care providers, and that each team have expertise in the following areas: pertinent clinical specialties, research design, literature synthesis (including meta-analysis), epidemiology, biostatistics, economics, decision analysis, survey research, data management, and research dissemination. PORTs are multi-institutional and, in some cases, international in composition. Box 2.1 shows the disciplines, institutions, and professional affiliations of members of the currently funded PORTs.

To enhance inter-PORT coordination MEDTEP has established six work groups to focus on specific methodological issues: meta-analysis, decision analysis, outcomes assessment, use of claims data, cost of care, and dissemination. Each work group comprises designated PORT representatives who will meet to discuss common problems and possibly common solutions for use by PORTs and other researchers.

PORT METHODS

According to AHCPR's *Program Note* on medical treatment effectiveness research (AHCPR, 1990), PORTs must include at least the following four components in their research:

1. *Comprehensive literature review and synthesis on the condition or treatment being assessed.* The literature review is the basis for developing research hypotheses to analyze associations between practice variations and outcomes and to identify gaps in knowledge.

Meta-analysis is a quantitative approach used to synthesize the clinical literature. It includes an explicit method for locating studies, the use of specified criteria for admission of studies, a system for classifying and coding study characteristics using a common scale, and methods for aggregating and interpreting study findings (Thacker, 1990). It includes studies ranging from large scale, double-blind randomized controlled trials to anecdotal reports as well as information from both published and unpublished sources. For instance, meta-analysis conducted in the Johns Hopkins University PORT study of cataract treatment will attempt to estimate probabilities of specified outcomes for each patient management strategy. Steinberg et al. (1990) estimated that more than 3,000 potentially relevant articles on cataract surgery were published during the past 10 years. Because most of this literature consists of observational studies rather than randomized controlled trials, the PORT will need to adapt traditional meta-analytic techniques (Steinberg et al., 1990). Methods of meta-analysis are still evolving; in aggregating findings for meta-analysis, at least one approach explicitly identifies biases in studies, estimates the magnitude of the bias, adjusts, and weights the results of the studies accordingly (Eddy, 1990; Eddy et al., 1990).

2. *Collection and analysis of data including variations in medical practice and associated patient outcomes.* PORTs are charged to identify "findings important for patient decisionmaking" and critical gaps in knowledge that should be addressed by subsequent studies (AHCPR, 1990:5). Sources of information may include Medicare and Medicaid data, hospital discharge abstracts, state health department records, chronic disease data banks, and insurance records. The availability of large data bases from insurance claims, such as Medicare Parts A and B and the Canadian provincial health data bases, makes it possible to estimate the probabilities of relevant outcomes. Data on mortality, repeat surgery, and other major complications are identifiable in the claims data bases.

To obtain primary data about outcomes and preferences that are not available from insurance data bases, PORTs may also conduct patient and practitioner interviews or surveys and abstract patient records. For instance, the Indiana PORT, which is evaluating total knee replacement, is gathering information directly from patients by conducting cross-sectional telephone surveys every six months in Indiana, western Pennsylvania, and Ontario to assess functional status and perceived pain (Freund et al., 1990).

PORTs may use decision analysis. This is a systematic approach to decision making in the face of uncertainty. It includes an explicit formulation of the problem, important outcomes, and alternative choices available to the decision maker. Associated with each outcome is the probability of its occurrence and an estimate of patient values (utilities) for that outcome (Mulley, 1990).

The Harvard and Dartmouth assessment teams, for example, use the methods described above. The Harvard PORT is studying treatment of acute myocardial infarction (AMI), more specifically the use of diagnostic and therapeutic interventions during and shortly after hospitalization for AMI and assessing their value in improving patient survival, health status, functional capacity, and quality of life in the chronic post-MI period. The first project in this effort involves a study of the value of aggressive management of patients during the first three months after an AMI. "Aggressive" in this context is determined by the decision to perform coronary angiography and then revascularization procedures: coronary artery bypass grafting and percutaneous transluminal coronary angioplasty. The PORT is using claims analysis (both Medicare and other data bases) to examine regional variations in use rates of coronary angiography and revascularization and their subsequent effect on patient outcomes and cost of care. The claims data will be used to define longitudinal cohorts of AMI patients starting in 1987 and in all available subsequent years to measure utilization, including hospital admissions for AMI-related procedures, and outcomes.

The PORT's decision-analysis working group will develop probability estimates for decisions to perform elective coronary angiography during the period immediately following an AMI; the group will then compare the results of this analysis to actual use of the diagnostic procedure as measured in claims data bases. Data on key probabilities such as life expectancy and quality-adjusted life expectancy for various patient subgroups will be derived from meta-analysis of the clinical literature. The meta-analysis group continually updates its literature search and performs statistical analyses to pool the results of randomized controlled trials.

The Harvard PORT will also gather primary data from patient surveys and medical records. The objectives of such primary data collection include (1) examining the reasons for regional variations in utilization of angiography, noninvasive tests, and revascularization procedures, (2) examining regional differences in a broad range of outcomes, including functional capacity and quality of life that are not obtainable from the Medicare files, and (3) providing data on case mix, process of care, and patient preferences (Pashos and McNeil, 1990; Chris L. Pashos, Project Director, personal communication, 1991).

The PORT will use the results of these analyses to develop and disseminate recommendations that will be used to help form clinical practice guidelines for targeted physicians. Simultaneously it will conduct a controlled trial of the effects of specific dissemination techniques on physician practice patterns.

The PORT has a senior national advisory board and a regional advisory board. It is seeking the cooperation and support of the American College of Cardiology, American College of Physicians, and the American Heart Association.

The Dartmouth assessment team study of benign prostatic hypertrophy (BPH) and localized cancer of the prostate actually antedates PORT funding. Its early studies of treatment for BPH focused on the reasons for and outcomes of three treatments: transurethral prostatectomy, open prostatectomy, and watchful waiting. The present study incorporates prospective assessments of emerging technologies such as the use of microwave diathermy, balloon dilation, and several new drugs. The Dartmouth assessment team has developed new methods to incorporate prospective evaluation and systematic follow-up of patient cohorts in each treatment arm because so few data on the new treatments are available in claims data bases (Wennberg, 1990a). Rather than employ classic randomized clinical trials, Wennberg and his colleagues rely on "preference trials," in which patients exercise their preferences by determining their treatment, thus providing direct comparison and follow-up of new and existing alternative technologies. The researchers have used large claims data bases to develop probability estimates for such outcomes as operative mortality and reoperations. In addition, they conducted interviews with patients before and after surgery to ascertain any changes in symptoms and quality of life in response to therapy. After demonstrating that surgery based on a preventive theory (that early surgery for BPH prevented later disability) was unfounded, the Dartmouth assessment team became convinced that patients must make their own decisions about surgery based on their symptoms and attitudes about the risks of surgery.

Practicing urologists from many regions of the country are members of the PORT team. Early findings about small area variations in rates of prostatectomy were shared with urologists in northern New England. A concurrent study to examine an apparent elevation in mortality rates for transurethral prostatectomies compared to the open prostatectomy is being conducted in collaboration with the American Urological Association.

3. *Dissemination of findings about effectiveness*. Based on their analysis and with the involvement of practicing physicians, PORTs are to develop recommendations related to the "prevention, diagnosis, treatment, and/or clinical management of health conditions" (AHCPR, 1990:5). These

recommendations and findings are to be disseminated according to an explicit plan.

To aid patients in making choices based on their symptoms, attitudes, and values, the Dartmouth assessment team has used interactive video technology to present information to patients in a consistent manner, to gather preference and outcome information for all relevant treatment strategies, and to estimate the impact of information on patient treatment choices. Such outcome information includes the likelihood, not now known, that men not undergoing surgery will develop acute urinary retention.

4. *Evaluation of the effects of dissemination*. PORTs are to evaluate the influence of their findings on provider behavior and assess how information can be most effectively presented to and assimilated by practicing health care providers. Their methods should encourage voluntary change, and their evaluations should assess the extent of reduced variation in practice patterns, more appropriate use of health care resources, and improvement in patient outcomes.

SPECIAL ASPECTS OF PORT RESEARCH

The research being conducted by PORTs is in many ways similar to traditional clinical, health services, and epidemiological research. By combining these types of studies, however, PORTs take on several features that justify giving them special attention in relation to conflicts of interest.

First, PORT research will be used in the development of practice guidelines. As such, PORT findings can be expected to influence medical practice more directly and broadly than the results of a clinical trial of a particular modality.

Second, research results that identify effective and ineffective practices are likely to influence third-party reimbursement decisions under public and private programs. In particular, as a high-visibility program backed by the desire of Congress to reduce health care expenditures, PORT research is likely to affect Medicare expenditures for conditions that are costly in terms of prevalence, technological intensity, or both. The findings of PORTs thus can have significant financial implications for both manufacturers of medical devices and drugs and for practitioners who rely heavily on modalities that may be found to be relatively ineffective.

Third, some PORTs may have multiple sources of funding in addition to federal funding. Finally, PORTs are multi-institutional and multidisciplinary. These last two aspects complicate the usual process of research oversight.

This summary of PORT characteristics suggests some ways PORTs differ from other forms of clinical research, especially randomized controlled trials. The difference between efficacy, as measured in clinical trials, and effectiveness, as measured in the community setting, is the primary distinguishing characteristic of outcomes research conducted by PORTs. Randomized controlled trial protocols are strictly determined at the outset, and outcomes are narrowly defined—generally, as survival or physiologic or anatomic end points. Clinical research faces many uncontrollable or unknown confounding variables—most notably patient variability, variability in health care delivery, variability in the quality of care provided by other health care professionals involved in patient care, the need to rely on data bases that were not designed for research purposes, and changing technology and practices. Clinical trials attempt to control for as much of this variability as possible by defining patient populations narrowly, using selected sites and practitioners, and restricting changes in technology. This makes it virtually impossible for clinical trials to be generalized to practice outside of highly skilled and carefully controlled settings. PORT research, however, seeks to measure the effectiveness of care in community settings. This results in large sources of variability and change which necessitate ongoing investigator judgment about study questions, design, and analysis.

Clinical trials usually compare a limited number of technologies (for instance, two surgical alternatives, or a pharmaceutical treatment compared with a placebo), rather than comparing all alternative treatments including new applications or "off-label" uses of older technologies (Wennberg, 1990a). PORTs, on the other hand, are expected to use retrospective data to compare all existing alternatives and to use prospectively gathered information to augment those data with a variety of outcome measures that are seldom part of randomized, controlled clinical trials.

Another research area that might be compared to the work of PORTs is so-called "pharmaco-epidemiologic" of three kinds: traditional postmarketing surveillance, cost-effectiveness research, and effectiveness research. Postmarketing surveillance involves the traditional recording of drug side effects, including both passive and active reporting systems. One example of an active reporting system is the prescription-event monitoring program in the United Kingdom (Inman, 1990). Cost-effectiveness research, like clinical trials, does not begin from a condition-specific perspective to compare all alternative treatments, but rather compares pharmaceuticals (e.g., the cost-effectiveness of antibiotic A versus that of antibiotic B in a hospital setting).

In searching for ways to promote the value of a new pharmaceutical in comparison to a competitor's, pharmaceutical companies have also

expressed greater interest in measures of clinical effectiveness and have begun to employ a variety of quality-of-life and health status measures (e.g., see Spilker, 1990). This form of effectiveness research does not focus on a condition to compare all alternative treatments either. Of the three kinds of pharmaco-epidemiologic research, work on clinical effectiveness is most similar to PORT research, especially to the extent that it uses measures in the public domain and reports the instruments and results of the research in the scientific literature so that they are accessible to other health services researchers (Bergner, 1990).

PORTs are notable for their combination of many of these methods, which opens up many points for researchers' judgment and discretion. For example, in reviewing the literature, PORT investigators must decide what studies to include and, once included, how much weight to give each of them. Thus, in the publication and peer review of PORT findings, careful attention must be given to the potential biases introduced during any stage of the research—analysis and synthesis of the literature, study design, incorporation of new treatment modalities, data analysis, and allocation of patients to alternative treatment groups. These issues are discussed in greater detail in Chapter 4.

SUMMARY

This chapter describes the structure and methods of PORTs. These methods include: review of the literature, including meta-analysis; data collection, including claims analysis, prospective data collection from records and patients, and decision analysis; dissemination of findings; and evaluation of the effects of dissemination. The chapter identifies special aspects of PORT research that distinguish it from clinical research and that justify giving PORTs special attention in relation to conflicts of interest. The next chapter describes the varieties of ties among individuals and institutions that may give rise to conflicts of interest and the ways they have been addressed.

Table 2.1 PORTs Funded as of October 1990

Title of Project	Principal Investigator and Institution	Funded Amount[a] (year)
Assessing Therapies for Benign Prostatic Hypertropy and Localized Prostate Cancer	John E. Wennberg Dartmouth College	$ 933,535 (1989)
The Consequences of Variation in Treatment for Acute Myocardial Infarction	Barbara J. McNeil Harvard Medical School	900,000 (1989)
Back Pain Outcome Assessment Team	Richard A. Deyo University of Washington	896,049 (1989)
Variations in Cataract Management: Patient and Economic Outcomes	Earl P. Steinberg Johns Hopkins University	899,986 (1989)
Assessing and Improving Outcomes: Total Knee Replacement	Deborah A. Freund Indiana University	999,993 (1990)
Outcome Assessment Program in Ischemic Heart Disease	David B. Pryor Duke University	901,498 (1990)
Outcome Assessment of Patients with Biliary Tract Disease	J. Sanford Schwartz University of Pennsylvania	1,076,980 (1990)
Analysis of Practices: Hip Fracture Repair and Osteoarthritis	James I. Hudson University of Maryland	1,007,785 (1990)
Variations in the Management and Outcomes of Diabetes	Sheldon Greenfield New England Medical Center	1,032,590 (1990)
Assessment of the Variation and Outcomes of Pneumonia	Wishwa N. Kappor University of Pittsburgh	980,674 (1990)

Variations in Obstetric Practice and Patient Outcomes[b]	Emmett Keeler The RAND Corporation

[a] The dollar amounts are for the first year of funding. Year is indicated in parentheses. The first four PORTs listed were funded through the Patient Outcome Assessment Research Program of the National Center for Health Services Research.
[b] This study is funded through a contract.

BOX 2.1 MULTI-INSTITUTIONAL CHARACTER OF PORTS: GRANTEE INSTITUTIONS AND ORGANIZATIONS OF KEY PERSONNEL AND SUBCONTRACTORS IN PORTS[a]

Assessing Therapies for Benign Prostatic Hypertrophy and Localized Prostate Cancer

Dartmouth Medical School
University of Massachusetts, Center for Survey Research
Massachusetts General Hospital
University of Connecticut
University of Copenhagen
University of Manitoba, School of Medicine
Oxford University
University of Wisconsin, School of Medicine
University of Iowa

The Consequences of Variation in Treatment for Acute Myocardial Infarction

Harvard Medical School, School of Public Health, John F. Kennedy School of Government, Harvard University
Beth Israel Hospital, Boston
Brigham and Women's Hospital, Boston
Mt. Sinai Hospital, Boston
Department of Veterans Affairs Medical Center, West Roxbury
Dartmouth University
Duke University

Back Pain Outcome Assessment Team

University of Washington, Department of Health Services, School of Medicine, School of Public Health
Department of Veterans Affairs Medical Center, Seattle
Group Health Cooperative of Puget Sound
Maine Medical Assessment Foundation
Massachusetts General Hospital

Variations in Cataract Management: Patient and Economic Outcomes

Johns Hopkins University School of Medicine, Center for Hospital Finance and Management, Health Services Research and Development Center, Dana Center for Preventive Ophthamology, School of Hygiene and Public Health
Georgetown University Medical Center

Assessing and Improving Outcomes: Total Knee Replacements

Indiana University Center for Health Services Research, School of Medicine
Research Triangle Institute
University of Toronto, School of Medicine
Pittsburgh Research Institute

Outcome Assessment Program in Ischemic Heart Disease

Duke University Medical Center
Dartmouth School of Medicine, Dartmouth-Hitchcock Medical Center
Harvard School of Public Health
Massachusetts General Hospital
New England Medical Center
Stanford University School of Medicine
Tufts University
University of California, Institute for Policy Studies
University of California at San Francisco, School of Medicine
University of Manitoba School of Medicine
University of Minnesota School of Public Health

Outcome Assessment of Patients with Biliary Tract Disease

University of Pennsylvania, Leonard Davis Institute of Health Economics, Wharton School, School of Medicine, Boston University School of Medicine and Public Health
Harvard University School of Public Health
Healthcare Research Affiliates, Inc. (Lemoyne, Pa.)
Medical College of Pennsylvania
New England Medical Center
Tufts University
Yale University School of Medicine
Geisinger Medical Center
Lancaster General Hospital, Lancaster, Pa.
Williamsport Hospital, Williamsport, Pa.
York Hospital, York, Pa.

Analysis of Practices: Hip Fracture Repair and Osteoarthritis

University of Maryland School of Medicine
Maryland Hospital Association
Merck, Sharp and Dohme Research Laboratories
University of Pennsylvania School of Medicine

Variations in the Management and Outcomes of Diabetes
New England Medical Center
Indiana University School of Medicine
Kaiser Permanente of Portland, Oregon
Massachusetts General Hospital
University of Michigan School of Public Health

Assessment of the Variation and Outcomes of Pneumonia
University of Pittsburgh School of Medicine, Graduate School of Public Health
Dalhousie University, Halifax, Nova Scotia
Harvard University School of Medicine, School of Public Health
University of Toronto

Variations in Obstetric Practice and Patient Outcomes
The RAND Corporation
University of California at Los Angeles School of Medicine

[a] This table includes affiliations of the principal investigator (PI), all co-PIs, and subcontractors as of October 1990 indicated in year 1 grant applications. Anticipated and unanticipated changes that may have occurred in subcontractors and consultants make this list illustrative rather than comprehensive.

3

Conflict of Interest

This chapter reviews definitions of conflict of interest used by other policy groups and institutions and provides a working definition. It also examines the categories of financial involvement that may give rise to such conflicts with particular attention given to university-industry relationships. Finally, it provides a brief overview of recent activities pertaining to conflict of interest in academic research and describes efforts in other sectors to deal with this issue.

DEFINING CONFLICT OF INTEREST

Conflict of interest arises in a situation in which (1) one is in a fiduciary relationship with certain others, and (2) one's financial or professional self-interest substantially differs from the interests of those others. The concern with conflicts of interest arises in biomedical research because of the possibility that such conflicts, both real and perceived, may erode scientific objectivity and engender the loss of public trust (Barber, 1983, provides a general treatment; Relman, 1989).

Because PORTs conduct research for the public benefit, PORT researchers have fiduciary obligations to the public. Yet their interactions with other groups (e.g., specialty or medical societies, pharmaceutical and device manufacturers), although necessary and even desirable, in some instances risk creating conflicts of interest.

Financial conflicts are of greatest concern to the public and Congress. They are also easier to regulate and less subjective than nonfinancial conflicts. This committee does not, however, consider financial conflicts of interest to be the only, or even necessarily the most important, concern related to sources of bias in PORT research. Observers of scientific research note that conflicts of interest and conflicts

of commitment[1] occur ubiquitously and unavoidably in professional life where the "coin of the realm" is some admixture of influence and power as manifested in personal prestige and career advancement, commitment to teaching, and furtherance of the activities of a research program, a university department, or the university itself. These professional conflicts of interest need not be conscious decisions on the part of the investigator; nevertheless, intellectual attachment or commitment to a particular scientific theory may pose some possible conflicts. All such interests may affect professional judgment and actions and thus constitute broader concerns than simply financial conflicts of interest.

Several definitions of conflict of interest reviewed by the committee placed particular weight on the financial aspects of such conflicts. [2] The committee took particular note of definitions of conflicts of interest that also addressed nonfinancial conflicts. The American Medical Association's Councils on Scientific Affairs and on Ethical and Judicial Affairs (1990) derived their definition of conflict of interest from *Webster's Third New International Dictionary*: a "conflict between private interests and official responsibilities of a person in a position of trust." This definition stresses private versus public interests where there is fiduciary responsibility. Similarly, the Association of Academic Health Centers (AAHC, 1990:7) offers the following: "A potential or actual conflict of interest exists when legal obligations or widely recognized professional norms are likely to be compromised by a person's other interests, particularly if those interests are not disclosed." This definition expands upon fiduciary responsibility by including legal and professional responsibilities, and it further implies that nondisclosure exacerbates the effect of a conflict of interest.

[1] As faculty members, most university researchers have a primary responsibility to the interests of the university (teaching, research, and possibly patient care). Conflicts of commitment arise when consulting arrangements or other outside ties, such as involvement with professional societies and participation on review panels, interfere with obligations to the university or receive undue benefit from investigators' research.

[2] For instance, at the workshop convened by the IOM committee, one participant suggested that conflicts of interest are "any interests, mainly any financial interests, that mitigate a researcher's desire to tell the truth about what he has found in his research." The definition of conflict of interest used by the National Research Council also stresses financial aspects: "any financial or other interest which . . . (1) could impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization" (National Research Council, 1989:5–6). Likewise, the Harvard Medical Center recently approved guidelines that refer specifically to financial interests and relate them to faculty research. The relevant section says, in part: "[C]onflicts arise from a faculty member's opportunities to benefit financially either from the outcome of his or her research or from the legitimate activities conducted in the course of his responsibilities as a faculty member."

Concern about the professional judgment of researchers is evidenced in the guidelines published by the Association of American Medical Colleges (AAMC, 1990). They state that the term conflict of interest refers to situations in which "financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research" (AAMC, 1990:6). The AAMC document acknowledges that the appearance of conflicting interests may be sufficient to discredit scientific results and undermine public trust.

The following sections of this chapter describe (1) financial conflicts of interest, and (2) academic and professional conflicts of interest.

FINANCIAL RELATIONSHIPS THAT MAY GIVE RISE TO CONFLICTS OF INTEREST

Financial ties that may give rise to conflicts of interest take two typical forms for clinical researchers. These are (1) equity or other financial relationships with a company that owns a technology that the researcher is evaluating, and (2) industry support for university research.

Equity and Other Financial Relationships

Financial interests can take several forms:

- equity interests, including stock and stock options, in a company that markets drugs or devices that are held directly by the investigator or indirectly through various financial systems or holdings by relatives;
- other profit-sharing arrangements;
- management or executive positions with such companies;
- royalties from licensing of intellectual property rights, including patents on inventions, copyrights (e.g., computer software), and sale of other proprietary materials; and
- consultant relationships and lectures for which honoraria are received.

When medical researchers acquire financial interests in the new drugs or clinical devices they are studying, or when they receive support for their laboratories from the manufacturer of those products, they face possible conflicts of interest. The degree of potential conflict of interest varies with the arrangement. Consultant relationships are common among university scientists and are thought to pose little risk to scientists'

objectivity, although some institutions routinely review such relationships to ensure that they do not create conflicts of commitment.

The formation of companies in which investigators retain equity interest, however, may pose substantial risk (Louis et al., 1989). Even more problematic, in the view of some, is investigators who purchase equity interests in existing companies that do business in their field of practice. For example, one participant in the IOM workshop stated forcefully, "I see no socially redeeming value in equity interest. This is just something any private person does who wants to play the stock market. It would seem to me that anyone who is doing medical research ought to play the stock market in some field other than health care." Other observers, however, fear that such strictures would discourage capable clinicians from participating in investigation and innovation. They believe that most conflicts arising from equity interests can be mitigated by disclosure.

Industry Support for University Research

University-industry ties are formed when industry enters into an agreement with an academic institution to support the work of an investigator. There are several types of arrangements for research and technology evaluation. Most arrangements that involve clinical trials of experimental diagnostics and therapeutics have one of the forms described below (MacCordy, 1988; American Medical Association Councils on Scientific Affairs and on Ethical and Judicial Affairs, 1990):

- Single projects in which a sole principal investigator is supported by one company. The research protocol may be devised by a drug company or other firm, designed by the investigator, or developed jointly;
- Program consortia involving multiple projects in a broad field of interest, many participating researchers, and both industrial sponsors and state or federal agency sponsors;
- Programs involving multiple projects and investigators but sponsored by a single company and without involvement by state or federal agencies; and
- Technology transfer cooperative agreements between industry and a university to promote rapid commercialization of new inventions such as those in biotechnology.

These last are of special interest to observers of PORTs because as PORTs develop special software, assessment instruments, and methods of dissemination of results, they may also engage in spinoff ventures.

ACADEMIC AND PROFESSIONAL CONFLICTS OF INTEREST

To concentrate on the extent to which people are motivated by money and to attribute any and all bias to personal greed ignores other powerful, noneconomic sources of bias that may be of special salience for professional groups. For researchers, desire for public recognition, publication, grant renewal, career advancement, or tenure may exert strong inducements to produce positive results. These outcomes may eventually lead to financial remuneration and increased financial security at some point, but this potential connection does not fully explain the intellectual satisfaction and similar psychological rewards not directly tied to academic advancement that can motivate researchers. Thus, professional conflicts of interest need not be conscious decisions on the part of the investigator. Subtle and unrecognized intellectual attachment or commitment to a particular theory can shape the design and interpretation of an investigation.

Although not unique to PORTs, the complexities of academic and professional conflicts of interest posed by the PORT approach to health services research raise special problems. PORTs' evaluations of clinical conditions depend on data from, and acceptance of their results by, professional groups and communities whose livelihood or professional behavior may be directly challenged by the research results. Wennberg has called attention to the effect of PORT research findings on the careers of both PORT investigators and those whose practices are examined (Wennberg, 1990b). If PORT members try either directly or indirectly to protect the subjects of their work, their colleagues, or themselves, such strong conflicting motives could cause bias in study design, data collection, data analysis, and dissemination of results. In addition to any bias in the collection and use of data, loss or distortion might occur when the results of PORT research are communicated to, and interpreted by, practitioners and patients. Dissemination of results by third-party payers or their consultants may add another source of bias (Wennberg, 1990b). Publication bias occurs when there is a greater likelihood of submitting and having accepted for publication positive results. Still other sources of bias stem from a desire to downplay the uncertainty that abounds in medical practice and which can result in the presentation of findings with greater implied certainty than is warranted (Thomas, 1983; Eddy, 1984; Wennberg, 1984).

Professional conflicts of interest arising from nonfinancial motivations are more difficult to identify, much less evaluate, than financial conflicts, and hence less likely to be amenable to direct university or federal regulations. The final section of this chapter reviews ways in which conflicts of interest have been addressed by academic institutions,

regulatory agencies and federal officials, and others with fiduciary responsibilities.

ADDRESSING CONFLICTS OF INTEREST

Until the 1980s conflicts of interest were usually managed by voluntary disclosure occurring within academic institutions, typically to the chairman of the department or other academic unit and, if appropriate, to a dean or other supervisor. Some state laws, however, prohibited public university employees from receiving compensation or engaging in other employment related to the subject of their research. During the late 1980s attention focused on several egregious cases involving clinical trials in which investigators appeared to have substantial conflicts of interest (Booth, 1988; Marshall, 1990).

In 1988 and 1989 Representative Ted Weiss (Democrat, New York) held hearings before the Human Resources and Intergovernmental Relations Subcommittee of the Committee on Government Operations. Although the 1988 hearings focused on fraud and scientific misconduct and particularly on delays and mishandling of such investigations (U.S. Congress, House Committee on Government Operations, 1989a), the 1989 hearings ("Is Science for Sale? Conflicts of Interest vs. the Public Interest," see U.S. Congress, House Committee on Government Operations, 1989b) focused on conflicts of interest and, in particular, conflicts deriving from industry-academic relationships in the field of biomedical technology. Other recent events related to conflict-of-interest issues in medical research are summarized by McNeil and Roberts (1990). Table 3.1 is a synopsis of the major events between 1960 and 1990.

Legislative Support for Technology Transfer

Among the many financial arrangements described earlier in this chapter, those concerning technology transfer have aroused particular fears about compromised objectivity, enhanced secrecy, and possible subversion of the mission of the university. These concerns center on equity holdings and spin-off ventures as components of biotechnology agreements with universities (Frankel, 1988).

The genesis of such agreements can be traced to legislative inducements in the early 1980s. In 1980, recognizing the increasing competition from foreign industrial nations and their government-supported incentives for technology transfer, Congress amended the patent laws to establish a presumption of ownership by universities of patentable

inventions produced by them under government-sponsored research. In addition, revisions of the tax code in the early 1980s created research and development limited partnerships; these offered tax shelters and high-investment income and may have attracted private capital to university research (Krimsky, 1988). At the same time, the potential rate of growth of biomedical research outpaced the federal money available for research stimulating researchers and their universities to seek funding elsewhere (MacCordy, 1988; Culliton, 1989; DHHS, 1989b; Harvard University Faculty of Medicine, 1990).

University-industry collaboration grew rapidly during the 1980s. The propensity toward commercialization of faculty inventions through more numerous university-industry ties became evident throughout biomedical research. This increasing number of collaborative arrangements between industry and academia raised questions in public and professional circles about their effect on the scientific enterprise.

EFFECTS OF UNIVERSITY-INDUSTRY COLLABORATION

PORTs examine the effectiveness of alternative treatments for clinical conditions. Because of their collected expertise, and the cost and time benefits of using existing patient cohorts, data, and investigative methodologies, drug and device manufacturers may offer financial support to PORTs that are willing to become involved in technology evaluations of the manufacturers' products. Such relationships may encounter the full spectrum of risks and benefits described above. In trying to anticipate them it is reasonable to review what is known about these risks and benefits.

To determine the effects of university-industry collaboration Blumenthal and his colleagues (Blumenthal et al., 1986a, 1986b; Gluck et al., 1987; Louis et al., 1989) conducted surveys in 1985 of faculty, postdoctoral students, and fellows whose work involved the new biotechnologies. According to the authors, faculty with industry support published more, had more patents, earned more, and served in more administrative roles than those without such support. Both groups devoted the same amount of time to teaching.

Compared to faculty with federal funding, faculty with industry support reported less "red tape" in conducting their research, increased rates of commercial application of their basic research, increased availability of resources, and enhanced career opportunities for students. These researchers reported, however, that their research involved more trade secrets (information kept secret to protect its proprietary value), although this only rarely affected their ability to publish; that they shared less

information with colleagues when it contained proprietary information; and that they were more likely than their colleagues without industry support to consider commercial applications in choosing research projects. Students and fellows with industry support occasionally reported fewer or delayed publications, some inhibition of scientific communication, and some restrictions on research. A few students reported that their advisors held equity in the companies for which the students were doing research.

RELEVANT EFFORTS IN OTHER SECTORS

In the last decade university-industry relationships have increasingly included the biomedical sciences; yet, as noted earlier, very few comparative assessments have been published on the risks and benefits of the variety of relationships adopted by universities and academic centers (on the one hand) and industries and for-profit and nonprofit external organizations (on the other). Policymakers do not have rigorous data about risks and benefits or data assessing the result of policies meant to affect these risks and benefits. There are many impressions, anecdotes, and a few well-publicized cases, and these tend to drive policy formulation (Hanna, 1989). For this reason, there is no single, proven, applicable model (much less an egregious case) to guide AHCPR in the development of industry-PORT relationships. Rather, investigators and AHCPR must proceed using their good judgment, knowledge of the attendant risks, and experience with other efforts to deal with conflicts of interest. The efforts described in this section may provide useful models for PORTs.

Regulation or Federal Employees

The federal government enacted ethical standards for all full-time and special employees through the Ethics in Government Act of 1978 and an explanatory memorandum in 1982. The act requires workers in executive, legislative, and judicial branches to make information about their financial interests publicly available through the Office of Government Ethics. All federal employees at grade GS-16 or higher must file an annual Executive Personnel Financial Disclosure Report (SF 278). In addition, DHHS issues standards of conduct for its employees that prohibit behavior regarded as a conflict of interest (see current standards in DHHS, 1989a). The Food and Drug Administration (FDA) has issued its own, even more stringent, standards for control employees —those who make regulatory decisions—in the FDA supplement to the HEW [Health

Education and Welfare] *Standards of Conduct* (45 CFR, Part 73a, February 24, 1978).

FDA Federal Advisory Committees

The FDA uses a specific disclosure form (FD 2637) and guide (FDA Staff Manual Guide 3118.2) for members of federal advisory committees to the Center for Drug Evaluation and Research. The form requests information on financial interests, current and anticipated contracts and grants, and professional employment and activities. The last include compensated or uncompensated consulting, lecturing, writing, teaching, and committee membership. The form also asks for service on behalf of corporations, state and local governments, societies, and so forth.

The United States Pharmacopeial Convention

The United States Pharmacopeial Convention is an independent, nongovernmental, nonprofit organization. Its Committee of Revision, which is composed of volunteer members, establishes and revises drug standards published in the *United States Pharmacopeia*, the *National Formulary*, and drug information monographs. Its rules include both disclosure and conduct. Prospective members of the Committee of Revision must state their industrial or commercial affiliations, sources of research support, companies in which the member or his or her family have financial interests greater than $10,000, any other interests that might be affected by revisions in drug standards, and any other relevant professional or financial interests or responsibilities. The rules of the committee stipulate that members shall not vote on the approval of any item or have sole responsibility for work on a monograph about any item for which they have a conflict of interest or the appearance of a conflict of interest (U.S. Pharmacopeial Convention, 1990–1995).

Professional Associations

Professional associations may also provide guidelines on conflict of interest in codes of ethics for their members. For example, the American Medical Association (AMA) has recently addressed conflicts of interest that may occur when practicing physicians are induced to prescribe a product in return for personal benefits. In December 1990, the AMA Council on Ethical and Judicial Affairs (American Medical Association,

Council on Ethical and Judicial Affairs, 1991) advised that the code of ethics for the medical profession would be violated by members accepting industry gifts including paid attendance at conferences and meetings. A similar and complementary report was adopted by the Pharmaceutical Manufacturers Association as a marketing code. The AMA report states that "gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value…. Cash payments should not be accepted." The report also recommends that subsidies for conferences should be used to reduce the conference registration fee rather than being given directly to physicians, nor should subsidies be used to pay for travel or lodging or to compensate for physicians' time. Reasonable honoraria and travel expenses for faculty, however, are considered acceptable. [3]

National Research Council

The National Research Council (NRC)[4] has adopted a statement on potential sources of bias and conflicts of interest for use in its studies (NRC, 1989). These studies are conducted by its volunteer committees that are appointed for their special expertise in the area of study. The NRC organizations make extensive efforts to assure that its reports are, and are perceived to be, free of any significant conflict of interest and that its reports are not compromised by bias in committee appointment process or by circumstances that may occur during the course of the committees' work. The NRC statement describes several situations that might occur during the course of a study and that might give rise to concern about conflict of interest. These include: any actions taken on the basis of reports that might later result in economic benefit or loss to particular individuals or groups; access to proprietary information; potential bias

[3] In the related area of pharmaceutical company influence on clinicians in academic health centers, some studies have found that both faculty and housestaff at teaching hospitals may have difficulty recognizing the degree to which actions by the pharmaceutical industry influence their own prescribing practices (Avorn et al., 1982) and the pervasiveness of such influence (Lurie et al., 1990). Lurie et al. (1990) used a survey to explore the nature, frequency, and effects of faculty and housestaff contacts with pharmaceutical representatives. Thirty-two percent of respondents reported having changed their practices at least once based on such contact. The receipt of honoraria or research support independently predicted faculty support for additions of a product to the hospital formulary.

[4] The National Research Council is the operating agency of the National Academy of Sciences and the National Academy of Engineering. The Institute of Medicine observes all procedures of the NRC.

arising from public statements and positions on a given subject; the design or implementation of procurements (including work statements or request for proposals); access to sensitive government information that might confer unfair competitive advantage; and problems caused by review of one's own work during the course of a study.

Individuals participating in studies and other activities complete a "Potential Sources of Bias and Conflict of Interest" form that elicits only information that is relevant and that merits disclosure in the light of NRC policies and the task to be undertaken. In addition, committee members are asked to discuss with one another possible sources of bias or conflict of interest at their first committee meeting and annually thereafter. Information regarding conflict of interest is considered by the institution in the overall composition of the committees and in the appointment or reconsideration of appointment of individuals to committees. The NRC approach is often to appoint members representing a balance of potentially biasing backgrounds or professional or organizational perspectives.

National Institutes of Health Grants Policy

The Public Health Service Grants Policy Statement entitled "Standards of Conduct for Employees" (Public Health Service, 1987:55) states that "recipient organizations must establish safeguards to prevent employees, consultants, or members of governing bodies from using their positions for purposes that are, or give the appearance of being, motivated by a desire for private financial gain." Each recipient institution must write policy guidelines on conflicts of interest that cover financial interests, gifts, gratuities, and favors. These rules must also indicate the conditions under which outside activities, relationships, or financial interests are proper or improper and provide for notification of a responsible, objective official within the grantee's institution, as well as notification of the grantee official, of any rule violations.

In September 1989, following a two-day conference sponsored by the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), NIH and ADAMHA issued, as a special issue of the *NIH Guide*, a request for comments on a proposed rule (DHHS, 1989b). The rule would have required that grant recipients avoid any prospective conflicts of interest and prohibited "personal equity holdings or options in any company that would be affected by the outcome of the research or that produces a product or equipment being evaluated in the research project (DHHS, 1989b:4). The rule also stated that no honoraria or fees should be paid to grant recipients and that there should be no disclosure of results to a sponsoring company until

such results were publicly available. Following a storm of protest by investigators, institutional spokespersons, and industry, the proposed rule was withdrawn in December 1989. NIH and ADAMHA held a public hearing ("Conflicts of Interest in Clinical Evaluation of Commercial Products") in late November 1990 to discuss approaches to rulemaking; it has promised to reissue revised guidelines in the *Federal Register.*

Academic Association and Institutional Guidelines

Early in 1990 both the Association of American Medical Colleges (AAMC, 1990) and the Association of Academic Health Centers (AAHC, 1990) published reports based on their ad hoc committees' considerations of conflicts of interest and commitment. Because PORTs are based in academic medical centers, the subject of the two publications overlaps with that of this report but is not coextensive with the issues addressed by this committee. Both the AAMC and the AAHC guidelines focus on financial conflicts of interest (though their definitions of conflict include nonfinancial concerns), and both stress the need for full disclosure of financial ties.

There are two mechanisms of disclosure. The first and more traditional is faculty initiated, although sometimes only if the faculty member is taking a management position or assuming an equity interest. The second is university initiated in which periodic reports are required of each faculty member. In some cases the university must approve consulting or sponsored research before it can be undertaken.

The guidelines recommend that institutions revise conflict-of-interest policies to enhance disclosure and argue that any prohibitions should be at the discretion of the institutions.

AAMC Guidelines

The AAMC guidelines call for disclosure of financial and professional interests. Such reviews are to be conducted annually and at the time any new relationships are anticipated; they should include both personal holdings and those of the researcher's immediate family. Questionable cases should be reviewed by the appropriate individual and, if necessary, referred to a standing committee that would have three roles: evaluation, adjudication and arbitration, and policy development. In its evaluative role the committee would review all information. In its adjudicative and arbitrative role it would determine whether a given situation was (1) unacceptable and thus prohibited, (2) permitted with the implementation of one or more committee recommendations to preclude

unreasonable levels of bias or inappropriate activities, or (3) permitted as disclosed. New policies or changes to existing policy would be formulated or reviewed by the standing committee, which would advise administrative officials on policy issues.

In part, the guidelines call for institutions to have appropriate mechanisms in place and, in particular, to develop and disseminate policies that clearly articulate the institution's position on "1) sponsored research, 2) acceptable types and levels of outside financial and professional interests, 3) the need to recognize and deal openly with real or apparent conflicts, and 4) the relationship of faculty and staff to outside institutions and third parties" (AAMC, 1990:9). Under the guidelines, institutions must "develop procedures for full disclosure to the institution, and to the interested public, of financial and professional interests that may influence, or may be perceived to influence, research activity or other scholarly responsibilities" (AAMC, 1990:9); implement enforcement procedures, including appropriate sanctions; assure management or resolution of conflicts of interest; respond expeditiously to questions raised; and avoid institutional conflicts of interest.

AAHC Guidelines

The AAHC guidelines call for the development of policies identifying activities that require prior approval and activities for which disclosure is sufficient. Thereafter, the guidelines recommend periodic disclosure of "[s]ignificant financial, personal, or professional relationships that raise a potential conflict of interest" not only to persons within the institution but also "in all speeches, writings, advertising, public communications, or collegial discussions . . ." (AAHC, 1990).

Academic Institutional Guidelines

Many universities have published or begun revisions of their conflict of interest and conflict of commitment guidelines to strengthen their oversight mechanisms and provide guidance to faculty members; to date, however, these guidelines are reportedly not widely known among researchers. Most research institutions expect to review contractual arrangements involving the institution to be certain there is no conflict of interest or conflict of commitment that would affect the university. A few have gone further and instituted required review of consulting arrangements. The emerging standards point to maximum scrutiny of a researcher's financial relationships with those organizations that produce

the drugs, devices, or other interventions the investigator is studying (McNeil and Roberts, 1990).

Johns Hopkins University and the Harvard University Faculty of Medicine issued revised guidelines late in 1990. The Hopkins guidelines ban ownership by a faculty member, a faculty member's spouse, and minor children of stocks or stock options in companies supporting a researcher's work, including the work of supervised faculty, nonfaculty employees, and students (Johns Hopkins University School of Medicine, 1990). The Harvard guidelines elaborate on categories of sensitive situations that are subject to particular scrutiny, including equity interests, consulting income, executive positions tied to the investigator's research, and certain forms of sponsored research (Harvard University Faculty of Medicine, 1990). These guidelines are described further in Chapter 5, "Managing Conflicts of Interest: General Models and Approaches."

Medical Publications

Hugh Clegg, former editor of the *British Medical Journal*, has stated "A medical editor has got to be a keeper of the conscience of the profession" (Lundberg, 1989:33). In keeping with this assertion, at least two journals publish explicit rules regarding disclosure of conflicts of interest in their "Instructions for Authors" (Lundberg and Flanagin, 1989; Relman, 1990). For example, the *Journal of the American Medical Association* (1990) requires a cover letter with submitted manuscripts that includes the following statement: "I certify that affiliations (if any) with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria, expert testimony) are disclosed below." The instructions further state that "[r]esearch or project support should be listed in an acknowledgement."

In April 1989, the *New England Journal of Medicine* adopted a similar disclosure policy for authors of articles. The following July, editor-in-chief Arnold Relman announced an even stricter policy for authors of review articles and editorials, who must have "no financial association with a company whose product figures prominently in the article or with a company making a competitive product" (Relman, 1990:56). In explaining the editorial decision, he wrote, "When authors have a financial as well as a scientific interest in their subjects, questions inevitably arise that cast doubt on this presumption of objectivity."

Judicial and Legal Approaches

In the field of law an attorney may decide that a conflict of interest is serious enough to disqualify him or her from representing a client, despite full disclosure and informed consent. Individual law firms have guidelines for their staff attorneys and complex systems for tracking representation of the various interests of their clients to ensure that conflicts do not arise. Similarly, judges, in certain cases, recuse themselves because of a possible conflict of interest. During the IOM workshop, Arnold Relman noted that both the judicial system and clinical research bear responsibilities as public institutions:

> The public would not accept the fact that a judge, however honorable and impeccable his legal background and however open he is to judicial review later on, should preside over a trial in which he has significant interest in one of the contesting parties. It just isn't done, because it's a public institution. Clinical biomedical research is a public institution in which the public makes an enormous investment.

SUMMARY

This chapter reviews financial conflicts of interest, particularly those that affect university-industry relationships, and nonfinancial conflicts of interest. It has described the ways that academic and professional organizations and other groups with fiduciary responsibilities have attempted to manage conflicts. Chapter 4 examines how these general categories of conflicts may apply to PORT research.

TABLE 3.1 Relevant Events, Publications, and Related Activities concerning Conflicts of Interest (COI) in Academic Medical Centers, 1960–1990

Period	Relevant Events[a]	Other Related Activities[b]
1960–1969	1964, Joint Statement of AAU and ACE Voluntary disclosure, self-regulation, and general guidelines stressed until 1980s	
1970–1979		1978, Ethics in Government Act May 1978, Extensive FDA regulations regarding COI applicable to FDAemployees with responsibilities related to regulatory decisions (FDASupplement to DHEW Standards of Conduct) March 1979, DHHS Standards of Conduct for government employees
1980–1988	1980, Stevenson-Wydler Technology Innovation Act (P.L. 96-480) establishes a national policy of encouraging cooperative arrangements among industry, government, and academic institutions	
	1981, Over-sight Subcommittee of the House Committee on Science and Technology calls on AAU Committee on University-Industry Relations to develop ethical guidelines—AAU concludes that uniform guidelines are unnecessar	1982, Implementing Memorandum for Ethics in Government Act

Period	Relevant Events[a]	Other Related Activities[b]
	1983, AAU establishes Clearinghouse on University-Industry Relations Some institutions initiate mandatory annual disclosures by faculty Enactment of state laws prohibiting public university employees from receiving compensation in connectionwith a business in which the employee has a substantial interest or from other employment that might impair judgment September 1987, NIH amendment to the PHS Grants Administration Manual(Standards of Conduct)—grantee institutions must implement writtenpolicies and establish safeguards for grant recipients to avoid COIor the appearance of COI	1986, Federal Technology Transfer Act (FTTA) (P.L. 99-502) establishes basis for cooperativeresearch agreements for NIH and other government investigators Federal regulations directed at institutions (e.g., prohibiting "wired" bidding" April 1987 President Rea-an signs Executive Order No. 12591 orderingenforcement and compliance with FTAA September 1988, Rep. Ted Weiss holds hearings (House Committee onGovernment Operations): "Federal Response to Misconduct in Science:Are Conflicts of Interest Hazardous to our Health?" (misconduct)
1989	January 1989, *NIH Guide for Grants and Contracts* states the agency's expectation that participating investigators "will not have financial interest in organizations that produce drugs, devices, or other interventions studied in a controlled clinical trial" (p. 1) April 1989, Healy and colleagues publish self-denying policy forPost-CABG Clinical Trials-key investigators will not buy, sell, orhold stock or stock options nor serve as paid consultants throughout course of study	March 1989, NIH establishes Office of Scientific Integrity and Office of Scientific Integrity Review (for investigation of scientific misconduct)

Period	Relevant Events[a]	Other Related Activities[b]
	April 1989, editor of *NEJM* calls for disclosure to editor of financial ties and at time of publication June 1989, conference of NIH and ADAMHA June 1989, Congressional hearings, "Is Science for Sale? Conflicts of Interest vs. the Public Interest" September 1989, NIH-ADAMHA "Proposed Guidelines for Policies on Conflict of Interest" would require researchers to avoid any prospective financial COI or disclosure of any industry-funded research results until the results are publicly available October 1989, *JAMA* publishes disclosure requirements for authors submitting articles for publication December 1989, after an avalanche of negative comments, NIH-ADAMHA proposed guidelines for policies on conflict of interest are withdrawn; new proposal to be published in *Federal Register*	August 1989, the PHS publishes in *Federal Register* "Responsibilities of Awardee and Applicant Institutions for Dealing with and Reporting Possible Misconduct in Science" (misconduct November 1989, AAU issues "Framework for Institutional Policies and Procedures to Deal with Fraud in Research" (fraud)
1990	February 1990, AAMC "Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research" advises members to develop policies for full annual disclosure	

Period	Relevant Events[a]	Other Related Activities[b]
	of potential financial and professional COI to their institutions and to the interested public, with consideration when appropriate by a designated institutional committee Spring 1990, AAHC "Conflicts of Interest in Academic Health Centers," Policy Paper No. 1, endorses full disclosure of possible COI to institution and in "all speeches, writings, advertising, public communications, or collegial discussions" March 1990, Harvard University Faculty of Medicine Guidelines on Conflict of Interest and Commitment elaborate on categories of sensitive situations, including those where equity interests executive positions, and certain forms of research support will be subject to maximum scrutiny July 1990, *NEJM* editorial and "Information for Authors" announces that henceforward, authors of review articles and editorials should have no financial association with a company reviewed or discussed November 1990, NIH and ADAMHA hold public hearings on "Conflict of Interest in Clinical Evaluation of Products" to discuss general principles and proposed approach	

NOTE: AAHC, Association of Academic Health Centers; AAMC, Association of American Medical Colleges; AAU, Association of American Universities; ACE, American Council on Education; ADAMHA Alcohol, Drug Abuse, and Mental Health administration; DHEW, Department of Health, Education and Welfare; DHHS, Department of Health and Human Services; FDA, Food and Drug Administration; *NEJM*, New England Journal of Medicine; NIH, National Institutes of Health; *JAMA*, Journal of the American Medical Association; PHS, Public Health Services.

[a] Events related to conflict of interest involving research in academic medical centers.

[b] Related events but not involving conflict of interest or academic medical centers.

4

Sources of Concern About Conflicts of Interest in PORTs

Chapter 2 examined several ways in which PORTs are different from other clinical research and that might therefore raise special concerns about conflicts of interest. Chapter 3 defined and described several kinds of university-industry relationships that may give rise to conflicts. This chapter describes in more detail 11 issues (Box 4.1) that are especially pertinent to PORTs. The first seven issues are inherent to PORTs as they are currently configured and funded by AHCPR. When non-AHCPR funding is added or as PORT members engage in new ventures related to their PORT research, additional concerns may arise; these last four issues are described in the latter part of the chapter.

ELEVEN ISSUES OF SPECIAL CONCERN

PORTs as Hybrid Entities: Research and Quasi-Regulatory Functions

PORTs as a Public Trust for Development of Scientific Knowledge

PORTs are highly visible examples of academic science and technology; as such, they are part of a sizable public investment in academic medical research that is intended to improve health. Such government-supported basic and applied biomedical research has over the decades resulted in major advances in scientific knowledge (Hamburg and Nightingale, 1984; Colloton, 1989; Schroeder et al., 1989).

There are three deeply held public views about these undertakings. First, academic science is seen by many as an engine of creativity and innovation that drives social welfare. Biomedical research has led to scientific discoveries and major technological applications for the care of

individual patients. Indeed, the academic medical center plays a central bridging role in the development and transfer of health care technology between industry and medical practice, regularly participating in the development, diffusion, and appraisal of appropriate applications and cost (Rettig, 1987). PORT investigation, a young and rapidly evolving science, consists of methods for evaluating and improving medical practice by considering the effectiveness of care through outcomes research. It is thus at the heart what has been termed "the new technology assessment" (Fuchs and Garber, 1990).

Second, academic scientists, through their participation in hundreds of advisory and peer review committees, are counted on as a source of impartial advice to the public and to funding and regulatory agencies; any challenges to their impartiality are seen as highly significant and are widely publicized. When serving as advisors on matters of public policy, academic scientists must feel free to publish, share data, and speak out in the public interest (Krimsky, 1988). Indeed, for the advisory process to work effectively it must secure unbiased, objective advice from individuals who are financially disinterested in the areas in which they consult. PORTs in particular have been designated by Congress to provide such advice to practitioners and to the Medicare program. By contrast, industrial scientists have visible affiliations with business and are not expected to be impartial.

Third, in undergraduate and graduate training, academic science teaches scientists, citizens, and future political leaders how science is conducted. To the extent that PORTs become a model for complex health services and clinical evaluation research of the future, they will certainly affect the values of graduate students. Moreover, the values of science that are learned in institutions help form each generation's social decision makers (Grobstein, 1988). All three of these public views—promoting health, providing impartial advice, and preserving the values of scientific inquiry—although not unique to PORTs, are important to consider when examining conflicts of interest.

PORTs as a Quasi-Regulatory Process

Is there good reason at this point to single out the research activities of PORTs for special requirements? PORT research is similar to other forms of research that receive intense and increasingly public examination from the standpoint of conflict of interest. PORT studies are also different from other types of biomedical or social science. Most prominently, PORTs will directly influence health care. Although PORTs will not themselves make decisions about insurance coverage for the

medical procedures they study, the results of their research will be a key factor in these decisions. Indeed, that is surely one reason why AHCPR has focused PORT research on conditions affecting chiefly the elderly beneficiaries of Medicare; furthermore, PORT findings may have more effect on professional norms than an individual clinical trial could have, in part because of the diverse clinical specialties involved and in part because of the likely wide visibility and dissemination of results in many clinical journals and health services research publications.

Protecting PORT Credibility

PORT findings are likely to be controversial from the viewpoint of clinicians, manufacturers, and other interested parties; whether they are "positive" or "negative," they may not be accepted without struggle. That struggle will probably involve examining all potential sources of bias, possibly with the intent of damaging the credibility of the PORT findings. A likely tactic would be to call into question the sources of PORT funding as a source of bias or the possible biases of its members.

These considerations argue for well-defined, irreproachable standards to address the appearance of conflict of interest as well as its actual occurrence. They may also call for a level of scrutiny and threshold of acceptability that are higher than those established for other research efforts—perhaps comparable to those for judges, public officials, and others with fiduciary responsibilities.

PORTs are strengthened by their multidisciplinary character and multisite teams, as well as by incorporating the multiple perspectives and literature of each discipline into their research. This diverse participation can mitigate the possibility that biases of individual investigators will distort the final analysis (Lave, 1990), a feature that PORTs may be required to demonstrate convincingly to would-be detractors.

Expectations of Cost Savings

Workshop participants and committee members noted the conflict inherent in a mandate from Congress that is intended not only to improve medical care but also to control federal expenditures. Some observers see this savings as the primary motivation for congressional funding of outcomes research. For this reason, there is an implication that AHCPR, or individual PORTs, may be at risk of losing their funding if their findings do not lead to cost savings. Consistent findings of under use of expensive technologies might be even less welcome.

In addition to the conflict engendered by the federal government's interest in cost savings, insurance companies might also place subtle pressures on PORTs. For example, those interested in reducing practice variations might develop consulting arrangements, offer to fund additional PORT research, or allow access to their data in hopes of identifying excessively costly practices. The intended or unintended effect of the PORTs' work and of collaboration with third party payers whether public or private, may be to reduce access by the public to various treatments. These pressures, which are not generally present in traditional clinical research, were recognized quite early by supporters of outcomes research. With respect to government funding, one important factor mitigating such pressure is the placement of MEDTEP in the U.S. Public Health Service rather than in the Health Care Financing Administration, even though much of the early initiative for effectiveness research originated in the latter agency (Roper et al., 1988). This decision was made because both DHHS and Congress feared that if the program were located in the Health Care Financing Administration, it would be seen as more interested in saving money for federal programs than in promoting good care for all citizens. PORTs thus have some protection from possible accusations of being tied too closely to federal cost-savings objectives, but the threat is not completely answered.

Concentration of Expertise

Many participants in the IOM workshop were concerned about the implications of the concentration of expertise that will occur in the multidisciplinary PORTs (a problem not unique to PORT research). This concentration may constitute an imprimatur (some observers have used the term "taxi medallion") based on expertise, credibility, and long-term funding that gives PORTs an advantage in continued funding and makes challenges to their findings difficult (Lave, 1990). It also makes the effect of bias at any stage of the research less easily or quickly detected. Other workshop participants disagreed with this pessimistic assessment. In their view, particularly in fertile clinical areas such as cardiac diseases, funding for PORTs is not sufficiently large to make PORT studies the dominant efforts in their field. In any case, understanding the ramifications of a concentration of people, experience, knowledge, and research support may have to await several years of sustained PORT funding—perhaps well past the first five years of the PORTs that are now operating.

Subjective Judgments and Multidimensional Outcome Assessments

The work of PORTs will necessarily involve many areas of uncertainty, and these will aggravate the risks of private and professional conflicts of interest. Although clinical research often has a subjective element, judgments in PORT research depend more heavily than do those in most clinical research on multidimensional, self-reported outcome data from patients. PORT investigators must also make subjective judgments and interpretations when weighing the importance of various health outcomes. Important dimensions of health status and quality of life include death, discomfort (both physical and psychological), various aspects of functioning (including physical, cognitive, social, and role functioning), and general aspects of well-being (Lohr, 1988; Patrick and Deyo, 1989; Patrick, 1990; Patrick and Bergner, 1990). Related economic outcomes might include both direct medical costs and indirect costs such as loss of productivity; opportunity costs, which describe the costs of alternative uses of resources, might also be estimated (Fries and Spitz, 1990). The measures selected to reflect outcomes (both health and economic), as well as the judgments derived from these measures, may be more vulnerable to bias than those based on traditional physiologic or anatomic end-point data, and these biases may be difficult to discern.

Choosing important outcomes and ranking them in comparison with other outcomes are likely to be influenced by professional concerns, financial interests, and personal preferences. Outcomes of a very risky and costly procedure, for instance, are likely to be viewed differently by the manufacturer of a device used in the procedure, a surgeon who derives satisfaction from achieving even a small benefit, or by patients with different tolerance for symptoms contributing to indications for the procedure.

Even where consensus on appropriate outcomes is achieved, developing a set of reliable, valid, and practical outcome measures for application to the diverse clinical conditions examined by PORTs is extremely challenging and complex. The work that must be done in choosing among existing measures and, when necessary, devising new or combined measures has just begun.

Researchers must also exercise subjective judgment in determining what materials are to be included in meta-analysis. Some published studies and most unpublished studies may be excluded because they fail to meet the inclusion criteria established by PORT investigators. Another possible source of bias is the selection of methods to conduct the necessary "cleaning" and transforming of insurance claims data tapes; yet, these methods generally are not described in detail.

Use of such data for decision analysis and the construction of guidelines for clinical decision making involves more uncertainty. The apparent precision of decision-analytic techniques and algorithms for care may lend weight and importance to information that must be treated more cautiously. Often data to provide probabilities for a given risk or benefit are missing or very limited—for instance, only mortality data may be available. A range of probabilities derived from several studies may differ enough that investigators will not be able to make specific clinical recommendations with confidence. Thus, another area of possible bias is in the dissemination of findings through practice guidelines. The science of developing clinical practice guidelines, however, is still so rudimentary and sketchily documented that these activities should also be considered highly subjective (IOM, 1990).

Biases Arising from Ties to Professional Colleagues and Associations

PORTs are designed to examine services that are costly or prevalent (or both) and that consequently are likely to provide a large proportion of the income of health care professionals, particularly in specialties related to the interventions being evaluated. PORT researchers must rely on the active participation of individual practitioners and professional societies to enroll patients in their studies and to conduct some primary data collection about patient preferences regarding risks and outcomes.

For example, the outcome assessment team at the University of Washington is investigating low back pain, a problem that is the second leading reason for all physician visits and the leading reason for visits to orthopedic surgeons and neurosurgeons. There are large variations in per-person rates by geographic area in the use of surgery, hospitalization, and diagnostic technology. The value and sequencing of diagnostic tests for improving the patient's quality of life (the primary purpose of treatment) are not well understood. The scientific evidence for the efficacy of most treatments is limited, yet the rate of lumbar spine surgery is increasing. The PORT will examine three surgical procedures on the spine—laminectomy, discectomy, and spinal fusion. Assessment of symptom resolution and improvement in functional status will be examined in a cohort study conducted by the Maine Medical Assessment Foundation. Most of the orthopedic surgeons and neurosurgeons in the state of Maine who perform surgery on the spine will contribute patients to this cohort study (Deyo et al., 1990).

PORTs generally have both regional and national advisory boards that include representatives of the specialties and other professional

associations affected by their research. This is a source both of strength and of potential bias; consequently, all PORT investigators will need to develop procedures to mitigate unconscious biases arising from a desire not to alienate colleagues and professionals who are cooperating and contributing patients to the PORT projects.

Another source of bias may arise in relation to professional societies and health delivery systems. PORTs may enter into consulting agreements with such groups to support them in related research that confirms or refutes findings or tests new technologies that might increase the range of skills of their members. The desire to help these groups may be another source of bias. This type of bias could also occur if PORTs begin to evaluate alternative health care settings (e.g., hospital intensive care, home care). Interested and concerned groups in this case would include the relevant health care organizations.

Access to Data

Workshop participants and members of the IOM committee were concerned about ensuring access to the data collected by PORTs to allow subanalyses and reanalyses by other groups. Such secondary analyses may well be valuable in their own right; they also offer an opportunity for skeptical audiences to confirm (or refute) PORT findings.

Access to Medicare data analyzed by PORTs is subject to certain restrictions. The same general points probably apply as well to insurance data purchased from private carriers or obtained from state data consortia. General access to these valuable data bases can be facilitated or restricted by AHCPR (through grant and contract specifications) and by the PORTs themselves. However, PORTs can, if they choose, constrain other groups analyses of already collected data. This is a common problem in science (e.g., see Cantekin et al., 1990) that presents no unique obstacle unless it is compounded by a conflict of interest.

Adequacy of Existing Institutional Guidelines

Multi-Institutional PORTs

Participants at the IOM workshop emphasized the importance of institutional monitoring, management, and resolution of conflict-of-interest issues. PORTs are multi-institutional (see Box 2.1); thus, investigators collectively have numerous "home" institutions. PORTs may, in addition,

have subcontracts with other institutions. As a result, single-institution policies are likely to be inadequate for these PORTs.

AHCPR considers the primary grantee or lead institution to be responsible for managing conflict-of-interest situations. Generally, the lead institution accepts the judgments of the institutions with which it has subcontracted and would expect to be notified of any relevant conflicts of interest that were revealed. Several participants at the IOM workshop and other health services researchers who have PORT subcontracts noted, however, that they are unaware of their own institution's policies on conflicts of interest or that those policies have not been revised for many years and may no longer suffice in the PORT environment. Further, awareness and acceptance by PORT members of a lead institution's policies represent only the first step towards avoiding conflict of interest. Should questions and issues arise about conflicts of interest in a PORT during the five-year course of conducting a study, the lead institution will need to have a mechanism for responding to these questions.

Nonuniversity Clinicians and Their Patients

Another special issue for PORTs is the research and conflict-of-interest implications of including or excluding nonuniversity clinicians and their patients. For research, the exclusion of certain clinicians might result in a nonrepresentative group of patients, thus jeopardizing the generalizability of the PORT findings. In terms of conflict-of-interest considerations, nonuniversity clinicians who have not been exposed to institutional conflict-of-interest guidelines may be unused to, and find objectionable, queries about their finances.

Matters that raise the issue of conflict of interest are not, however, foreign to nonuniversity clinicians. There have been numerous reports, for example, of brokers who offer physicians stock in companies that manufacture drugs that the physicians presumably prescribe (Morris, 1990); offers of direct payment for prescribing certain medications (Wolfe, 1990); of drug companies that offer to pay for conferences as an inducement to try a new product (Jenike, 1990; Schonberg, 1990, Wolfe, 1990); and of investment opportunities in laboratories to which physicians could refer their patients for testing (Rodwin, 1989). That such inducements are common does not make them acceptable or lessen the need to guard against their influencing PORT findings. If clinicians in private practice are to participate in PORT research, as seems both necessary and appropriate, attention must be paid to including nonuniversity clinicians in the administration of any prohibitions, limitations, or disclosure

requirements that may be implemented to protect against conflict of interest.

Private Funding for Technological Modifications and New Practices

The issues above pertain to PORTs supported only with federal funding. PORT methodology is evolving, however, and now may include the collection of prospective data involving new types of health status measures as well as patient-administered outcome measures among specified (although not randomized) groups of patients. Aspects of controlled trials thus may come to be incorporated in PORT design, and private funding of many kinds may be grafted onto core PORT funding. These factors, as well as the more usual questions related to equity interests in products under evaluation, raise special issues regarding conflict of interest, and are described in the remainder of the chapter.

During PORT investigations, which presently are expected to last approximately five years, PORTs are likely to need (or at least attract offers of) additional funding from industry, other federal or state agencies, and insurers. MEDTEP expects PORTs to evaluate existing practices, but it is quite possible that these practices will change during the grant period. Although current annual funding levels per PORT are approximately $1 million (direct plus indirect costs), there is no guarantee that this level of support will be maintained in the future. In addition, more problems invite in-depth investigation than can be studied with current AHCPR funding. As ready-made groups of investigators and study sites, PORTs are an attractive vehicle for industry research funding. The committee envisions three main kinds of agreements: additional study arms, secondary protocols, and consulting and other financial arrangements. The development by PORT investigators of spin-off ventures and copyrights on intellectual property rights are yet other possible financial arrangements.

Additional Study Arms

Corporate sponsors recognize the potential of PORTs to influence significantly the adoption and dissemination of their innovations. Thus, mixed financial agreements might support the investigation of new devices or drugs as added study arms within an initial PORT study. With an agreement of this kind, PORT researchers could be assured that their findings represented up-to-date practices; physician and patient decision making could be well served by having all alternatives included in a study.

In addition, private, rather than public, funds could be used to support any evaluations with possible commercial value.

Despite the potential advantages of this form of collaboration, the committee also sees certain hazards. One is concern about the scientific legitimacy of studies that are developed as contracts rather than as peer-reviewed grant proposals. Another concern is the implication of any special agreements restricting communication or publication of results (discussed in greater detail in a later section) or otherwise compromising the rights of the investigator or university. This may be especially problematic for institutions that may come to be involved in PORTs at some later time and that do not have the well-established review and monitoring systems of PORTs funded earlier.

Industry might also use such a relationship to "advertise" its association with a PORT. This might, in turn, raise doubts externally about the objectivity of the PORT effort. Moreover, PORT findings that endorse a product whose evaluation has been paid for by its manufacturer appear suspicious, giving an appearance of conflict of interest even where none exists. For all these reasons, the expectations and limitations of the collaboration must be made clear when agreements are fashioned.

Secondary Protocols

A second possible form of PORT-industry collaboration is the performance of secondary protocols by one or more PORT investigators concurrently but separately from PORT investigations. Assignment of patients to one study rather than another might represent a nonscientific or scientific conflict of interest. For example, a nonscientific conflict of interest might occur if an investigator whose continued secondary funding depends on enrolling a sufficient number of cases recruits patients preferentially to the secondary protocol. A scientific conflict of interest might occur if systematic recruitment weakens the power of the PORT study, (i.e., the ability of the investigators to find statistically significant differences or to draw strong and proper inferences from their data).

Consulting and Other Financial Arrangements

A third form of PORT-industry collaboration can occur if members of a PORT are offered consulting arrangements with manufacturers that produce related products and services or with a private consulting firm that is under contract with the manufacturer. Companies would benefit from having the most current information in designing their own studies and

using the most advanced health status measures. From the vantage of clinicians and their patients, such industry studies would benefit in their design and methods from the expertise of senior investigators in PORTs. Nothing in PORT grants now precludes consultation or other arrangements with firms that are developing devices or drugs related to those under evaluation by the PORT or that are competitive with those under evaluation, yet this would seem to pose a hazardous potential for conflict of interest.

Spin-Off Ventures and Intellectual Property Rights

Another form of industry-PORT relationship might occur when, in the course of their study, members of the PORT develop special expertise. This might, for instance, involve special software for claims data analysis, survey tools to assess outcomes, approaches for assessing utilities or patient preferences, and educational programs describing alternative treatments. Primary data collection on patient preferences for various outcomes could be seen as extensive pilot testing (Asch, 1990). Over time the accumulation of such expertise or related products could lead to the monitored or unmonitored formation of businesses in which members of the PORT have a financial interest (McNeil and Roberts, 1990). Although such developments would likely serve many social goals, members of PORTs would also be uniquely positioned to benefit from these commercial applications.

Other expertise might also be commercialized in a manner analogous to the technology transfer so encouraged by tax provisions and other legislation. For instance, knowing that insurance companies might be eager to purchase information on the appropriateness of various medical practices, sideline consulting firms (developed by PORT or nonPORT investigators) might provide services designed to assess appropriateness using relevant intellectual property developed with federal PORT funding.

Equity Interests of PORT Investigators

As with other forms of research, members of PORTs are at risk for conflicts if they have equity interests in the subject of their research or in related or competing companies. Because PORTs focus on existing products and services with direct market implications for their findings, such collaborations may present heightened opportunities for exploiting inside information for financial benefit (Asch, 1990).

Freedom of Communication Within PORTs

The evolving methods and large size of PORTs require flexibility and an ongoing exchange of information among investigators and with industry; when industry provides funding, however, it may seek to protect patent rights and investment by limiting the exchange of information. As described in Chapter 2, secrecy has become more common in the field of biotechnology (Blumenthal et al., 1986a,b; Krimsky, 1988). To the extent that voluntary or involuntary restrictions on free discussion inhibit PORT evaluations, they represent a conflict of interest for PORT researchers (Eisenberg, 1988).

In particular, when agreements are made between manufacturers and biomedical researchers, they commonly include so-called secrecy and exclusivity clauses temporarily restricting the investigator from interactions that might compromise the patentability or competitive advantage of the product at issue. For instance, such clauses might prohibit, except with the manufacturer's approval, the disclosure of confidential proprietary data, or knowledge pertaining to the research, development, marketing, or any other aspect of the company's products. Secrecy clauses might restrict the freedom to publish results or to discuss information about the products that are being evaluated by a PORT. Exclusivity clauses refer to restrictions on PORT members, when they are acting as consultants, that prevent them from consulting with or communicating with competing companies. For instance, a clause of this sort might prohibit an investigator from consulting with any other person or entity on matters pertaining to the areas covered by the agreement for a stated time period.

Some observers worry that freedom of communication among all PORT investigators could be compromised if collaboration requires adherence to overly restrictive secrecy and exclusivity clauses. This in turn might jeopardize, or be perceived as jeopardizing, the work and results of the PORTs (both individually and collectively).

Another concern is related to possible restrictions on publication. When industry funds the evaluation of an alternative treatment as part of what is essentially federally funded research, the risks in terms of overall outcome should be understood. "Good" results can be an enormous advantage to the company, but "bad" results are possible. If the results of a PORT evaluation are not encouraging, the company might wish to restrict publication of the data. On the other hand, if the data are very positive, the manufacturer might wish to publicize them widely (or constrain any counter analyses).

SUMMARY

This chapter describes eleven sources of special concern about conflict of interest: (1) PORTs as a new hybrid entity having both academic medical research and "quasi-regulatory" functions; (2) congressional expectations regarding the cost-containing effects of PORTs; (3) the concentration of expertise in PORTs; (4) PORT use of qualitative, subjective, and patient-reported qualitative judgments in outcome assessments; (5) the potential for biases arising from professional and collegial ties to the nonPORT practitioners; (6) the need for access to PORT data bases; (7) the possible inadequacy of existing institutional guidelines for PORTs; (8) the likelihood of private funding to evaluate technological modifications and new practices; (9) of financial arrangements related to spin-off ventures; (10) of bias resulting from equity interests held by PORT investigators in companies whose products are being evaluated; and, (11) the need to ensure freedom of communication within PORTs despite university-industry collaborative agreements. Ways to approach these conflicts of interest generally and with reference to PORTs in particular, are taken up in Chapters 5 and 6 respectively.

BOX 4.1 SOURCES OF SPECIAL CONCERN ABOUT CONFLICTS OF INTEREST IN PORTS

1. PORTs are a new hybrid public trust entity having both academic medical research and "quasi-regulatory" functions. Expectations that they will influence public policy confers special expectations and obligations on them.
2. Congressional expectations regarding the cost-containing effects of PORT findings may result in a powerful potential bias.
3. A concentration of expertise in PORTs may give them a continuing advantage over other researchers in obtaining grants and contracts, disseminating findings, and influencing insurance reimbursement and other policies.
4. The use of subjective, patient-reported qualitative judgments in outcome assessments, in contrast to the usual physiologic and biologic end points of clinical research, makes PORTs more vulnerable to subtle biases.
5. PORT researchers are vulnerable to biases arising from professional and collegial ties to the non-PORT practitioners who supply the patients being studied and to professional colleagues generally.
6. General access to valuable PORT data bases can be facilitated or restricted by the PORTs.
7. Existing institutional guidelines may not be adequate guidance for multi-institutional PORTs and nonuniversity clinicians.
8. Private funding to evaluate technological modifications and new practices may influence PORT research.
9. PORT members are likely to enter financial arrangements related to spin-off ventures using intellectual property rights as a result of their PORT research.
10. Equity interests of PORT investigators in companies whose products are being evaluated present special hazards in the appearance and possibly the reality of conflict of interest.
11. Freedom of communication within PORTs may be compromised by university-industry collaborative agreements.

5

Managing Conflicts of Interest: General Models and Approaches

The management of conflict of interest might be approached from two different models. One is based on a *presumption against* any relationships that might present a conflict. This we call a "prohibition model," although such a prohibition might be overcome with a demonstration of sufficient social benefit. The other is based on a *presumption for* such relationships with a provision for disclosure and review. We call this model "disclosure and peer review."

TWO MODELS OF CONFLICT OF INTEREST MANAGEMENT

Prohibition Model

The prohibition model discourages any arrangement, particularly financial, that might create a conflict of interest unless that arrangement provides a sufficiently countervailing social benefit. Implementing this approach requires that those who advocate it establish a framework within which certain conflicts of interest may be acceptable. Within this framework the first consideration is whether the activity presenting the conflict of interest has any redeeming social value. If it does not, a process is required for prohibiting the activity and hence the conflict of interest. Second, if there is redeeming social value, does it clearly outweigh the risk of biased or incomplete conduct or reporting of research? If not, a process is needed to examine the arrangement or activity further and probably to prohibit it. If the putative benefits do sufficiently balance the conflict-of-interest risks, a process is needed to minimize the risks through disclosure and management.

At least four examples of social benefits have been seen as outweighing the risk of bias: improved transfer of medical innovations to

the bedside, creation of jobs, furtherance of economic development generally, and facilitation of private support of research programs and public universities. Secondary benefits include efficiencies in the conduct of specific research studies.

Many investigators have unique expertise. If senior researchers are prohibited or severely restricted by federal or university regulations from such activities as serving on an advisory board, consulting with commercial entities, or holding stock in a firm related to their research, they might decline involvement in federally supported research. Conversely, they might decline to provide that expertise to industry where it might be in the public interest, another loss of social benefit. The prohibition model may therefore promote loss of social benefit, another factor that must be weighed in deciding on approaches to managing conflicts of interest.

Disclosure and Peer Review Model

The disclosure and peer review model holds that conflicts of interest are unavoidable and that financial conflicts of interest are only the most visible and perhaps the least scientifically dangerous. Acknowledging potential sources of bias promotes an awareness of different points of view and the possibility of developing some kind of balance within PORTs—provided also that a strong peer-review process is in place and that there are opportunities for secondary data analysis. Because PORTS are part of a political process created by Congress with a number of expectations that may engender conflicts of interest, some observers believe that disclosing and balancing biases to the maximum extent possible is a more realistic goal than trying to eliminate them. According to this view, blanket prohibitions are not needed. Strong peer review within the PORTs and by journal reviewers and public evaluation by other researchers would counteract or detect unacceptable biases. Knowing that their most valuable asset is credibility in the field, this perspective argues that it would be irrational for individual PORT researchers to jeopardize this credibility for a given study.

Many biases, however, may be exceedingly subtle and hard to detect (as discussed in Chapter 4). This factor may preclude dependence on disclosure and peer review alone to control the bias resulting from certain (especially nonfinancial) conflicts of interest.[1] Such sources of unintended bias include determining what materials are to be included in meta-

[1] The same problem would arise under the prohibition model if the social benefits were deemed great enough to justify the potential conflict of interest, provided that disclosure and other forms of remediation were instituted.

analysis; "cleaning" and transforming of insurance claims data tapes; choosing and constructing outcome measures, data analyses, and presentation of data; and developing clinical practice guidelines.

GENERAL APPROACHES TO DEALING WITH CONFLICTS OF INTEREST

Assuming that under both models attention is given to the climate and support for ethical standards in the PORT environment, what implications might we draw about managing conflicts of interest under these two models? Seemingly, both the prohibition and the disclosure and peer review models would permit PORT studies to continue despite real or apparent conflicts of interest. Where they significantly differ is in their underlying presumptions and in where they draw the line between prohibition and management, though not necessarily in the means used to deal with conflicts of interest. These means, which are discussed in the remainder of this chapter, include mandatory disclosure, financial distancing, self-regulation, defining categories of acceptable activities and implementation of oversight mechanisms, defining unacceptable activities and implementing prohibitions and where necessary, sanctions. The two models would rely on different mixes of these mechanisms in attempting to forestall, control, or manage conflicts of interest.

Disclosure

Disclosure of relevant interests and activities (whether on a mandatory, periodic basis or as studies are initiated by the investigator) was once considered too intrusive or simply "impolite," but it is now virtually universally endorsed as a key means of coping with conflicts of interest. As one workshop participant said,

> We have to change the nature of the discourse to make it clear that it is not only polite, but essential, to understand people's financial interest in areas that affect their work, just as it is essential to know where they came from and who they did their work with because of other subtle biases. You have to get that information so that others can judge [it] in the context of their work (C. K. Gunsalus).

Some state laws and some university policies require disclosure of certain categories of activities. Typically these include service as an officer or director of any commercial entity, investment of more than a given amount in any one company whose product is related to the individual's work, ownership interest of more than a given percentage in a partnership or corporation, and consulting arrangements that result in remuneration greater than a set amount (AAHC, 1990). Disclosure might include all financial interests of the investigator and his or her immediate family. The National Research Council requests disclosure of any prior public statements, including publications, relevant to a topic under study (NRC, 1989).

Financial Distancing

Regarding financial conflicts of interest, one possible method of reducing the influence of corporate money on research is to establish financial pools or mechanisms that increase the distance (real or perceived) between the funding source and the PORT or its members. There is considerable disagreement over this approach, as evidenced by this exchange between two participants at the IOM workshop:

> MR. HUTT: . . . You said, "What if it [the funding] comes from the foundation versus the company?" I would hope people would realize there is no difference between those. What has troubled me . . . is the idea that laundering it through the university as opposed to giving it directly to an investigator somehow makes a difference . . . . Everybody knows where the money is coming from and where it is going . . . . I have always been offended by the thought that this laundering process somehow magically converts tainted money into clean money. We ought to get rid of that fiction and understand that the money is going to go . . . from Mega Pharmaceuticals [a fictional corporation used in the scenario] for the purpose of first-rate academic research. It is then the responsibility of the university to supervise the doctor and to make sure there is adequate peer review within the university and that something untoward does not occur . . . . If you cannot stand before the public and defend an academic researcher receiving money from whatever the source may be, whether it is a pharmaceutical or any other company, and you have to pretend it is being laundered . . . then you shouldn't be doing it . . . The question of where

the money came from is not the issue. The question is whether the science was valid, good, strong, academic, unbiased, straightforward, peer-reviewed science.

PROF. CAPRON: Some people would suggest that there is no such absolute animal. . . . As a dean, Dr. Korn, do you agree with Mr. Hutt's statement?

DR. KORN: . . . I don't understand laundering because it is not a concept that I use. When I was talking before about the Mega Foundation's money, I was thinking of it as grants that were coming into very specific people for very specific research projects, but coming in as grants through the university. That is not a laundering phenomenon. It is simply a matter of tracking the research portfolio that is going on within a place at any one time and assuring that whatever institutional assurances have to be met by federal and other regulations are in conformity. That is all. There is no laundering involved. There is no deception involved.

PROF. CAPRON: Would you feel differently if it were a no-strings-attached annual grant?

DR. KORN: You mean a gift?

PROF. CAPRON: Yes.

DR. KORN: Sure. We get gifts. Everybody gets gifts. That is the difference between a gift and a grant. A gift is a general award of funds for some very general use, and a grant is much more specific and targeted, usually with a named investigator and expected outcomes. They are different and equally acceptable.

PROF. CAPRON: What happens to the adage, "Don't bite the hand that feeds you?"

DR. KORN: It is a good one [laughter].

Such "financial distancing" by foundations may be quite variable. The Lilly Foundation, for instance, will support no research in the health area; other corporations, however, use their foundations to promote their own views.

Another form of financial distancing is the blind trust, in which control of equity is transferred to a fiduciary for the course of a researcher's involvement in a study. Such an arrangement might lessen, at the margin, the likelihood of insider trading. It would only affect personal financial gain, however, not prevent biased research, and it is the latter that reflects the intent of financial distancing. For instance, a blind trust would not provide a solution for the investigator who has a substantial holding in a closely held company whose product is involved in PORT studies (or is competitive with such a product) because the investigator is not really "blind" to this holding in the hands of the fiduciary.

Self-Regulation

One way to deal with problematic arrangements is to establish rules internal to the research group. For instance, Healy and her colleagues (1989) described decisions by the key investigators in a new multicenter clinical trial of treatment after coronary-artery bypass graft surgery. Among their decisions were not to buy, sell, or hold stock or stock options in the companies manufacturing or distributing the medications they were testing and not to serve as paid consultants to these companies throughout the study (Healy et al., 1989). This arrangement has been hailed as sound protection against this form of financial conflict of interest (Relman, 1989). Another example is the decision by members of the Dartmouth assessment team not to accept honoraria or consulting fees and not to own stock whose value is affected by urologic treatment, the area under study by their team (Wennberg, 1990b).

Defining Categories of Acceptable Activities and Implementing Oversight

Several ways to define acceptable activities and the oversight procedures to permit those (and only those activities) might be outlined in theory. In practice, the approach of the Harvard University Faculty of Medicine offers some useful guidance.

The Harvard University Faculty of Medicine's (1990) new rules distinguish three relationships: (1) those requiring special attention and specific approval, (2) those permitted with oversight, and (3) those that are routinely allowable. Further, they require five actions by all faculty members. Specifically, faculty must (1) make a full annual disclosure of their potential conflicts of interest to university administration; (2) seek explicit approval before embarking on studies funded by companies in

which they or their families have a financial interest; (3) receive approval before sitting on a review committee that judges a technology in which they or their families have an interest; (4) receive approval to serve as a managing executive for a profit-making biomedical company; and (5) disclose to the public their financial interest in any subject that they discuss in a research publication, a formal presentation, or an expert commentary, and do so "simultaneously," that is, as they speak or publish.

As recommended by the guidelines, the dean of the medical school has appointed a standing committee of the Harvard Medical Center, the Committee on Conflict of Interest and Commitment, to review activities that are disclosed and implement procedures for approval and oversight.

Defining Categories of Unacceptable Activities and Implementing Prohibitions

Although differing in their presumptions, both the prohibition and the disclosure and review models recognize that when ameliorative approaches are insufficient to ensure adequate conflict-of-interest protection for researchers, prohibition may be required. Consequently, several schemes have been proposed to delineate permissible from impermissible activities. These range from simply advocating the use of common sense, developing only those prohibitions that are tied to a specific danger to the public, or creating entire categories of unacceptable behavior, such as those included in the (now withdrawn) September 1989 *NIH Guide for Contracts and Grants* (DHHS, 1989b). Other examples include the *New England Journal of Medicine*'s policy not to accept reviews or editorials by authors with financial connections to the product being reviewed (Relman, 1990) and the Johns Hopkins University policy that permits researchers to hold paid consultancies but not equity interest in companies that support their research (Johns Hopkins University School of Medicine, 1990).

The American Medical Association's Councils on Scientific Affairs and on Ethical and Judicial Affairs (1990) have published a report entitled *Conflicts of Interest in Medical Center/Industry Research Relationships*. In this report the two councils strongly endorse full disclosure to medical centers, funding organizations, and journals. The report further asserts that researchers "cannot ethically buy or sell a company's stock until the involvement ends and the results of the research are published or otherwise disseminated to the public" (p. 2793). It affirms, however, that a researcher may ethically share in economic rewards that are commensurate with the value of his or her actual efforts (such as royalties), and

it recommends that medical centers develop policies to provide clear guidelines to clinical researchers.

Sanctions

Research sponsors can withdraw funding or apply penalties when their rules regarding conflict of interest are broken. Institutions also sometimes apply sanctions. For example, the Harvard University Faculty of Medicine's approach to conflicts of interest specifies the following sanctions in rough order of severity: formal admonition; inclusion in a personnel file of a letter from the Office of the Dean that an individual's good standing as a member of the faculty has been called into question; ineligibility for grant applications, institutional review board approval, or supervision of graduate students; nonrenewal of appointment; and dismissal from the faculty.

SUMMARY

Two models provide the main approaches for managing conflict of interest. A prohibition model is based on a presumption against relationships that might present a conflict; a "disclosure and peer review" model rests on presumption that such relationships are unavoidable but manageable. Although the models differ in their underlying presumptions, in where the line is drawn between prohibition and management, and in the means used to deal with conflicts of interest, both models are likely to use one or more of the following mechanisms for dealing with conflict: disclosure, financial distancing, self-regulation, defining categories of acceptable activities, implementing oversight of those activities, defining categories of unacceptable activities, and implementing prohibitions and sanctions. Chapter 6 considers these procedures as applied to PORTs.

6

Points to Consider

When you assemble a number of people to have the advantage of their joint wisdom, you inevitably assemble with those people, all their prejudices, their passions, their errors of opinion, their local interest, and their selfish views. From such an assembly, can a perfect production be expected?

—Benjamin Franklin September 15, 1787, Constitutional Convention

This chapter raises issues regarding the management of conflicts of interest for consideration by PORTs and their sponsoring institutions, the AHCPR, the health services research community, the pharmaceutical and medical devices industry, and Congress. Many of the points noted here are addressed to PORTs and their institutions because the committee believes that the primary role of AHCPR should be to insist that institutions have a method in place for acknowledging, exploring, and managing these potential conflicts. *The committee was not charged to develop these points as formal recommendations, nor does it regard them as such*, and it recognizes that individual PORTs and AHCPR may generate additional or different mechanisms to achieve the goals described. Box 6.1 provides the framework for discussion that guided these points to consider.

As the committee considered conflicts of interest that may arise from both financial and nonfinancial sources, two conclusions emerged. First, regarding financial relationships, the committee recognizes that AHCPR cannot assume the role of sole supporter of PORTs and PORT investigators. PORTs may need, or even require, other sources of funding, such as industry, insurers, or other public agencies. The manner in which such

funds are juxtaposed with agency support needs serious consideration in each case and careful management to safeguard the conclusions of the PORTs from the conflicts of interest inherent in accepting such funding.

Second, regarding nonfinancial sources of bias, such as those arising from professional training and loyalties and other academic pursuits, PORTs must be diligent in ensuring multidisciplinary representation. They should also actively encourage internal and external examination to recognize and counterbalance any nonfinancial sources of bias.

ASSUMPTION

One product of scientific research—including the particular form of health services research conducted by PORTs—is inference. Beyond using the best and most powerful scientific means available in their studies, researchers seek to maximize the validity of their inferences by identifying sources of bias and by minimizing the effects of those biases on their findings. The committee recognizes that biases from conflicting interests, whether financial or nonfinancial, are but some of the many sources of bias that should concern researchers. The central purpose of this report is to help PORTs identify the risks posed by conflicts of interest and to suggest measures that will enable them to reduce those risks.

The committee believes that PORTs—from a self-interested desire to enhance and maintain their own credibility—will be responsive to suggestions for reducing bias. As a result, the committee has concluded that PORTs should not be constrained by a full set of prescriptions about how they should behave, and the committee advises restraint in the promulgation of rules. Yet investigators need guidance in recognizing a conflict of interest and knowing when to disclose it. The committee also recognizes, that complete reliance on informal mechanisms does not address the fact that the scientific community has not always been adequately self-regulating, especially when the expectation of replicability does not apply. Moreover, on the clinical side, physicians have, until lately, been reticent in bringing forward and examining marked differences in medical practices.

PORTs, which combine research with involvement in clinical medicine, need to pay special attention to the appearance as well as the reality of conflict of interest, given the relevance of PORT findings to physician-patient interactions and policymaking and the consequent public scrutiny to which PORT research methods and findings will be exposed. Real or apparent conflicts of interest involving sources of support, other activities of PORT members, and the adequacy of representation of differing viewpoints will be primary targets for critics. Earlier chapters have shown that PORT research is similar to biomedical research or

clinical trials. In response to problems in the general scientific community, research institutions as well as research sponsors have begun to insist on more elaborate methods to protect the integrity of research from untoward effects of conflicts of interest. It seems reasonable that PORTs should use these methods and modify them, if necessary, to address unique features of their work. Every effort should be made to avoid separate processes that would be redundant or unduly burdensome for research institutions.

At the same time, to the extent PORTs fall into a special, "quasi-regulatory" category they may require procedures for monitoring conflicts of interest that are more stringent than those for clinical trials, more like those that apply to officials in a regulatory agency. For example, if exacting rules govern the conduct of persons who approve new drugs, is it appropriate to allow broad latitude to a research process that can have as great an impact on the practice of medicine? Surely, the presence of a possible role in policy making for PORTs would seem to temper sole reliance on the institution for management of conflicts. Both approaches to managing conflict of interest—those based on a view of PORTs as belonging to the paradigm of academic clinical research and those based on a view of PORTs as a quasi-regulatory entity—have considerable merit and will be addressed below as the committee presents considerations for PORTs, their parent institutions, and others concerned with supporting, using, or overseeing outcomes research.

CONSIDERATIONS FOR PORTS AND THEIR INSTITUTIONS

Attributes of Conflict of Interest Management

At this stage in the evolution of PORTs the committee believes it is more important to describe the attributes of a good conflict-of-interest management process than to devise specific rules. Such a process should include the following elements:

- education about conflicts of interest for researchers, faculty, and students;
- clearly stated expectations for early and complete disclosure of relevant interests;
- well-formulated, well-implemented institutional processes for responding to disclosures; and
- emphasis on the role of the principal investigator in managing conflicts.

Education for Researchers, Faculty, and Students

PORTs need to elicit information about conflicts of interest and biases and help team members identify high-risk situations. PORT teams have clearly identifiable duties—for example, to report their methods and findings accurately and in a timely manner, to protect the credibility of their research, and to provide access to their data. These duties are comparable to those of investigators engaging in other forms of research, but PORT investigators may need help and resources to assist them in understanding potential areas of conflict that could prevent them from carrying out these duties.

The committee assumes professional integrity on the part of PORT investigators; it assumes further that PORT researchers place a high value on independence in the conduct of their work and on maintaining collegiality. When difficult circumstances or potential conflicts are encountered and the PORT is unable to resolve them, it may want to seek the counsel of other PORTs. Under these circumstances, a PORT needs information about how others have acted in similar situations, the kind of assistance they may have received, and the results that were achieved. PORTs might wish to establish a working group on conflicts of interest comparable to those sponsored by MEDTEP to examine methodological problems (see Chapter 2).

Faculty and others engaged in PORT research may not be aware of how their arrangements are perceived from outside because it is sometimes difficult for scholars to recognize or acknowledge their own conflicts. Discussing a related issue, Gunsalus and Brown (at the University of Illinois at Urbana-Champaign) caution:

> The benefits to both the institution and the individual entrepreneur [in regard to the licensing of spin-off technology in public universities] may be so clear to those intimately involved in the decisionmaking process that it may not occur to them that, taken out of context, the decisions might appear to be ill-founded. Reporters see themselves as watch dogs for the public. They are, by nature and by training, skeptics, and they are particularly sensitive to the abuse of the public trust and the misappropriation of public funds. In these cases, the appearance can be just as damaging as the reality. If a story about possible wrongdoing appears on Page One of the local newspaper, a follow-up story months later, setting the context or demonstrating exoneration, cannot undo the damage.

It may be difficult for the typical academic scientist, who is equally committed to principles of honesty and openness, to understand what could lead a reporter to question his or her motives in commercializing ideas developed with public funds. Nonetheless, it is prudent to expect motives to be questioned, and to be prepared to explain exactly why the course of action embarked upon is the one that best serves the public interest (Gunsalus and Brown, 1989:5–6).

To overcome some of these investigator blind spots, PORTs may require education about the risk of being misperceived, about the obligations of PORT members to avoid giving that impression, and about how to recognize and manage conflicts. Examples of educational strategies are given below.

Core course for research fellows. Currently, few university resources are dedicated to communicating professional standards and the ethics of research practice to young scientists (IOM, 1989). One direction for education might be to provide course work in ethics for young investigators. NIH now requires a core course for fellows supported by NIH training grants. Along with covering such topics as laboratory methods, research design, use of human subjects, and cases of scientific fraud, resource material for such a course might include case studies, workbooks, and other instruction on conflicts of interest in research.

Conferences. Education need not involve formal course work, however. Departmental grand rounds or more informal conferences or seminars could be led by senior investigators to educate other faculty as well as students and to underscore the importance of addressing conflicts of interest. Such conferences could examine real problems, describe actions that were taken in response, and identify resources available within the institution.

Clearly Stated Expectations for Early and Complete Disclosure

Requirements for regular, detailed, and mandatory financial disclosure that includes relevant information about researchers, spouses (or companions), and dependents have increased during the past decade (McNeil and Roberts, 1990). This committee concurs with the AAMC and AAHC guidelines in this matter and endorses their call for annual disclosure within the research institution of relevant significant interests (such as equity, officership, consultant fees, or honoraria) to identify sources of possible research bias.

All research proposals should be reviewed by the principal investigator's academic department for any conflict-of-interest issues and preconditions. Reviews of routine university-initiated disclosure (e.g., annual faculty reports) could be conducted efficiently by specifying "red flags" that would trigger further inquiry. These review requirements would apply to ongoing activities of PORT investigators when the PORT is formed and to contemplated activities during the course of the study. The committee also supports investigator-initiated review of proposed collaborative agreements or other studies in which the investigator has financial ties to the subject of the PORT. Scrutiny would be greatest with respect to equity relationships. Other ties, such as consulting and management positions, would be given greater scrutiny if the positions involved a direct role in the evaluation or testing of actual or prospective products.

A self-denying rule of the type voluntarily adopted by several major clinical research projects in recent years, whereby key scientific participants agree to forgo all financial ties to interested businesses during such studies, provides credibility for PORT studies (although not a qualitatively different credibility than would prohibition). Nevertheless, disclosure, supervisory controls, and monitoring may be sufficient to allow certain financial relationships to continue, provided (1) monitoring mechanisms are stringent and provide reasonable and publicly acceptable assurances that research will be free from bias; (2) there is no early, financially advantageous disclosure or exploitation of research results; and (3) any reference to the relevant research in speeches, writings, advertising, or collegial discussions is accompanied by disclosure of the financial relationship (McNeil and Roberts, 1990). These measures may not prevent the press, however, from viewing such arrangements with suspicion.

Well-Formulated and Well-Implemented Institutional Processes and Responses

In addition to the need for policies on and full disclosure of situations involving possible conflicts of interest, the AAMC guidelines point to the need for implementation of a wide array of enforcement procedures (including appropriate sanctions), review of research proposals, expeditious response to questions that are raised, and effective, appropriate management and resolution of conflicts of interest.

Universities ought to play a large role in implementing conflict-of-interest guidelines, and the guidelines ought to be part of the institutional process. Each institution, or each PORT, or both, should have some declared model for disclosure and consultation. A PORT principal

investigator (and his or her institution) has a responsibility to ensure that institutional requirements for disclosure and any other relevant policies are met by all team members including subcontractors. A PORT might decide to implement additional mechanisms on its own if the home institution does not fulfill this role as fully as the PORT deems necessary. Whether the conflict-of-interest processes and policies of the lead institution are acceptable to members of PORTs at other institutions is an issue to be raised and resolved early in a PORT project.

Each PORT should consider the following areas:

- the provision of a mechanism for open discussion among its members of potential conflicts and biases,
- clear identification in advance of the means by which differences in the interpretation of data will be presented and managed, and
- ground rules established in advance on access to PORT data both within the group and by outside researchers.

PORTs might consider documenting all such decisions. Asking that someone with no interest in the arrangements be part of the review and approval process is another possible safeguard. At some later time PORTs might review this oversight process to determine whether it is effective, ineffective, or overly burdensome (Gunsalus and Brown, 1989).

Other internal mechanisms and resources that will allow PORTs and their institutions to anticipate and manage possible conflicts of interest and to learn from one another are offered below.

Institutional review of investigator agreements. Most research institutions expect to review contractual arrangements that involve the institution to be certain they present no conflict of interest or conflict of commitment; a few have gone further to require review of consulting arrangements. This review ensures that investigators do not give away data, patents, or other intellectual property that belong to the institution. In this case, the primary concern of institutional attorneys and administrators is to protect the institution rather than the investigator.

This same mechanism might, however, be used voluntarily by the PORT investigator for advice on contemplated agreements—that is, universities might develop an "intramural consultancy" to provide support to principal investigators of projects or programs. Using such a service, investigators might ask for review (e.g., by the university counsel, the office of grants administration, the vice president or dean for research) of new contracts with outside agencies or industrial entities in order to understand their options and responsibilities under the terms of the proposed contract. Particular attention might be given to those attributes of the agreement

that might entail risk for conflict of interest. The elements reviewed could include access to and release of information, conditions under which the proposed work could be terminated, and so forth.

There may be good reason to review statements pertaining to ownership rights or copyrights in cases where new instruments for outcomes measurement, clinical decision making supported by emerging new technologies, and other tangible goods are envisioned as a potential result of PORT work. For example, currently such new instruments as case-mix measures and measures of functional health status are copyrighted and may or may not be available for general use.

Well-negotiated agreements with outside research sponsors might include specific attention to the following:

- selection of subjects (to avoid competition for participants with other secondary protocols);
- direction and control of the research (if external sponsorship depends, for instance, on interim results to determine incremental funding, discontinued funding by that source will jeopardize the PORT's continued study of that alternative technology);
- conditions under which the research design could be changed (again, because such changes may affect the PORTs work and the value of its data);
- peer review and outside sponsor evaluation of results (to ensure credibility); and
- acceptable conditions of secrecy (for instance, the rules that govern sharing of information with students, colleagues, and the scientific community through publication). Data that are gathered in part with public funds should be publicly available. Rules concerning student involvement should be clear and not involve excessive delay in the defense or publication of a dissertation.

Establishment of a forum or other advisory group for discussion of ethical issues related to research. The 1989 IOM report *Responsible Conduct of Research in the Health Sciences*, refers to "the moral and professional climate of the research environment, which influences everyday

practice and sets the tone for future generations of researchers" (p. v). Manifestations of "climate" include provisions for discussion of these issues and assistance with problem solving and enabling structures, such as departmental research and ethics committees. An example of such an enabling structure that might be helpful to PORTs as well as other nonPORT investigators is a departmental, divisional, or other internal forum for disputation and problem solving regarding conflict-of-interest issues.

If such institutional processes are available, conflict-of-interest problems may be examined and avoided prospectively—or at least dealt with more readily when they arise. For example, the IOM committee learned of one clinical department in which a research ethics committee operating under the aegis of the department chair has examined several difficult issues: seeking third-party payment for "experimental" clinical procedures undertaken in the context of a randomized trial; deciding when "state-of-the-art" treatments should be used for randomized trials rather than implemented nonexperimentally to "keep pace with the progress of medicine"; and the advisability or inadvisability of "finder fees" for residents who recruit subjects into trials. None of these questions yields a single best answer under all foreseeable circumstances. A forum such as the one suggested might not have decision-making authority, but if clear processes have been established to provide supportive resources to an investigator, at least the individual is not left to grapple with the questions alone. Such a role might also be filled by a experienced "conflict-of-interest consultant" provided by AHCPR (see Considerations for AHCPR).

Emphasis on the Role of the Principal Investigator

The role of research team leaders is a crucial one. The team leader should determine what will permit or foster the maintenance of trust and collaboration among PORT members, convey the informal norms and values of science to the group, and anticipate problems regarding the mission of the PORT. He or she should also ensure that agreements with outside research sponsors are properly negotiated, that guidelines for PORT members' conduct are promulgated, and that a conflict management process is implemented within the PORT.

Professional Conflicts and Implications for PORT Research

PORT research involves clinicians whose livelihoods may be affected by the conclusions reached by the PORTs. Specialty associations and medical societies might be expected to protect their members' economic interests, thus complicating the PORTs' efforts to conduct their studies. To gain the support of these groups PORTs may need to help them understand the potential short-and long-term effects of PORT findings. For instance, despite early findings highlighting large variability in the approach to management of prostatectomy and disputing some therapeutic approaches, the American Urological Association has been supportive of Dartmouth's study of treatments for BPH, recognizing its potential for improved care despite possible financial implications of the research. In some cases, however, appeals to professionalism may be unrealistic because the possible findings threaten entire specialities, subspecialities, medical or surgical approaches, or delivery systems.

Researchers—especially the clinical members of the PORT who provide the treatments under study—may also have unrecognized personal biases and attachments to groups, organizations, and medical practices under study. Little can be done formally to obliterate such biases beyond assuming them as a given and seeking to detect them. This entails insisting on a priori disclosure of professional bias, prohibiting the most egregious appearances of conflict of interest, securing a multidisciplinary mix that is diverse enough and candid enough to ensure that such biases will be challenged internally as well as through an external process, and being open to post hoc secondary analysis of (as well as internal challenges to) methodology and findings by other, non-PORT health services researchers.

A separate consideration is how to protect PORT researchers from petty or unwarranted accusations. In addition to early public as well as intra-PORT disclosure of relevant financial relationships to other members, individual researchers might minimize the appearance of bias and vulnerability to accusations in several ways:

- invite critics to look at their previous work;
- seek a mix of sources of funding for a given project;
- frequently include "memos to the file" on study decisions that might be later questioned;
- consider having data analysis handled by a center that is separate from the centers gathering data;
- blind analysts to the type of intervention (e.g., surgery, medication, watchful waiting);

- not publish data until the findings are robust;
- not "overinterpret" results;
- call attention to areas of uncertainty; and
- make an effort to publish negative and equivocal results as well as positive results.

Freedom of Communication for PORT Researchers

The IOM committee believes that collaborative research agreements with industry should ensure freedom to publish the outcomes of studies, whether favorable or unfavorable, and that they should provide reasonable latitude for communication among PORT investigators and industry. These issues were discussed in Chapter 4; the discussion continues in this chapter in the later section "Considerations for Industry." Particular concerns include the kinds of information (e.g., ideas, specific. instruments or outcomes, preliminary findings) PORT investigators develop and may want to provide to either one specific group or all interested groups before information is available publicly. PORTs must determine and announce their policy on this issue early in the project to avoid giving a competitive advantage to any party.

CONSIDERATIONS FOR AHCPR

Because most PORTs are still at an early stage in their methodological development, organization, and experience, detailed direction of PORTs by AHCPR at this point would be premature. The PORTs' "quasi-regulatory" role requires that they be scrupulous about any appearance of conflicts of interest and have well-formulated policies for dealing with them. Nevertheless, like other forms of scientific investigation, PORT research is best carried out by people complying with the basic objectives of science; consequently, rules and regulations that excessively constrain that process add little and may actually impede it. For this reason, and for the time being, agency policy should avoid detailed guidelines and instead give broad direction.

Thus, the committee believes that AHCPR ought not at this time to promulgate its own regulations regarding conflicts of interest and self-dealing in PORTs. However, it should, in awarding its grants, contracts, and cooperative agreements, require that a PORT (or its institution) have in place an appropriate conflict-of-interest mechanism or a process by which relevant conflicts of interest and biases are revealed. The PORT should be required in its funding application to file copies of the conflict-

of-interest policies of the home institution and of its proposed subcontractors. Requirements regarding conflict of interest should be at least as stringent as those that apply to clinical investigators. Where institutions distinguish between bench and animal research on the one hand and clinical trials on the other, PORTs are more like the latter in terms of their direct effect on medical practice. Like clinical research, PORT research will have direct impact on patients; this engenders a greater ethical burden.

Standards regarding equity holdings appear to be evolving. It seems likely that equity holding in a product under study by investigators in Phase III clinical trials will eventually be discouraged or forbidden by federal regulation. It seems reasonable that PORT researchers (and their immediate families, including minor dependents) should not generally be equity holders in firms producing technologies used for the conditions being studied because such holding would be considered too strong a source of bias. There may be some appropriate exceptions to this. For instance, a PORT researcher who is an expert in a given technology might have developed an invention prior to any involvement in the PORT and been given an equity interest by the corporation that further develops his or her invention. Because such technology transfer has been actively encouraged by Congress through special legislation, it would be inconsistent for AHCPR to insist that there be no equity holdings in those cases when finding a suitable replacement for a prospective member of the PORT may not be possible or when divestiture would be unduly burdensome.

If AHCPR does establish minimum agency standards, it should do so in collaboration with NIH to avoid conflict with NIH standards of conduct for grantees and their institutions. Past experience in which several federal agencies have had conflicting rules governing the same area (e.g., animals and human subjects research) testifies to the importance of coordinated standard development. Minimum standards might include requirements for disclosure, for institutional mechanisms to manage conflicts of interest, and for education of PORT members to recognize and manage conflicts of interest.

AHCPR might consider providing PORTs with a "conflict-of-interest consultant." Such a person would have to be an individual respected by researchers and clinicians. The consultant would consider concerns brought before him or her as confidential and would provide guidance to individuals or to PORTs.

Because of concern about the concentration of expertise, AHCPR might also consider funding two or more PORTs to study the same general topics or clinical conditions. The Department of Defense sometimes contracts with two defense manufacturing companies for a

product with given specifications and makes a decision about which to fund for production after prototypes have been developed. In this way the Department of Defense attempts to obtain a better product and control costs. In the case of AHCPR and outcomes research, such duplicate funding might provide greater credibility for PORT methodology generally and for a particular PORT's work if two such PORTs had similar findings.

Industry-Sponsored Research

Although the committee believes it is too soon to issue detailed regulations, at some point AHCPR may find it necessary to provide specific guidance regarding industry-sponsored research. In so doing, the agency will need to give careful consideration to the impact of guidelines, rules, or regulations on the development of new technologies and the transfer of these technologies to practice. The adoption of stringent prohibitions to avoid conflicts of interest could slow the development of new technologies or inhibit the participation by senior clinicians in PORT research. The ways in which industry relationships may positively or negatively affect technology transfer need to be better understood.

Because of the importance of assessing potential new treatments and devices in parallel with the evaluation of existing practices, a disclosure and peer review orientation would mandate that PORT members be allowed to consider proposals from commercial firms for prospective evaluation of drugs or devices. Care should be taken to ensure that any such industry-sponsored "arms" of a study in no way inhibit the conduct of the PORT research, free exchange of information among PORT members and the timely release of PORT findings; that is, timely publication of results must not be delayed or constrained by the progress and completion (or lack of it) of the commercially sponsored study. All PORT members should disclose to the PORT as well as to the public any relationships either as consultants to, or as recipients of, research grants from industry, certainly at the time findings are released, if not well before. This would not prohibit a PORT member from serving as a consultant to commercial entities, as long as such relationships are fully disclosed and considered acceptable to PORT leaders.

A different view, based on the prohibition model discussed earlier, asserts that in the area of incorporating industry-sponsored research into PORT research or conducting it concurrently, the appearance as much as the reality of conflicting interests is of considerable concern. PORTs may study products and technologies of varying sponsorship, exclusivity, and commercial value, but they receive the bulk of their funding from government sources. Although for some observers, government sponsorship

of health care evaluation is worrisome because it is believed to imply a cost-containment approach, for many others it adds a significant measure of objectivity and detachment from commercial objectives. It is understandable that sponsors of newer technologies would want a relevant product included in an outcomes study and that PORTs themselves would want to include newer technologies to increase the timeliness of their findings, but if such a study is undertaken the conflict of interest issue will need particular attention.

Given the importance of avoiding any appearance of conflict of interest, the prohibition model further argues that industry-sponsored research should be kept at arm's length. For instance, a first step would be to allow PORTs to seek supplemental agency funds to add studies of other relevant products or technologies. Second, if obtaining supplemental funds is unrealistic but a high test of relevance and social benefit is met, industry funding could be considered. If so, the agency should seek mechanisms to protect investigators against the appearance of conflict and allow PORTs—with government sponsorship—to fold new technologies into their studies while preserving maximum public credibility.

Other protections might also be instituted whether one proceeds from the prohibition or the disclosure and peer review model. For instance, in accordance with policies already adopted by major journals, all sources of funding should be disclosed in all publications emanating from the PORT. Sponsors might be allowed to offer comments on draft articles and reports, but they should not be allowed to edit the research reports.

Access to Data

Grant specifications should include a requirement that both internal and bona fide external investigators have access to primary PORT data (as noted earlier, use of Medicare data is subject to restrictions as may be some insurance data bases). Given the scope and impact of PORTs, the data should be available within a specified time frame and in specified modalities—for instance, data tapes with patient identifiers deleted and adequate demonstration and documentation for secondary users. Such rules would allow the PORT to exploit its own research efforts in conducting and performing original analyses without precluding timely reanalysis by others, including PORT members acting independently.

To become accessible resources for research, the PORT data sets need unusually well-developed documentation, recommended "test analysis" routines, code books, and so forth. Technical assistance for new users may have to be provided by PORT staff. All these requirements, however, pose financial and other costs to PORTs; if they are desired, AHCPR

should build appropriate auxiliary funding into PORT support. For instance, AHCPR might consider administrative funding for PORTs for a sixth year during which the PORT would prepare technical reports and documentation. The expectation of providing public-use documentation and justification for decision rules would also encourage PORTs to examine their biases during earlier years.

Intra- and Inter-PORT Differences

PORTs are too early in their development as institutions for this IOM committee to advise that AHCPR consider preempting all PORT differences by issuing uniform guidelines on managing conflicts of interest. Certainly there is no generally "right" method beyond what might be established as a minimum, core set of federal rules. Instead, PORTs need to be certain that all resources and approaches currently in use for avoiding or ameliorating such conflicts are known and that each group makes choices advisedly.

PORTs and their institutions should be encouraged to develop a common understanding of what constitutes a conflict of interest. Development of such an understanding might eventually negate the need for specific rules regarding permissible behaviors; conversely, it might lay a foundation on which a sensible set of rules might be built. The committee does not at this time advocate the imposition of uniform standards for the sake of uniformity only, or for eliminating the supposedly competitive advantages that might accrue to an institution adopting particular conflict-of-interest rules and processes (especially permissive ones). Although differences in ways of addressing possible conflicts of interest may, in fact, put individuals in the same PORT or in different PORTs at a significant advantage or disadvantage, this seems a necessary price of academic freedom. Institutions will have as many reasons for developing their own rules on conflicts as on other matters (e.g., salary scales, research environments), and all will inevitably result in some differentials in competition for faculty and for research support.

As noted earlier, within multi-institutional government-funded studies—as is the case with PORT grants—the primary grantee or lead institution is responsible for ensuring compliance with conflict-of-interest rules and other regulations such as those for the protection of human subjects and animals. Among the collaborating institutions of a PORT, either the policies and processes of one institution (e.g., the lead institution) should be accepted by all, or a separate agreement on such issues and their process of resolution should be specially developed if the lead

institution's policies are not entirely acceptable. Investigators might agree to be bound by the least or the most restrictive institutional policies.

There may also be a role for infrastructures similar to those used in multicenter clinical trials, such as policy boards and data management committees. For clinical trials these structures are specified in the instructions from the funding agency and judged as part of the application, but it is not clear who sets, or should set, the policies for such groups. Resolving this problem for PORTs could be helpful to other areas of clinical research.

Review of Grant Applications

AHCPR might also consider using a standard disclosure form for study section grant reviewers to ensure that reviewers do not themselves have conflicts of interest and that biases are identified. The process of garnering information from review panels should aim to obtain only relevant information (e.g., financial or other interests in a company operating in a field that might be affected by the outcomes of the study). Beyond financial interests, other biases can be sought by plain questions about positions the individual has taken or practice patterns to which the individual is committed.

As Chapter 3 notes, several groups have developed disclosure forms. For instance, FDA advisory committees have disclosure forms and rules of conduct (see 45 CFR, Part 73a, February 24, 1978), and, the quasi-public U.S. Pharmacopeial Convention also has guidelines for its Standards Revisions Committees (1990–1995).

The National Research Council (NRC) of the National Academy of Sciences uses a statement-of-bias form (NRC, 1989) when assembling each of its study committees. (Biases do not necessarily preclude serving on a committee, however, because everyone approaches topics on which they are expert with some bias.) These sources might provide useful models for the AHCPR study sections to adopt or adapt.

CONSIDERATIONS FOR THE HEALTH SERVICES RESEARCH COMMUNITY

The principles or attributes of PORT conflict-of-interest management apply to other forms of health services research. The convening by AHCPR of work groups on methodological issues is an intriguing model for discussing the management of potential conflicts of interest, particularly for new PORTs. Relevant professional groups such as the Association for

Health Services Research should direct attention to these issues during their professional meetings and provide other informal channels of communication or forums for the exchange of ideas. If the agency is unable or unwilling to undertake such an activity, professional associations should consider assuming leadership or, at the very least, aid the agency in any steps it takes to foster communications and to develop appropriate standards.

CONSIDERATIONS FOR INDUSTRY

Just as there is a need for exchange of information and education within and among PORT researchers, there is a similar need among firms involved in funding academic research. Individual companies should consider establishing internal rules and standards of conduct comparable to university guidelines. Industry as a whole, through an association or another representative group, might also wish to establish industry-wide rules and standards within the limits of antitrust law. Industry should also consider whether it desires representation during any conflict-of-interest deliberations that may take place in PORTs.

Publication and Communication of Findings among PORT Members and Industry

Any agreements with pharmaceutical or device manufacturers who include their products as alternative treatments in PORT evaluations should neither distort the research design nor prevent or unduly delay publication of results. Although some delay of publication to allow for patent applications is reasonable, it should be held to the necessary minimum. Restrictions on the freedom of PORTs to publish the outcomes of their findings (other than the generally acceptable brief delay to permit patent evaluation and filing) are, in the view of the IOM committee, indefensible and unwarranted. Having evaluated a diagnostic procedure or treatment, the PORT must be able to report its findings and allow secondary analysis by others who may challenge them. Secrecy or exclusivity clauses should be tailored to address realistic dangers and permit collaboration with PORT investigators that might not otherwise be feasible under rigid restraints on communication. Generally, PORT investigators do not need access to what might be considered trade secrets. Maintaining confidentiality of proprietary information is a reasonable requirement on the part of industry, but prohibiting contact with other manufacturers is not. PORT investigators need to be able to talk freely

with manufacturers and one another (within the PORT) if they are to conduct their studies adequately. Such communication is also to the advantage of the manufacturer in ensuring that the most up-to-date information is available to the PORT when it analyzes its data.

To allow PORTs to obtain these data from all relevant parties, the standard clauses that apply to basic biomedical research should not be applied to PORTs. In recent years, companies have modified their policies in collaborative agreements (CRADAs) with investigators at NIH and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA). NIH and ADAMHA CRADA agreements permit only two special stipulations: a brief delay of publication to allow companies to file patent applications or intellectual property applications, and nondisclosure by investigators of information marked by the company as "confidential" (NIH/ADAMHA, 1989a,b). This designation confers an exemption from Freedom of Information Act requests (P. Chen, Associate Director for Intramural Affairs and Chairman, NIH/ADAMHA Patent Policy Board, personal communication, 1990). As PORTs develop, they or AHCPR may need to develop similar model agreements with industry.

Industry might wish to apply secrecy agreements to data with proprietary value (e.g., data involving the results of evaluations). An example might be when an off-label use of a pharmaceutical is being considered for FDA approval. Similarly, information about a company's plans for development or about the efficacy, safety, manufacture, or mechanism of action of a device or pharmaceutical may have enormous implications for the company and the value of its stock. It may be reasonable to insist that PORT investigators not share such proprietary information with competitors. Nevertheless, it is important for PORT investigators to know, for example, how a device is being modified by other firms or the characteristics of patient subgroups for which it may be desirable or undesirable.

Industry agreements might well allow for secrecy to the extent that PORTs could not share with competing companies technical information (e.g., the chemical composition of a drug) that the investigators may need to do their work. Such secrecy would not compromise PORTs' ability to disclose their own findings. Agreements could stipulate that at the time of publication any information must be included that would be necessary to make the research findings understandable to the reader.

A particularly thorny issue is agreements that seek to restrict or prohibit a PORT consultant from discussions with other investigators when the investigator has a consulting agreement or contract to evaluate a modality that is separate from but related to his or her PORT research. As remarked by Barbara Mishkin, a workshop participant who is not involved in a PORT, "I know from my own personal experience . . . that

the older we get, and the more experience and knowledge we accumulate, the harder it is to identify the source of any particular data. I just don't think it is possible for people to have split responsibilities and split allegiances and try [to] factor out information that came from A and B and from X, Y, and Z." The committee had considerable reservations about the propriety of arrangements that constrain communication. It concluded that such arrangements should always be disclosed to the lead institution and that the lead institution might sometimes find such an arrangement is unacceptable.

A related problem concerns the kinds of information (e.g., ideas, specific instruments or outcomes, preliminary findings developed by the PORT) that PORT investigators will provide to outside interested groups before any information is publicly available. For instance, a PORT might learn during the course of its research that certain health outcomes that have not been previously measured seem to matter a great deal to patients. It is reasonable that investigators would want to share such information with others (e.g., those developing products, the subjects of evaluation, health services researchers outside the PORT).

Three separate matters may be raised in this regard. The first is whether information shared with any party is to be shared with all, because to provide any information that is publicly available to one party but not another might give a competitive advantage. This issue might be particularly troublesome for a PORT researcher in his or her capacity as a consultant where one's professional obligation is to provide the best information to a client. The second matter is the timing of any information sharing. Although the best policy seems to be to make all such information available as it is developed, PORTs are likely to want to publish their results in peer-reviewed journals and will not wish to jeopardize this possibility by prior public dissemination of results. The third is the manner of dissemination, such as whether it should be public (e.g., press conference or professional meetings) or only through technical forums. Policies on these questions need to be discussed and formulated early in the PORT's studies.

CONSIDERATIONS FOR CONGRESS

Outcomes research has been funded for a variety of reasons, including improvement in information and knowledge, and better quality of care. Outcomes research projects, and PORTs in particular, have been funded with the hope of learning more about effective practices in medicine. Another aim of such research is rationalization of the nation's allocation of health care resources.

Additionally, there is a hope, if not an expectation, that health services, effectiveness and outcomes research, including PORTs, will save money for federal programs. In the short run, however, they may not specifically save money for the Medicare program, especially because it will take time for their work to become integrated with other efforts of AHCPR in facilitating the development of practice guidelines. The findings of some PORTs might even point toward appropriate increases in certain services and hence greater health care expenditures. Thus, PORT teams should not be overtly or subtly required to recommend cost-saving practices as a basis for renewed funding. By extension, continued or increased AHCPR funding should not depend on whether PORT findings are or are not consistent with congressional cost-containment objectives.

Because PORT findings must necessarily rely heavily on observational studies, incomplete data bases, and qualitative outcomes, decision making should not be based on PORT results alone. Clinical trials, when available, remain important sources of new clinical information.

Secure, multiyear PORT funding commitments are one way to minimize the risk of entanglements with conflicting interests. Congress should be alert to the fact that if outcomes research becomes well established and respected as a health services research activity, lower federal funding levels in later years will almost surely drive research teams toward private compensatory relationships with device and pharmaceutical manufacturers or toward other sources of funding, such as private insurers, whose primary motivation may be to find ways to reduce health care expenditures.

CONCLUDING REMARKS

This study was initiated following a request from the (then) National Center for Health Services Research to convene a workshop on potential conflicts of interest in its new patient outcomes research program. After AHCPR was established in 1990, it confirmed an interest in anticipating any conflict-of-interest issues that might affect PORTs. Thus, following its June 1990 workshop the IOM committee examined the issues that had been raised, with the purpose of providing the agency with "points to consider."

During the work of this committee, new PORTs were funded, and new methodological issues were raised. Thus, the report represents the committee's views at a very early stage in the development of PORTs, a fact that has considerably influenced its thinking. As PORTs become established and, it is hoped, make valuable contributions to health services

research, unanticipated problems will undoubtedly arise, and the issues raised in this report will probably need to be revisited. The MEDTEP activity in AHCPR holds out the promise of greatly improving the value and effectiveness of the health care system. A fear that conflicts of interest may arise in PORTs should not inhibit commitment to outcomes research or the continued evolution of what must be seen as a bold new "social invention" on the part of Congress.

BOX 6.1 FRAMEWORK FOR DISCUSSION

- Like other scientists, PORT researchers seek to maximize the validity of their inferences by identifying sources of bias and by minimizing the effects of those biases on their findings.
- The varieties of PORT relationships with other entities are evolving, and any pitfalls resulting from financial and professional conflicts of interest cannot yet be well delineated.
- PORTs may be exposed to accusations of conflict of interest because of connections to industry, professional associations, and the like, possibly with the intent of discrediting their findings when such results are at odds with the interests of other parties.
- PORT investigators need guidance in recognizing a potential or real conflict of interest and knowing when to disclose it.
- Each PORT or its home institution should have in place an appropriate mechanism by which relevant conflicts of interest and biases can be revealed and addressed.
- Each prospective PORT should be required in its funding application to file copies of the conflict-of-interest policies of the home institution and of its proposed subcontractors and to describe the process it will use to manage conflicts of interest.
- Requirements regarding conflict of interest should be at least as stringent as those that apply to clinical investigators. Where institutional rules distinguish between bench and animal research on the one hand and clinical trials on the other, PORTs should be subject to the rules that apply to the latter.
- Methods of dealing with conflict of interest include disclosure, followed by assessment and management or, where essential to the integrity of the research, outright prohibition. The PORT members and their institutions are best placed to determine the process by which they will manage conflict. Important aspects of such a process include education about conflicts of interest for researchers, faculty, and students; clearly stated expectations for early and complete disclosure of relevant interests; well-formulated, well-implemented institutional process for responding to disclosures; and emphasis on the role of the principal investigator in managing conflicts.
- Collaborative research agreements with industrial entities (firms) should ensure freedom to publish the outcomes of studies, whether favorable or unfavorable, and latitude for communication among PORT investigators and industry.
- Generally, PORT researchers (and their immediate families, including minor dependents) should not be equity holders in firms that produce technologies used for the conditions being studied.

- To counteract nonfinancial sources of bias, such as those arising from professional loyalties and training and from other academic affiliations, PORTs should actively encourage internal and external scrutiny and should ensure that the team has representation from the full range of relevant clinical and scientific disciplines.
- PORTS of necessity rely heavily on observational studies, incomplete data bases, and qualitative outcomes, and their findings are no substitute for traditional clinical trials and should not be the sole basis for clinical or public policy decisions.
- Outcomes research (and PORTs in particular) has been funded for a variety of reasons including improvement in knowledge, and quality of care, and rationalization of the nation's allocation of health care resources. Although there is a hope, if not an expectation, that PORTs will save money for federal programs, this is unlikely in the short run, and PORT teams should not be overtly or subtly required to recommend cost-saving practices as a basis for renewed funding.
- Since AHCPR cannot assume the role of sole supporter of patient outcomes research, PORTs may need, or even require, other sources of funding, much of which may come from industry. The manner in which such funds are juxtaposed with agency support, however, needs serious consideration in each case and careful management to safeguard the conclusions of the PORTs from the appearance or reality of a conflict of interest.
- Uniform standards for conflict of interest and self-dealing in PORTs are not needed at this time. If AHCPR does establish minimum agency standards, it should do so in collaboration with the National Institutes of Health.
- Grant specifications should require that both internal and bona fide external investigators and analysts have reasonable and timely access to PORT data.

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Appendix A

Institute of Medicine Workshop on Conflicts of Interest in Patient Outcomes Research Teams

PROGRAM AND SUMMARY

On June 11 and 12, 1990, the Institute of Medicine (IOM) sponsored a workshop on Conflicts of Interest in Patient Outcomes Research Teams (PORTs). The workshop was planned by a steering committee formally appointed to the task by the IOM. The purpose of the IOM workshop was to assist the Agency for Health Care Policy and Research (AHCPR), PORTs, and other parties to anticipate conflicts of interest and to identify issues to consider in dealing with them to ensure the credibility of PORT assessments.

Invitations to attend the conference were sent to the principal investigators of all currently funded PORTs and planning grantees and to others who represented the perspectives of academic institutions, industry, health services research, law, third party payers, policymakers, AHCPR, and congressional staff. About 60 participants and IOM staff attended the one-and-a-half day meeting. Background materials, such as recent policy statements on conflicts of interest in academic centers and papers commissioned for the workshop, were distributed to participants before or at the time of the conference.

The first day of the workshop included introductory remarks by Samuel O. Thier, president of the IOM, and a presentation by John Wennberg, principal investigator of the Dartmouth PORT. J. Jarrett Clinton, acting administrator of AHCPR, provided an update on and his views of the Medical Treatment Effectiveness Program.

The remainder of the first day included panel and participant discussions of three scenarios written for the workshop. Topics raised in the scenarios ranged from relatively straightforward equity and consulting

issues to more elaborate situations involving possible academic and professional conflicts of interest and joint ventures involving industry, payers, academic institutions, PORTs and AHCPR. The discussions were led by the chairman of the committee, Alexander Capron. After each scenario a rapporteur summarized the discussion (Appendix C).

On the second day, Christine Williams, a member of the staff of Senator George Mitchell, spoke about "Congressional Views and Expectations for the PORTs." Judith Lave, a health economist, discussed PORTs' impact on health services research, technology innovation, and payment policy. The conference concluded with a discussion among a panel composed of the committee chairman, the rapporteurs of the three scenarios, and all workshop participants.

The workshop discussions illuminated the difficulty of forming specific rules for dealing with problematic and complex cases. Such decisions tend to be made more on the basis of what is perceived to be common practice than on consideration of whether such common practice constitutes a reasonable and defensible action. Participants expressed a wide spectrum of views about the inherent danger of any given activity. Understanding how such *ad hoc* rules would affect researchers, research, funding and, more distantly, the public welfare, are beyond our current capacity. Such complex cases will, however, form the "case law" for managing conflicts of interest.

As an exercise for the committee, the discussions helped to make concrete the risks and benefits of various financial and professional relationships intrinsic to the PORT methodology. They broadened the views of the committee to include the experiences and expectations of current PORT investigators and others.

Agenda

Day 1: Monday, June 11, 1990 (Salons D&E)

8:00 a.m.	Registration and Continental Breakfast
8:40 a.m.	Welcome and Opening Remarks
	Samuel Thier, President
	Institute of Medicine
9:00 a.m.	PORT Structures and Methods
	John Wennberg, Dartmouth Medical School
9:30 a.m.	Discussion
9:45 a.m.	Scenario I: Presentation and Panel Discussion
	Moderator: *Alexander Capron*
	Panel: *Bernard Barber, Bruce Brennan, Barbara Hansen, Barbara Mishkin, Earl Steinberg*
	Rapporteur: *David Blumenthal*
10:30 a.m.	BREAK
10:45 a.m.	Continue Panel Discussion and Participants' Views
11:45 a.m.	Rapporteur Summary
12:00 p.m.	LUNCH (SALON H)
1:00 p.m.	Luncheon Speaker: Update on Activities of the Medical Treatment Effectiveness Program
	J. Jarrett Clinton, Acting Administrator
	Agency for Health Care Policy and Research
1:30 p.m.	Scenario II: Presentation and Panel Discussion
	Moderator: *Alexander Capron*
	Panel: *Marilyn Bergner, John Brown, Peter Budetti, C. K. Gunsalus, David Pryor*
	Rapporteur: *Marcia Angell*

2:15 p.m.	Participants' Views and Discussion
2:45 p.m.	Rapporteur Summary
3:00 p.m.	BREAK
3:15 p.m.	Scenario III: Presentation and Panel Discussion
	Moderator: *Alexander Capron*
	Panel: *Peter Barton Hutt, David Korn, Bryan Luce, Barbara McNeil, Lawrence Morris*
	Rapporteur: *Michael Pollard*
4:00 p.m.	Participants' Views and Discussion
4:30 p.m.	Rapporteur Summary
4:45 p.m.	What Emergent Issues Have Not Been Revealed by the Scenarios?
	Discussion
5:30 p.m.	BREAK
6:00 p.m.	RECEPTION (SOUTH GALLERY)
6:30 p.m.	DINNER (SALON H)

Day 2: Tuesday, June 12, 1990 (SALON II)

8:30 a.m.	Continental Breakfast
9:00 a.m.	Congressional Views and Expectations of Outcomes Research by PORTs
	Christine Williams, Legislative Assistant
	Office of Senator George J. Mitchell
9:30 a.m.	Envisioning the Role and Significance of PORTs for Health Services Research, Technology Innovation, and Payment Policy
	Judith Lave

10:00 a.m.	BREAK
10:30 a.m.	Anticipating and Managing Conflicts of Interest: Points to Consider for AHCPR, PORTs, Industry, and Others
	Roundtable Discussion and Participants' Views
	Alexander Capron (Moderator), Marcia Angell, David Blumenthal, Michael Pollard
11:30 a.m.	Summary of Discussion
Noon	Adjourn Workshop
12:15 p.m.	Executive Luncheon Session of Steering Committee
	(SALON C)

Appendix B

Workshop Participants

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Appendix C

Scenarios and Rapporteur Summaries

APPENDIX C1. SCENARIO I

Dr. Limestone is a professor of medicine in the Department of Preventive Medicine at State University and a recognized expert in the diagnosis, prevention, and treatment of osteoporosis. An internist, Dr. Limestone devotes 25 percent of her time to teaching and research at State and 25 percent of her time to private practice and related outside activities. The remaining 50 percent of her time she devotes to responsibilities as chief of health policy at the Quadrangle Corporation, a private non-profit institution associated with the university that conducts policy research in a variety of scientific and technical fields. Quadrangle is funded by federal and state agencies and by foundations and other private sources. Dr. Limestone is the principal investigator of a PORT awarded by AHCPR to Quadrangle to evaluate current management strategies for the prevention and treatment of osteoporosis.

As a member of the Academy of Internal Medicine (AIM), a medical professional society, Dr. Limestone serves on the 10-member Technology Assessment and Medical Practices Committee that meets three times a year. The committee is charged with developing and issuing statements on the safety, effectiveness, cost-effectiveness, and related guidelines for the appropriate use of new, generally used, and potentially obsolete procedures and practices. Committee members serve three-year rotating terms and receive no payment for their services other than travel and out-of-pocket expenses related to their committee work. In addition to responding to requests for guidance from the AIM membership, the committee fields approximately ten requests per year from government (usually concerning Medicare) and private sector third party payers for statements regarding procedures and related guidelines for appropriate use.

Dr. Limestone is also on the 75-person medical reference panel of the Piecerock Insurance Company. Panel members are on retainer to Piecerock. Each member receives $100 per hour, and can devote no more than 20 hours in any one week to this work. In the past two years, Dr. Limestone has devoted approximately 5 hours per week to medical reference work for Piecerock. In most instances, panel members in appropriate medical specialties provide consultation regarding a variety of issues related to insurance claims and related coverage issues referred to them by the medical director of Piecerock. On occasion, panel members are called upon to review new or revised company policies on the coverage of medical and surgical procedures. Dr. Limestone has also held many consultancies to pharmaceutical companies over the last 20 years.

Several months after the announcement of the PORT award to Quadrangle, Dr. Limestone has been offered a consulting arrangement from the Pharmatek Company to obtain her insight and guidance on Estrocal—451, a new drug being developed by the company for the management of osteoporosis. Estrocal—451 is currently undergoing Phase II clinical trials. Pharmatek currently has no drug on the market that has been approved by the FDA for the management of osteoporosis.

The consulting agreement with Pharmatek would provide $1,000 per day for up to 10 days of Dr. Limestone's time during calendar year 1990, plus reimbursement for travel and out-of-pocket expenses associated with this consultancy. As part of the consulting arrangement, Dr. Limestone is asked by Pharmatek to agree to the following:

- Without prior Pharmatek approval, she may not use or disclose any proprietary data, information, or knowledge pertaining to the research, development, marketing or any other aspect of Estrocal—451 or of any other of the company's products.
- Any inventions or discoveries that she may make or transfer to practice as a result of this consulting agreement, regardless of their patentability, would be the sole property of Pharmatek.
- She may not provide consulting services to any other person or entity on matters pertaining to the areas covered by the agreement for at least one year from the start date of the consulting agreement.
- At the end of 1990, or at any time before then at the request of Pharmatek, she must return all papers, computer files, and other documents that the company has provided to her in connection with the consultation.

Discussion of Scenario I

David Blumenthal, M.D.[1]

I was pretty optimistic about the way the session started out because we ran pretty quickly through a series of topics that we could have stumbled on. First we dealt with the issue of conflict of commitment. The regular university rule, which is true of my academic institution, as well as many others, that you are allowed a certain number of consulting days seemed to go down pretty well with everybody. There seemed to be ready acceptance of the idea that it is acceptable for faculty members to exceed time rules concerning conflict of commitment—such as the 50 days a year rule—in the case of a closely affiliated non-profit organization. There was no discussion of what would happen if this had been a for-profit spinoff of the university, and perhaps we can hold that for another discussion.

There was a discussion about the importance of following due process in formulating guidelines or recommendations in affiliated institutions or completely independent institutions. For example, in the Academy of Internal Medicine case, there seemed to be agreement that as long as the process used to formulate a recommendation was open and that disclosures of conflicts were made, then participants didn't have to worry about getting sued, and it was okay to charge a fee. Whether it was okay to make a profit for making recommendations was not discussed and is also an issue that I am sure would come up if we followed this issue to its logical conclusion.

The question of who should monitor faculty was raised briefly: the department chair, the university, nobody at all—again, this is not a trivial matter when it comes to actually specifying in a practical way how you go about handling disclosures, following up the results of disclosure, following up on conformance with rules if these are ever actually formulated.

As we anticipated, the issue was really joined over conflicts of interest resulting from consulting, which was what this case was meant to illustrate and I think did a fairly good job of illustrating. The most basic question related to consulting was never directly raised—whether consulting is an acceptable activity for PORT participants.

There seemed to be a sense that, yes, it is alright for PORT members to consult. In this regard, one issue that was not discussed, but which has

[1] Dr. Blumenthal, who was a member of the IOM committee, is Senior Vice President at the Brigham and Women's Hospital, Boston

been critical in the deliberations of some universities, like my own, is whether PORT work is "clinical" work or whether it is more like preclinical or laboratory research. Some universities have chosen to formulate different standards for consulting with respect to clinical and non-clinical work. I think that is an issue of some interest which should be pursued further. Conflicts from consulting in clinical work are sometimes viewed more skeptically than non-clinical things. If consulting is in, then, we get into a second level question, which seems to have been raised repeatedly here in many different forms; that is, what is in and what is out among the various types of consulting that faculty can do?

One issue was whether the type of institution or company investigators consult for has some importance. There was a general sense that consulting to insurance companies seemed to be more comfortable than consulting to a drug company. Professor Barber raised quite explicitly the question of the reputation of the company, implying that this should be taken into account.

There was the issue of the amount of money involved and the amount of time involved with a particular client or consulting institution. I heard differences of opinion about whether the income in relation to salary in the university ought to be a factor considered. If the compensation is very high, compared with university salary and to work performed, that seemed to make some people uncomfortable.

One difficult question concerned what it is appropriate for a consultant to disclose. Some felt that PORT investigators had to be scrupulous not to share with commercial employers any unpublished study results. Since this would require constant vigilance on behalf of a consultant, commentators asked whether it was practical for the right and left brains, as it were, of the consultant to remain detached in this way—in other words, whether this non-disclosure standard could be met.

In my mind, however, this issue of confidentiality hints at a more fundamental underlying question: what is the purpose of PORT members consulting to commercial entities? What benefit does this activity have, especially for society at large? What are the attendant risks?

Certainly in the biomedical research area, which is one that most universities are now pretty comfortable with, the disclosure of unpublished information has been acceptable. Indeed, the fact is that one of the reasons for these consulting relationships is that people bring to them a vast range of information that can be transferred somewhat more rapidly in a consulting relationship than it can be in published form.

So, the question is if you can't disclose the unpublished content of your PORT work, does that diminish or fundamentally interfere with the purpose of consulting?

Participants raised the inevitable question of whether we should be concerned only with real conflict of interest or whether appearance should be a very important factor in determining what is allowable and what is not. I am sure there will be differences of opinion on this.

Should the number of relationships on the part of a PORT participant be a factor? There are any number of possibilities for line drawing there, but it clearly is one of the factors that was troubling to people in the audience and on the panel.

One unaddressed problem concerns how to review conflicts of interest in universities. There must be a balance between rule-making and evolution of practice, or the use of a "case law" approach. At my particular institution we have decided not to draw many firm rules but allow precedent developed over time to be dominant. This was one of the issues that was raised in relationship to the role of the Institutional Review Board (IRB). Do we want an IRB-like structure and if we do, how much license should it have to approve and disapprove particular cases?

The discussion of this scenario also addressed some questions related to what technical terms should be incorporated into a consulting relationship. How do you protect a university's right to information? How do you protect the organization to which the individual PORT director or PORT member is consulting? What about exclusivity in consulting? Is that allowable? Allowable by whom? By the university, by the federal government? What happens when more than one university and thus, multiple sets of policies are involved?

In most cases, when individuals are subject to multiple policies, it is usually the most stringent terms that seem to govern. When university rules and federal rules are in conflict a side issue is, should this pattern prevail? What about the case of multiple people from multiple different universities? Clearly, there is an issue of consistency that needs to be addressed.

That covers most of what I thought I heard this morning. I am sure that there were a number of other issues. The issue that struck me as implicit and in some ways most fundamental was this matter of what is the purpose of permitting relationships that pose potential conflicts of interest? What are the societal stakes involved here? If there is no benefit to those relationships, then why do we permit all the problems that may arise from them?

Certainly in the biomedical sciences there is a general sense that there are benefits and that the benefits have to do with the technology transfer process. That is certainly the rationale behind the federal legislation that governs in this area and the question is, if that same benefit is present here, what do constrictions around disclosure and non-disclosure mean in

terms of that technology transfer process? Who is being protected, and how much of the appearance of conflict do we want to allow in order to capture those benefits?

APPENDIX C2. SCENARIO II[2]

AHCPR has awarded a grant to Golden University for a PORT to assess alternative modalities for the management of coronary arteriosclerosis. Among the medical, drug, and surgical modalities, some are distinctly device-embodied, including laser atherectomy and balloon angioplasty. The following three modalities would be reviewed:

First arm: a high daily-dose regimen of Deplak; it appears to be safe to use before signs of myocardial infarction and is currently the most promising nonsurgical intervention

Second arm: laser atherectomy

Third arm: balloon angioplasty

All other aspects of care will be controlled for. Administrative claims data for a total of 5,000 patients will be reviewed retrospectively, split fairly evenly across the three modalities. This 5-year PORT will also provide a total of three years of prospective observation. The PORT will require one year to get started and to identify and enroll patients to collect health status and quality-of-life measures not generally found in medical records or claims data; it will take the last year of the grant to analyze its data.

CARDPAK: Start of Study

In addition to data from insurance claims files and medical records, a key component of this 5-year study—specified in the AHCPR notice of grant award—is to test the utility of the computer software package CARDPAK in the study of arteriosclerosis. CARDPAK uses a specially designed health status index and simulation program to assess and project changes in cardiovascular health status and quality of life in patient populations subject to diagnosis and treatment of heart and respiratory disease. Dr. Hart, a cardiologist at Golden University and the principal

[2] Some of the elements in this scenario are adapted from one written for the IOM workshop by Dr. Sal Gorgiani and Jane Newman of Pfizer Pharmaceutical, Inc.

investigator of the Golden PORT, developed CARDPAK; the university owns the rights to CARDPAK, and Dr. Hart receives a share of the royalties paid for its use. Two other physicians participating in the PORT are Dr. Stenose a cardiac surgeon who is an expert on cardiovascular devices and on the faculty of Golden and Dr. Atherton, a cardiologist in the community. Her patients will be recruited for participation in the PORT study.

Cathco Inc. is a medical device and instrumentation company. Cathco has developed a highly innovative balloon-tipped catheter for use in angioplasty. The new device is currently undergoing clinical testing under an investigational device exemption in preparation for submittal of a premarket approval application to the FDA. Cathco management knows that at least one major health care product corporation is considering acquiring Cathco, and that success of its new catheter would significantly enhance the company's asking price.

As the Golden PORT is nationally recognized in the study of the management of arteriosclerosis, Cathco has approached the PORT concerning a proposed research contract. Specifically, Cathco is offering $2.5 million to the Golden PORT over a 4-year period to conduct a series of studies of Cathco devices, beginning with the new catheter. Cathco is especially interested in demonstrating improvements in patient outcomes and cost-effectiveness among patients who have undergone procedures with its products, e.g., angioplasty using its new catheter.

Cathco has made this offer contingent upon the availability of CARDPAK for use in the proposed study. Although Cathco would follow through on the offer if it simply had to pay the going royalty fee to Golden, it prefers to acquire CARDPAK outright, and has offered $200,000 to the university for it. If Cathco were to acquire CARDPAK, Dr. Hart would continue to receive his share of royalties indefinitely, and Cathco would honor any licensing arrangements in effect as of the date of the transfer of CARDPAK from Golden to Cathco. Cathco would retain ownership of the CARDPAK data.

PORT members recognize that the Cathco offer would provide an important boost to their overall research capacity. Although none of Cathco's current product line is involved in the Golden PORT study now supported by AHCPR, the PORT study does involve a product manufactured by one of Cathco's competitors, a Swiss company.

Outside Activities of the PORT Members

The principal investigator for this PORT project, Dr. Hart, is a recognized expert in laser atherectomy at a medical center in the midwest

and has published more than 60 primary research articles on this topic, including eight-year survival data on several hundred patients derived from randomized clinical trials (RCTs) of alternative invasive approaches to arteriosclerosis. He is also frequently an invited speaker at international conferences on these techniques.

Another member of the PORT, Dr. Stenose, has been asked by the FDA to serve on its advisory panel on cardiovascular devices. According to the financial disclosure form required by Golden University of all of its professional staff, Dr. Stenose has no financial interest in any health-related company, though his daughter owns $5,000 worth of stock in Cathco.

Dr. Stenose does not currently hold stock in Summit Laboratories, a company that manufactures Deplak. Until two years ago, Dr. Stenose had significant holdings in Summit. He sold his holdings after he completed a Phase III study of Deplak sponsored by Summit. This study contained very positive information supporting Deplak, and after presentation of the data at a conference, led to a stock price increase of $5 per share. This is disclosed on Dr. Stenose's financial holdings statement.

Dr. Atherton currently has stock holdings in several pharmaceutical and medical supply companies that market products used in surgical treatment of arteriosclerosis. These combined holdings amount to less than 10 percent of her total practice income.

Preliminary Results of the PORT Analyses: Four Years into the Study

Although results of the PORT investigation showed slightly better patient outcomes for the second and third arms than for the first arm, the differences among the three treatment groups were not statistically significant at the 0.05 level. The cost analysis indicated the treatment arms using surgical techniques to be substantially more costly.

Despite these findings, Dr. Hart is convinced that prospective data on invasive techniquest collected over many years at his center supports laser atherectomy as a preferred technique, particularly since recent advances in the technique seem to have improved survival rates. He is attempting to persuade the other PORT investigators that his prospective RCT data on eight-year survival rates should outweigh the findings of their three years of "case-control" observational data in the PORT study and that publication should be delayed pending longer-term survival data.

Discussion of Scenario II

Marcia Angell, M.D.[3]

First, I would like to compliment the person who dreamed up this scenario. When I first read it, all of these intertangled financial connections seemed too fantastic. Then I read it again, and I realized that it represented real life rather well. What I would like to do is very briefly summarize what I heard as the salient features of this scenario, because it is very complicated.

The PORT study is comparing a medical treatment, Deplak, with angioplasty and with laser atherectomy for the treatment of coronary artery disease. It thus has three arms. It also includes, evidently, the charge that a software package, CARDPAK be tested as a method of analysis, not just used. Into this very brief scenario leaps Cathco, a company that makes a rival catheter to the one being evaluated by the PORT. Cathco says to one of the three major members of the PORT, "We will give you, Dr. Stenose, two and a half million dollars if you look at our catheter independently of your function as a member of the PORT."

So, with that brief recapitulation, what do we have? We have three major members of the port. We have Dr. Hart, who designed CARDPAK and is receiving royalties on it and who at the end doesn't like the way the PORT study came out and decides he doesn't want to publish it.

We have Dr. Stenose--this is quite a cast of characters--who was offered the two and a half million dollars to study the Cathco's catheter and who in the scenario--Alex didn't mention this--sits on an FDA panel reviewing a Cathco application. His daughter, furthermore, owns stock in Cathco. Stenose, himself, did have stock in Summit, which was the company that developed Deplak, but he sold that at a tidy profit at exactly the right moment. Thus, he has quite a track record in financial entanglements.

Then we have Dr. Atherton, who wasn't mentioned, who owns stock in just about everything just in case. So, there are our players.

The panel began by addressing the issue of how industry might properly give money to researchers and institutions—if they may. Dr. Budetti had some reservations about whether they should at all, but the others addressed themselves only to finding the right way to do it. They were asked whether it was proper for Cathco to offer Dr. Stenose, through his institution, two and a half million dollars to be used for Dr. Stenose's

[3] Dr. Angel is the executive editor of the New England Journal of Medicine. She is a graduate of Boston University School of Medicine, where she trained in internal medicine and pathology, and she is co-author of the textbook *Basic Pathology*. She writes frequently on research and clinical ethics.

research on their catheter. Most of the panel felt at the outset that that was all right.

Nothing was said about whether Dr. Stenose would do the analysis of the study or whether he would just be a hired gun who supplied patients, with the analysis and interpretation being done by Cathco. I think that is an important question that wasn't addressed.

Another question that *was* addressed was whether the company would be granted rights to restrict publication of the results or to dictate the terms of publication. The panel felt that their approval of this arrangement was contingent on there being no such restrictions, that the investigators could publish the data from the study as they saw fit, although the panel did agree that it might be permissible for the company to see the results of the study before publication, provided the delay was not too great.

In all of this, there was the incidental discussion of the ownership of stock by Stenose's daughter. She owns stock in Cathco and it seemed to matter to everyone how old she was and how much she owned. It was decided that if she wasn't too young and she didn't own too much, it was permissible.

This was the skeleton of the consensus on how investigators should receive money from industry. Then the question became more complicated by introducing the fact that Stenose was a member of the PORT. Was it permissible for him to look at Cathco's catheter and at the same time be a member of the PORT, which was investigating a rival Swiss catheter as a part of its charge? Most members of the panel seemed to think that it was permissible if the money continued to flow not directly to Stenose but through the institution, with the usual guidelines that the institution would put on the receipt of such money, and if the two studies were entirely separate—that is, if the Cathco study were separate from the PORT study. But some members of the panel felt that to carry out these two investigations simultaneously, while receiving this much money from Cathco, compromised the independence of Dr. Stenose.

There was no attention given to the fact that Stenose, with his PORT hat on, was going to be evaluating a competitor, who was not paying him, but with his Cathco hat on, he was going to be evaluating the Cathco catheter and getting paid for it.

Now, there was some talk about how many catheters one can evaluate at once, and there was some kind of scientific concern that if one were evaluating too many devices or drugs at once, it might somehow affect how objective one could be. There was no focus, however, on whether money is changing hands from the owner of one product as opposed to the other.

Dr. Budetti disagreed with the general view that because the Cathco arrangement is a common way for research to be funded by private

enterprise, it is proper. He wanted to separate what was common from what was wise. He also mentioned—I thought this was interesting—that researchers were too valuable a commodity to waste as hired guns doing whatever research private companies pay them to do.

Dr. Hart, who developed CARDPAK, which is owned by his institution, gets royalties. The panel felt in general that this arrangement is all right, probably in part because this, too, is very common.

Hart, as a member of the PORT, is required by the agency to use CARDPAK, the software program that he developed and on which he receives royalties, as a part of the PORT project. Now, I can't imagine—this is the only part of the scenario that I can't imagine would happen in real life—that he would be asked to evaluate a product that he has both a strong intellectual and a strong financial interest in. CARDPAK is his creature and the better it does, the better he does. So, just on scientific grounds, I am not so sure that I would want Dr. Hart to be evaluating CARDPAK.

The panel didn't look at CARDPAK as something that was being evaluated as a part of the PORT project, but instead just the method to be used. The panel seemed to feel that if, in fact, it had already been evaluated and it was a reasonable method to use and the idea for using it came from outside the PORT, then that was all right. It strikes me that if the agency had no interest in evaluating CARDPAK, it would be peculiar to tell researchers what their methods must be, but there it is.

There was some discussion of the fact that Cathco wanted to buy CARDPAK, which would be used in the study that they were asking Dr. Stenose to do. Nobody knew quite what to make of that because I think nobody knew whether this would mean that the company would bury CARDPAK or whether they would merely collect royalties, as the institution was now doing.

The fact that Dr. Stenose had once owned stock in Summit and sold it at a profit was taken by the panel members not to be a problem in the present context, but perhaps to be of value in alerting people who care about these things that he might be fairly insensitive to ethical considerations.

At the end of the PORT study, Dr. Hart disagreed with its results and decided that he didn't want to publish them yet. He said he was also involved in a separate, clinical trial of invasive approaches to arteriosclerosis that was a better study and gave different results. We are not told whether his other study has been completed and published; the implication is that it has not been published. The other members of the PORT are evidently to take Dr. Hart's word that it is a better study, and it shows something else. The panel, quite rightly, said "no" to altering the handling of the PORT results for this reason.

APPENDIX C3. SCENARIO III[4]

Dr. Sharp is the president and CEO of British Medical Intelligence, Limited (BMI), a data processing and utilization review company that developed a highly sophisticated computerized patient record system. BMI currently operates in 2,000 physicians' offices in the United Kingdom. The system links physicians' offices with a centralized data bank in London that enables BMI to generate detailed information on physicians' therapeutic decisions and practice patterns. In addition, the system can be programmed to provide drug interaction warnings and prompt physicians to consider alternative therapies (including specific products and brand names) when they enter certain diagnoses or orders for medical equipment or pharmaceutical products. BMI sells the data it generates to pharmaceutical, device, and equipment manufacturers, and contracts with the National Health Service and private insurance companies to convey current clinical information to practicing physicians.

BMI recently entered into a joint venture with Unicorn, Inc., a U.S.-based third party claims processor, and Mega Pharmaceuticals, the largest U.S.-based pharmaceutical company with a full line of top selling therapeutic agents, including agents for the management of all major chronic diseases such as hypertension and diabetes. The joint venture will install computers in 5,000 physicians' offices in the United States and will sell data on physicians' prescribing patterns to pharmaceutical companies, contract with insurers to develop patient and physician profiles, and contract with health maintenance organizations to assist with implementing their utilization controls. Unicorn is responsible for the computer set ups and data processing. Mega is providing the capital for purchase of the computer hardware and placement in the participating physicians' offices. Dr. Sharp and his development staff from BMI will oversee the 18-month start-up phase of the U.S. venture.

Dr. Sharp's practice monitoring and management system is the most advanced in the world. Others have tried to establish similar systems, but have failed. Dr. Sharp owns all foreign and U.S. copyrights on the software that drives the system. Because the BMI system combines a problem-oriented and diagnosis-based medical record with the capacity to measure the outcomes of various medical interventions at the level of the

[4] This scenario was contributed by Michael Pollard, Esq. of Michaels and Wishner. Mr. Pollard was a member of the IOM committee.

physician's office, and is a proven success in the United Kingdom, the Agency for Health Care Policy and Research is interested in entering into a collaborative agreement with BMI in order to gain access to the patient and physician practice data that will be generated by BMI in the U.S.

Prestige University, a private institution that has a PORT concerned with the outpatient management of diabetes, is also interested in establishing a working relationship with BMI and Dr. Sharp. Data on outpatient, office-based physician care from the BMI-Unicorn-Mega joint venture would be used for the PORT. Prestige plans to offer Dr. Sharp an adjunct professor appointment and intends to tell him that he will have access to graduate students to assist him in adapting his system to medical practice, in the U.S. The Mega Pharmaceuticals Foundation, a not-for-profit, grantmaking institution established by Mega Pharmaceuticals, makes grants of approximately $1 million annually to medical researchers on the faculty of Prestige University Medical School.

Discussion of Scenario III

Michael Pollard, Esq.

The panel did a very good job of bringing out the key points in the case. We began our discussion by focusing first on the mechanics of the system that Dr. Sharpe had developed. There were concerns about invasion of physician privacy and possible disclosure of confidential information having to do with physician prescribing patterns. There was some disagreement among the panel members about how this ought to be handled, and the panel did not reach a consensus position.

The panel talked about the prompting function and how that might be misused selectively to prompt the use of drugs marketed by Mega Pharmaceuticals, but Alex clarified that we should assume that was not going to be used in such a way as to advantage Mega.

The use of the patient data by insurers possibly to exclude certain groups raised a number of concerns about the appropriateness of that practice. The panel felt fairly strongly that there was a big difference between physicians who would volunteer to participate in the BMI system and physicians and patients who would be involuntary participants in such a system. With regard to involuntary participants, it would be very important to respect their privacy. Everyone felt a little bit more comfortable once we determined that the physicians' participation would have to be voluntary. The question of sale of the information gathered by the software system, however, was one that continued to bother a number of participants, and we did not reach any resolution on that aspect of the scenario.

On the issues concerning possible collaboration with Prestige University, the university people on the panel felt much more comfort with the notion of contracting with the BMI/Unicorn/Mega joint venture than with a more collaborative sort of process, and the panel did not explore how a collaborative process might work.

The use of graduate students was another issue the panel addressed. Here the question of exploitation and whether the experience of the graduate students in working with Dr. Sharp—in trying to adapt his system to the U.S. system—would be a bona fide learning experience for the students. If it were, then it would probably be alright.

With regard to the Mega Pharmaceutical Foundation support, the initial reaction by some panel members was that this was not an overt conflict of interest, but we returned to this question, thanks to Mr. Hutt, in terms of the so-called laundering issue—whether it makes a difference if the support flows to the university or goes directly to the individual researcher under some kind of consulting arrangement. The panel agreed that it was very important to engage in full disclosure, and to have careful review of the design of the research and the individuals receiving grants or consulting monies. There might be some safeguards that could be employed if there were a question about appropriateness, such as using a co-principal investigator.

The danger of bias was a theme that pervaded much of the discussion by the panel. Again, Mr. Hutt raised some important questions. He stressed the need to focus both on sources of financial bias and on other forms of bias, and he suggested ways to deal with it including full disclosure and a sound peer review mechanism within the university. This would include review both of the results of research and a mechanism to look at the design of studies and some of the structural elements that go into setting up a study.

The panel concluded by looking at the issue of an exclusive license for the Prestige University for the use of BMI data. The panel had a considerable discomfort about this arrangement and a reticence to permit that kind of monopoly by one university in an environment where presumably researchers engage in some degree of professional collegiality and sharing of information.

Some of the discomfort about exclusive use of data may have arisen from an assumption that many of us are making, that PORTs are probably going to specialize in one area and that they will not be crossing over into other areas. There is nothing to stop that happening, however, and this case provided an opportunity through the BMI database for a PORT to develop the capacity to look at procedures across a wide array of interventions.

Appendix D

Background Papers

APPENDIX D1. PORT RESEARCH COMPARED WITH CLINICAL RESEARCH: CONFLICTS OF INTEREST IN PATIENT OUTCOMES RESEARCH

David Asch, M.D.[1]

Introduction

Several forces in the last two decades have worked to increase the collaboration of industry, government, and academic biomedical research centers.[1] First is the increasing scope and expense of medical research programs. Second is the threat of a simultaneous contraction of federal research support for these projects. Third is the competitive pressure to facilitate efficient translation of the products of academic research into marketable goods and services. The resulting growth of different collaborative agreements among universities, industries, and government-supported researchers has highlighted concerns about the kinds of conflicts of interest that can result from these complex arrangements.

An enlarging literature addresses these concerns. It is a given that even the most conscientious investigators cannot eliminate the subtlest biases that affect their work. But when researchers receive support from the companies that produce the products or services they are investigating, when they enter into consulting arrangements with them, or when they share in the ownership of these products, their commitment to upholding professional norms may be or appear compromised. Such personal economic interests increase the likelihood that researchers will lose their

[1] Dr. Asch is Assistant Professor of Medicine at the University of Pennsylvania.

objectivity—consciously or unconsciously—and so widen the opportunities for misleading research results. And even when objectivity is preserved, the public recognition of such potential conflicts of interest may erode confidence in biomedical research.[2]

The substance of these concerns is illustrated in the recent controversy surrounding several investigators who conducted research supporting the wide indications for an ophthalmic ointment while owning large amounts of the manufacturer's stock.[3, 4, 5] Later research by different investigators challenged the original findings.[6, 7] Attempts to address these problems have recognized the need to balance the potential for misguided research with the legitimate social goals underlying economic incentives. The many advantages to these economic incentives have been extensively discussed elsewhere. Links between investigators and for-profit concerns create efficiencies not only in the conduct of research, but also in the commercialization and distribution of the products of research. In part because of this continuum between efficiency and conflict, conflict of interest in this setting has defied simple definition.[8] There is, nevertheless, widespread consensus that conflicts of interest by any definition need attention from within the biomedical research community. The past few years have seen statements by federal funding agencies,[9] universities,[10] scientific journals,[11] professional organizations,[8, 12, 13, 14] and individual research teams.[15]

None of these statements, however, distinguishes among various types of biomedical research or among the differences in research goals or methods that may encourage or deter conflicts of interest for investigators. One relatively new form of medical research uses somewhat nontraditional research methods to compare and evaluate the effectiveness of different medical practices in achieving desired patient outcomes. These projects are supported by the Agency for Health Care Policy and Research (formerly the National Center for Health Services Research) under their Medical Treatment Effectiveness Program. Research is conducted by multidisciplinary Patient Outcomes Research Teams (PORTs) using novel methodologies that span a wide area of expertise. The methodologies employed by PORTs are novel enough, and the intensity of their projects are deep enough, to raise concerns that the existing guidelines on conflicts of interest need to be expanded.

This paper introduces principles of outcomes research and examines ways in which members of PORTs may be at risk for conflicts of interest different from those faced by more traditional clinical researchers.

Patient Outcomes Research Teams

The goal of PORTs is to foster effective medical approaches to specific clinical problems. They seek to achieve this goal by evaluating and comparing the outcomes of existing variations in medical practice, and disseminating that information in the form of practice guidelines. The principle underlying outcomes research is that medical practices—for example the use of particular surgical techniques or diagnostic tests—ought to be subject to the same standards of safety and efficacy as are pharmaceutical agents. The measured outcomes themselves ought to be robust enough to include most of the parameters patients typically value: survival, health status, functional capacity, and quality of life. Medical practices will be more effectively and appropriately utilized if their existing variation is perceived as an observational forum for natural selection. Through the Medical Treatment Effectiveness Program those practices that achieve expressed goals will be identified and will continue, while those that fail to achieve these goals will fall into disuse. The hope is that medical practices will evolve in the right direction with this kind of cherry-picking. These natural evolutionary forces may substitute for the expensive, time consuming, and cumbersome randomized clinical trials that have been the traditional way to evaluate alternative treatment strategies.[19]

Each PORT focuses on a specific clinical problem, for example benign prostatic hyperplasia or gallstones, with the aim of evaluating the medical alternatives to this problem and identifying those that best achieve desired patient goals. While each PORT may be narrowly focused on only one clinical problem, it approaches that problem in an extremely comprehensive way. This depth requires that PORT research be divided into a sequence of interrelated subtasks. The model for PORT research is to: (1) review and synthesize existing published evidence regarding treatment alternatives in order to identify current practices and controversies, to obtain first estimates for decision outcomes, and to identify gaps in the scientific knowledge base; (2) analyze insurance claims databases to estimate the probabilities of relevant outcomes, for example mortality, reoperation, and other complications; (3) interview patients and practitioners to obtain primary data regarding preferences, decision making, and outcome measures not available from insurance databases; (4) develop decision analytic models to provide a rational framework for understanding the tradeoffs in probability and outcome involved in the examined treatment alternatives, and to help explain observed variations in medical practices; (5) formulate practice guidelines based on the findings in the earlier steps; (6) disseminate these guidelines, and examine their effects on service utilization and appropriateness, practice variation, and patient outcome.

The diversity of these subtasks requires that PORTs be complex multidisciplinary teams with expertise in epidemiology and biostatistics, clinical decision and utility analysis, claims data analysis, psychometrics and survey research, medical education, and the relevant clinical disciplines. While these teams may focus narrowly on a single clinical problem, they approach those problems with great depth.

Although PORTs are designed to evaluate existing alternatives in the management of common clinical syndromes, they serve a related goal of linking medical management decisions with specific patient outcomes. Patient preferences for these outcomes are diverse. The better able physicians are to predict the various outcomes of treatment alternatives, the better equipped they will be to tailor their medical management to the individual goals and risk preferences of their patients. Because the personal goals of many patients may be best achieved by medical strategies of "watchful waiting,"[20] resource utilization and the intensity of medical service delivery may actually decrease as physicians learn to better tailor their decisions to reflect patient preferences. On a case by case basis, outcomes research helps not only to define the best treatment alternatives, but also to define how much is too much.

The emphasis that PORTs have placed on individual patient preferences has important societal consequences. Evidence from the studies of benign prostatic hyperplasia suggest that the individual interests of many patients may be best served by less costly medical strategies. [20] It is certainly no coincidence that the opportunity to articulate convincingly that less may be better arrives in the setting of deafening societal cries for reduced health care expenditures. At the same time, the emphasis PORTs place on individual patient preferences, on the understanding of practice variation, and on the development and dissemination of practice guidelines, dovetails neatly with rising patient consumerism, the perception of health care as a commodity, and the recognition of the health care system within an industrial model. Patients and payers have become more influential stakeholders in the medical enterprise, and PORTs evaluate medical treatment alternatives in a format that is particularly well adapted to the interests of those stakeholders. Understanding the effects of power shifts among stakeholders may help us predict the different kinds of conflicts of interest to which PORTs may become susceptible.

Conflicts of Interest in Patient Outcomes Research Teams

Like the outcome research supported by PORTs, randomized clinical trials also are designed to compare and evaluate treatment alternatives

according to predetermined outcome measures. While the outcomes evaluated in clinical trials may be more narrowly defined—survival alone, for example—there is nothing intrinsically different between the goals of the Medical Treatment Effectiveness Program, and the goals of more traditional randomized clinical trials. PORTs rely on insurance claims data systems for their analyses, and so must focus their efforts on existing medical products and services. Only these treatment alternatives have the track record necessary for the kinds of analyses that PORTs do. Prospective clinical trials are not limited in the same way. Aside from this difference in potential subjects for study, however, PORTs and more traditional investigators involved in clinical trials differ only in their methods. By and large they share common goals. PORTs are likely to find themselves susceptible to qualitatively the same kinds of conflicts of interest as more traditional investigators.

Opportunity and Motive

Vulnerability to conflicts of interest is a story of opportunity and motive. Although investigators' personal interests may conflict with their professional responsibilities, they will not really be at risk for betraying those trusts if they have no opportunity for infecting their research with bias. Investigators engaged in clinical research can be influenced, consciously or unconsciously, in their research design, in their interpretation of findings, and in the timing and forum they choose to report their results.[11] Peer review does much to reduce these opportunities for bias, but does not eliminate them. Moreover, the peer review system requires that investigators act responsibly in revealing all aspects of their study design so that referees can knowledgeably review the findings. There are abundant opportunities for conflicts of interest in traditional clinical research.

PORTs also are vulnerable to infecting their methods, consciously or not, with interests that conflict with professional research goals. Some might argue that compared with investigators involved in randomized clinical trials, PORTs are less vulnerable because they rely so heavily on secondary data sources that are, by and large, out of their control. Insurance claims data, for example, exist already on computer tapes waiting to be analyzed.[21] But within the complex research design and multiple subtasks necessary for outcome research are many areas of vulnerability. The techniques of meta-analysis of the existing literature are highly subjective: some published studies (and, in general, most unpublished studies) will be excluded because they fail to meet criteria for rigor established by the investigators. While insurance claims data tapes already

exist, the data must be "cleaned" and transformed to make it suitable for the kinds of analyses PORTs do. It may be difficult for publication referees to review these transformations. When primary data must be collected about functional status, for example to assess outcomes with greater resolution than mortality or reoperation rates, biases and subjectivity can as easily be introduced as in any other primary research. The development of practice guidelines, although based on the initial subtasks of outcome research, is highly subject to personal interpretation.

These are not necessarily weaknesses of the PORT methodology, but they represent PORTs' vulnerabilities. While PORTs rely heavily on secondary data sources, they do not remain at arm's length from those data. Numerous opportunities exist for conflicts of interest to bias the methodologies of these teams. These opportunities are multiplied by the large numbers of diverse team members required to complete these complex projects. At the same time, pluralistic teams may introduce checks and balances that limit opportunities for bias. PORTs are at least as vulnerable to conflicts of interest as are investigators involved in more traditional clinical research.

These vulnerabilities represent the opportunity for personal interests to alter the direction of research so that it satisfies different goals. What might those interests be? Given the opportunity to redirect research findings, what might be the motives?

Traditional Conflicts of Interest: Funding, Consulting, and Equity

Investigators in PORTs might be subject to the same kinds of conflicting interests as investigators in clinical research. It is not uncommon for investigators involved in clinical research, particularly pharmaceutical research, to have all or part of their research supported by the industries whose products they are evaluating. While outcome research in general is less likely to receive direct funding from industries, industries may understandably look upon PORTs as centers of excellence in their clinical areas and so choose to support related research by members of the team. This is especially likely to occur in PORTs because they are designed to approach narrow clinical problems with depth. Moreover, because of the expense of these large scale research programs, and the incentives to limit unnecessary duplication of research efforts, PORTs may have near research monopolies on their clinical problems. This concentration focuses industry interests on a smaller group. For the same reason, members of PORTs are especially likely to be offered and enter into consulting arrangements with industries that produce related products and services. If PORTs really have their clinical playing fields all

to themselves, the absence of competing and confirming research teams will make the potential end results of conflicts less easily or less quickly detected.

Nevertheless, there are obvious social advantages to such academic and industry collaboration, because it embodies the kind of information and technology transfer that makes for the efficient commercialization of academic findings. Industries often are able to support such research efforts with products, services, and information that would otherwise be unavailable. Both industry and agency funds, for example, may support the staff that is in effect the machinery of the PORTs. While this overlap represents an efficiency, it highlights the difficulty researchers may have in keeping their interests separate. Conflicts may arise because the findings of PORTs in their outcomes research may have profound effects on the industries that support their other research. PORTs are particularly vulnerable to this kind of conflict because they focus on existing services and, among these, the big ticket items.

Besides receiving industry support for related research, and the possibility of having conflictual consulting arrangements, members of PORTs are at risk for conflicts if they have equity interests in related companies. The conflict created when an investigator has a direct financial stake in the results of his research is not fundamentally different between investigators in outcome research and in other kinds of research, but members of PORTs may be particularly susceptible. Like investigators involved in pharmaceutical research, PORTs focus on existing products and services. The end results of their research may have clearer market implications than the results of investigations undertaken at a more basic level. At the same time, industries providing established products and services are more likely to be publicly traded and so offer better defined avenues for exploiting the inside information available to PORTs.

Spinoff Ventures and Intellectual Property Rights

Although PORTs focus on existing medical practices, there are nevertheless opportunities for entrepreneurialism that may conflict with the goals of academic research or may represent the diversion of federal funds for private gain. One not so surprising finding of the PORT investigating benign prostatic hyperplasia, for example, is that the subjective importance of various symptoms and outcomes varies greatly among patients with prostatism.[22] If patients knew more about these outcomes and the probabilities of achieving them, they would be better equipped to make informed choices to reflect their personal preferences and goals. For this reason the PORT is developing an interactive

computer video disk to help inform patients of various options and outcomes. The video disk can be perceived as a diagnostic test to determine true patient preferences.[16]

Such video disks have obvious commercial potential, not only for prostatism, but also for innumerable other common conditions for which patients and practitioners want educational tools. Although the commercial development of such products will serve many social goals, members of PORTs will be uniquely positioned to benefit from these commercial applications because they have investigated precisely those issues necessary for such educational tools. Moreover, their primary data collection on patient preferences for outcomes can be seen as an extensive predevelopment marketing survey that will convey additional advantages in bringing such a product to its commercial potential. Small publication delays will enhance these competitive advantages.

PORTs with different kinds of expertise might be able to commercialize other talents as well. Insurance companies are potentially hungry audiences for information about the appropriateness of various medical practices in different clinical situations, and members of PORTs may be particularly qualified to provide this information. Sideline consulting firms with competitive advantages sustained by PORT research represent, in part, the harnessing of the federally funded PORT machinery for private gain. Even though PORTs are not specifically involved in new product development, they are nevertheless vulnerable to conflicts of intellectual property rights.

Changing Stakeholders

Investigators in any kind of research are vulnerable to conflicts that arise because of funding or consulting arrangements with industry, owning equity in evaluated products, or participating in spinoff ventures. PORTs and their members may be vulnerable, in addition, to pressures from stakeholders typically unrepresented in more traditional research. Because PORTs may be perceived as influential evaluators of existing medical practices, for example, they represent a potential challenge to the providers of those services.

Such perceptions may play out in different ways. The fundamental justification for the PORT methodologies is to hasten and improve the evaluation of medical practices. Practitioners heavily invested in existing technologies may feel vulnerable when those practices come under evaluation.[23] PORTs rely on such practitioners in their primary data collection about preferences for risks and outcomes. In 1986, 32 percent of urologists' Medicare revenue came from transurethral prostate

resections.[24] Can a practicing urologist, who might receive most of his income from transurethral prostate resections, objectively contribute to a study that may suggest that this procedure does not yield the most desired outcomes?[25] By the nature of research priorities, PORTs focus on the "cash cows" of clinical services, and physicians may feel that these practices are on trial.

It is not only individual physicians who may introduce these conflicts. While investigators in more traditional clinical trials may develop conflicts through the participation of industry collaborators, PORTs may develop conflicts because of the participation of professional societies. These societies may offer consulting arrangements to PORTs or support them in related research to confirm or refute findings or test new technologies that might increase the portfolio of skills that their members share.[26] PORTs may be especially vulnerable to such arrangements because of their relative exposure on their clinical playing fields and the influence they therefore may carry. It is unusual to be concerned about the direct effects of conflicts introduced by clinician stakeholders or their professional societies.

Health insurers are another group of stakeholders likely to be drawn to outcome research. Practice guidelines represent one promising arm in a general strategy to reduce health care costs. The ability to compare the health outcomes of high intensity and low intensity geographic areas introduces the appealing possibility that cost and quality may not always be in conflict. While there are already societal pressures on PORTs to support findings of this sort, insurance companies may intensify these pressures, as well as bring them within arm's length. Like other industries, insurance companies may introduce conflicts through consulting arrangements, or by funding related research. Even without these arrangements, however, PORTs must collaborate with insurers for access to claims data. Even the nonprofit insurance systems cannot be perceived as disinterested in the findings. These potential conflicts are not fundamentally new, but they are pressures from stakeholders not generally represented in more traditional clinical research.

Conclusions: What's Different about Outcomes Research?

If there is really something that distinguishes outcome research from more traditional types of clinical research it is that it was born in a period when power in the medical enterprise was shifting among the various interest groups. PORTs have available to them powerful tools for evaluating the medical profession from the outside. For this reason, they are well positioned to meet the awakening interests of patients and payers,

and they also pose a substantial potential threat to the autonomy of existing practitioners and the integrity of the medical profession. [27] It is difficult to speculate how influential PORTs may become, but their emphasis on evaluation and the development of practice guidelines is consistent with broad trends in health care. Through their efforts, PORTs may facilitate access to information about medical treatment decisionmaking and so increase the chance that market forces of supply and demand— rather than medical professionalism—will determine the efficient delivery of health care. These are distant goals, but the direction is clear and the first steps are taken.

Because the PORT methodology is so well adapted to these social agendas, members of PORTs are vulnerable to the conflicts of interest introduced by those interested in cost containment. At the same time, members of PORTs are likely to feel reactive pressures from clinicians and professional societies struggling to defend their professional and monetary interests from previously silent stakeholders. These are pressures investigators involved in more traditional clinical research are not likely to feel.

The products of outcome research are of concern to more interest groups than are the products of more traditional clinical research. But is outcome research sufficiently different that separate guidelines need to be constructed to prevent the socially undesirable consequences of industry links? The stakes may be higher, and there may be a few extra players, but the object of the game is fundamentally the same. Separate guidelines constructed for different types of medical research establish multiple standards. If certain collaborative arrangements are tolerated in clinical research but not in outcome research, which standard is right? The tendency to gravitate toward the strictest standards can de facto impede future social progress.

Complex interrelationships among governmental, academic, and industrial institutions create opportunities for social progress while creating opportunities for potentially destructive conflicts of interest. Restrictive guidelines that eliminate the possibility of conflict will also eliminate opportunities for the efficient translation of research findings into marketable goods and services. The best institutional guidelines will not eliminate industry collaboration, but will help investigators navigate toward its socially desirable products and away from its socially undesirable products. Those who write guidelines must fight the urge to increase restrictions and instead work for specificity in their applications. What is needed is clarity, not increased strigency.

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APPENDIX D2. PORTS: THEIR IMPACT ON HEALTH SERVICES RESEARCH, TECHNOLOGY INNOVATION, AND PAYMENT POLICY

Judith Lave, Ph.D.[1]

Introduction

I was asked by the staff at the Institute of Medicine to write a paper on the impact of PORTs on health services research, technology innovation and on payment policy. They asked that the paper be a provocative and forward looking document rather than a scholarly one. It is difficult to resist such a charge. But before turning to my charge, it is important to discuss the PORTS themselves briefly.

PORTS are the major component of the medical effectiveness initiative of the Agency for Health Care Policy and Research. PORTS and the POARP studies that preceded them are large scale, multi-faceted multi-disciplinary projects that must meet special requirements. The goals of the PORT project are to "identify and analyze the outcomes and costs of current alternative practice patterns in order to determine the best treatment strategy and to develop and test methods for reducing inappropriate variations." The basic model to be followed is one developed by John Wennberg and his colleagues at Dartmouth University. Each PORT will be funded at a level of at least $5 million dollars. PORTS thus represent a huge commitment of resources.

PORTS are the most visible symbol of a new era in health services research. In recent years there has been an increased effort to expand the boundaries of traditional research endeavors. In my field, economics, researchers have moved beyond examining the linkage between payment policy and utilization change to examining the effect of utilization changes

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on health outcomes. In the clinical arena, researchers have moved from studying the effect of an intervention on specific clinical indicators to examining its effects on a broader set of health status measures. RAND has brought us both the National Health Insurance Experiment and the Medical Outcomes studies. Dartmouth has brought us the variations study and almost everything you want to know about prostatism. The University of Pittsburgh has not been isolated from these trends. In the past year I have been involved in the development of proposals to study the cost effectiveness of alternative methods for treating depression, to examine alternative treatments for epilepsy, to evaluate a geriatric assessment project, and to investigate enteral feeding and COPD. These projects, which are still in the developmental or review stages, are characterized by their interdisciplinary nature.

With this introduction, I will now turn to my charge and consider briefly PORTS and health services research, technology innovation and payment policy. This is obviously a mammoth and impossible charge—and so I will only touch on the more salient issues.

Health Services Research

The effect of the PORT initiative on the field of health services research should be significant. It should lead to a nonmarginal expansion in the relevant human capital because it will further legitimize health services research within academic medicine as well as attract economists, sociologists and others to the field. Thus, young and ambitious researchers will be attracted to health services research because it will be viewed as an area of inquiry that will be blessed with federal funding. This expansion of capacity will increase the likelihood that the effectiveness initiative will be a successful one.

PORT projects should lead to significant methodological advances in a number of different areas. I expect that we will make significant advances in the analyses of claims data. We will develop better methods of linking files to produce information on episodes of illness as well as in assessing the effect of treatment by determining surrogate health status measures from the procedure and diagnostic information contained in such files. We will make significant improvements in the development of health outcomes measures—and in creating measures that are useful for policy makers and clinicians. I also expect that there will be some advances made in methods for disseminating information. I am hopeful that the improvements in methods which result from this initiative will exceed those resulting from the RAND national health insurance experiment another

large research project which brought together researchers from the many disciplinary backgrounds that make up the field of health services research.

Let me discuss outcomes measurement in more detail. I expect that PORTs will evolve in such a way there will be some outcome measures that will be used by each of the teams. This will allow researchers to compare the effectiveness of treatments both within and across conditions. I also expect that there will be major advances in determining methods of finding out what is important to patients in treating specific conditions. This will create a variety of outcome measures that will complement the traditional set of outcome measures used by clinicians.

It is useful to look at some specific characteristics of PORTS. Here I consider briefly the structure of the design of the PORTS, the cost of implementing the PORT initiative, and some of the implications of developing visible centers of expertise on certain conditions.

Structure

The structure of the funded POARPs and PORTs is modeled after the study on prostatism that was pioneered by Wennberg. Briefly, large interdisciplinary teams will conduct meta-analyses of the condition of interest, examine claims data files, undertake some prospective clinical studies, develop models of care, inform practicing physicians about their findings, implement educational programs to change physician practice patterns, and evaluate the success of these educational interventions. This is a set of heroic tasks.

This project design has many strengths. One of the major strengths is that the condition of interest will be examined by a multidisciplinary team. This means that the perspective that each of the disciplines brings to bear on the problem should be integrated in the various analyses undertaken by the team. I have often been impressed at how little members of one discipline search out the research results of scientists in another discipline, even when they are both examining aspects of the same question. For example, do gynecologists know as much about post-hysterectomy depression as do sociologists, psychologists and psychiatrists?

As an aside, it should be pointed out that the multidisciplinary nature of the team may mitigate against some of the conflict of interest concerns. Each team will have to work out arrangements for managing conflict and for determining rules for accessing data collected by it. It is likely that the working arrangements that need to be developed to keep the multi-site, multidisciplinary group together will lessen the probability that bias in the point of view of a particular investigator will be reflected in the judgments taken by the team or in the final analyses.

Second, since the design of each PORT project is similar, each team will face a common set of problems, and working groups have been (or will be) established to address some of these problems. As noted above, this should lead to significant advances in analytical methods and measurement. Additionally there should be enough similarity in the analytical approach taken by each PORT that it will be relatively easy to compare their findings.

Third, I expect this research initiative to lead to improvements in how we measure and convey differences in the effectiveness and the cost effectiveness of treatments for different conditions. Although we will learn that some practices are simply inappropriate, and that some are in fact harmful, we will also learn that different practices differ in their effectiveness or that they are more or less effective for different clinical populations and in different settings. Health services research will have to do research on better methods of "risk assessment" and "risk communication."

Possible Threats to PORT Success

There are, however, some problems with this project design that may threaten the success of the PORTs. Given the visibility of PORTs, it is important to be aware of such threats. Some of these are discussed below.

Flexibility. The approach taken is fairly inflexible. Although the POARP and PORT studies are not contracts, there may be a tendency for the project officers to "force" the projects into a standard approach. Although, as noted above, standardization is a positive feature of the PORTs initiative, if it is too rigidly enforced it could restrict, rather than encourage, creativity.

Use of Claims Data. One has to be careful not to put more weight on the findings that the nature of the analytical data can support. We have come a long way in making use of claims data, and no doubt we will move much further along as a result of the PORT initiative. However, claims data do not contain clinical information nor do they contain much information on *specific* treatment technologies. This is particularly true in cases where the procedures under investigation involve the insertion of devices or prostheses which are continually being modified. Claims analyses will often lead to hypotheses that must be tested through the collection of additional primary data rather than to concrete conclusions.

Prospective Data Collection. All the PORTs are planning to collect data prospectively. In general, these studies will be conducted in a limited

number of sites. These studies are designed to study *how* medical care is actually practiced, and by using statistical controls, to determine whether there is any difference in the outcomes associated with different practices that are in effect today. This prospective component is a major strength of the project. (The alternative strategy is to conduct large multi-site clinical trials.) However, critics may argue that the sites are too limited and that therefore the results are not generalizable, or that the types of questions being addressed by the teams should be asked only in the context of a clinical trial. These criticisms are more likely to be raised if the findings of the teams are used in setting payment policy.

Study Population Size. The clinical condition of the patient can vary significantly. The PORT findings about clinical effectiveness could be subject to the criticism that they were based on inadequate data. Are the proposed clinical studies large enough so that it will be possible to determine the effect of treatment on many different groups of patients?

Legal Implications of PORT Recommendations. Each PORT is multidisciplinary. However, there is one discipline that is lacking—the legal one. If the PORT teams end up making recommendations about the practice of medicine, are there any legal implications to these recommendations about which they should be aware?

Scope of Task. Finally, PORTs are responsible for undertaking many tasks. I am concerned that the research programs may be too ambitious and that, as a consequence, they may fail at some of their assigned tasks. In particular, PORTS are supposed both to implement an educational program to inform physicians about their findings and then to determine whether the educational programs have influenced physician practice patterns. While there is no doubt that this is a critical component of the PORT initiative, is it reasonable to expect that successful campaigns can be mounted; and that, even if the programs are successful, that their success rates will be discernable over this time period? Although a number of studies have shown that physician practice patterns do respond to economic incentives, the effects of *educational* strategies are not encouraging—particularly in the short run. This point is made in an editorial in the May 24 1990 *New England Journal of Medicine* which was commenting on a study in which researchers tried to change physician test ordering behaviors:

> I often hear physicians lament the difficulty of changing their patients' behavior regarding issues such as diet and smoking, even when the medical data are incontrovertible. Despite our common

frustration with individual patients, however aggregate changes in life style have probably contributed substantially to the impressive decline in mortality from coronary heart disease in the United States. Perhaps we as a profession should complain less about the difficulty of altering patients' behavior and learn more about how to change our own lest the pot be accused of calling the kettle black.

Cost of the PORTS

The PORTS are very expensive, and the expense of the PORTS may have some implications for the field of health services research. Three implications are discussed below.

Allocation of Health Services Research Funds. A significant proportion of the funds of the new agency are to be allocated to effectiveness research. It is possible that this area of research will flourish while others will be seriously underfunded. Some of these areas, such as research on alternative methods or strategies for paying for new and evolving technologies and research on alternative delivery systems, are complementary to the effectiveness initiative.

Allocation of Effectiveness Research Dollars. There are many approaches that can be used to study the effectiveness of medical care. In the short run, PORTs may absorb most of the effectiveness dollars. This, of course, will mean that most of the funds will go to a small number of researchers located in a few centers across the country. This strategy could stifle the research efforts of other individuals who are interested in effectiveness work but who are not interested in undertaking projects on the scale of the PORTs. However, Gordon De Friese at University of North Carolina does not believe that this will be a significant problem. He argues that we are simply going to illustrate that it is the well-designed study that can answer the types of fundamental questions raised by the PORTs, not just the size of the grant that supports the research.

Allocation of Resources to Study a Particular Condition. How will the existence of PORTs influence decisions to fund other proposals to study a condition which is being examined by a PORT? Can anybody but Wennberg get funded to do health services research for prostatism? If somebody submits a proposal to examine knee surgery; will the "knee jerk" response be that "Indiana is taking care of that?" Along the same lines, how will ROls by members of the PORT teams to study additional questions related to the PORT be received? Given a limited research

budget, it may be appropriate that additional funding to study a given condition be limited, although such decisions need to be carefully assessed.

Concentration of Expertise

The existence of PORTs will mean that some centers and individuals will develop a particular type of expertise on treatment approaches for a particular condition. Does this concentration of expertise have any important implications for the field of health services research?

Consulting. Expertise in the field will mean that the members of the teams will be called upon to use that expertise in the role of a consultant. Drug companies, firms that manufacture prostheses, and home health associations beckon. Is there anything different about PORTs? Do the members of PORTs need to follow a different set of rules or guidelines as they consider the options available to them? The answer to this question depends, in part, in whether PORTs are viewed as being significantly different from other groups of researchers who study and develop expertise in specific conditions. However, I would imagine that the same conflict of interest and consulting arrangements that guide faculty members should be applicable here.

Contracts. Members of the PORT teams will have a comparative advantage in responding to any Requests for Proposal or Program Announcements related to the condition of interest. They will have assembled data bases, organized networks of providers, and obtained an "institutional" knowledge base that should enhance their ability to compete for funds. However, they are no different from other expert teams who because of their expertise have an advantage in the competitive market place.

Reviewers. Because of their expertise, members of PORTs will be called upon to serve as reviewers of other proposals related to their field or of articles that have been submitted for publication. However, it is unlikely that this role is likely to give them any measure of "control" in a particular field. Although they are experts, there will be many other experts in the field who also will be called upon to serve these functions. Although PORT teams have received significant levels of funding from the new agency, the size of this funding fades into insignificance given the amount of funding other researchers have received from NIH.

Technology Innovation

It is difficult to determine the impact of PORTS on technology innovation without a clarification of the role of PORTs. PORTs could be considered to be simply groups of investigators who are conducting large scale research projects on particular conditions, or they could be considered quasi-regulatory groups whose mandate it is to evaluate new and emerging technologies that are related to the condition of interest. Initially, PORTS followed the earlier model. They focused on general treatment strategies such as the decision to operate, or the decision to admit patients to an acute care facility rather than treating them on an ambulatory basis. The practice patterns examined by PORTS were established practices, and it is difficult to see how studies of this sort would have much of an impact on technology innovation. However, it would be naive to assume that PORTs should or will continue to have such a benign role. The members of the teams are in an ideal position to identify new treatments and new procedures as they are being introduced into medical practice. They also may be called upon to conduct some technology assessments by manufacturers who may want a "PORT Seal of Approval."

One force leading to the effectiveness initiative was that procedures are often introduced into medical practice without formal evaluation. [1] Thus PORT researchers will be called upon to do and will initiate a number of technological assessments. From the perspective of health services research, the teams should improve methods for technology assessment. In addition, the teams should make advances in determining:

[1] In fact as a recent exchange of letters in the New England Journal (Heilbrunn, 1990; Strandness et al., 1990) suggests there is sometimes doubt as to whether formal evaluations have been done.

The writer of the first paper objected to the title of a paper called "The Indiscriminate Use of "ser-assisted Angioplasty. . . ." The letter begins by stressing the importance of technology evaluation. "An organization representing all the specialties involved should be established to act as a governing body. Several of its objectives could include the establishment of guidelines for the optimal use of new forms of technology, training requirements for the persons involved and the collection of data to assist in the comparative analysis with alternative interventions." It goes on to suggest that this is not needed for laser technology. "Finally the adjunctive use of laser technology— for example, to facilitate the use of balloon angioplasty in the case of chronic totally occluded arteries—is not experimental and is therefore entirely appropriate for reimbursement by third parties insurers and Medicare." The authors of the original paper agreed with many of these comments particularly the ones dealing with the need for evaluation. However, the authors argued, "The use of laser technology to traverse occlusions hasn't been proved superior to the standard endovascular approach. Where is the proof? At best the data are anecdotal. . . . How can we talk about cost effectiveness for a therapy that has not been tested against current methods? It is evident that prospective randomized trials should have been done."

(a) methods for deciding which technologies should be evaluated, (b) methods for deciding at what particular part of the product life cycle a technology should be evaluated and (c) methods for determining when a product should be reevaluated.

Technology assessment has become an important activity. It is difficult to see how PORTs will be any more than one of the many participants in this activity. However, I think that we can be sure that the ultimate effect of all of this evaluation will be that technology innovation and diffusion will be different than it would have been in the absence of such activity.

Payment Policy

The research conducted by PORTS will generate much needed information about the effectiveness of certain treatments. PORTs must also determine methods for disseminating their findings both to practicing physicians and to patients. We can expect this information to be used in many ways.

Kinds of Uses for Information

Physician Decision Making. PORTs should provide information to physicians that will influence their decision making. In fact, as noted above, each PORT is required both to develop strategies for disseminating their findings to the physician community and to evaluate their impact on physician practice patterns. Thus physicians will have much better information about what works and what does not, and on how effective certain treatments are. They will also have better information about the implications of alternative treatment strategies. This should both influence their practice directly as well as influencing the type of information that is given to patients as treatment options are considered.

Consumer Choice. Information about PORT findings should facilitate consumer choice. Different treatments for the same condition will have different outcomes, and patients will place different values on these outcomes. For example, surgery for prostatism may decrease symptoms of prostatism; at the same time it carries its own risks. The Dartmouth team has developed videos that convey to patients the implications of "watchful waiting" versus "surgery"—information that is designed to enable patients to make more informed choices about their therapies.

Managed Care. The nature of the data generated by PORTs should be useful to organizations such as PPOs and HMOs in their analysis of the practice patterns of physicians who are either affiliated with these organizations or who are being considered for possible affiliation. These organizations will have much better information against which to assess the practice patterns of physicians who manage the kinds of conditions that are the focus of specific PORTs.

Payment Guidelines. We can expect that PORT findings will be used in the development payment guidelines by the Medicare program, the Medicaid programs, and by other third parties that reimburse providers on a fee-for-service basis. At minimum we would expect payors to develop policies to deny payment for treatments or procedures that were found by PORTS to be harmful or inappropriate. We would also expect the information to be used to form the basis for guidelines on care that was found to be marginally ineffective.

Magnitude of Impact

While we can expect that the findings of PORTs will certainly influence payment policy, it is difficult to determine the *extent* to which they will influence payment. The nature of medical treatment is complex. (The term treatments is used generically here—it can be used to refer to a procedure, a device, a decision to admit, etc.). Some treatments may be clearly useless; some treatments may be clearly harmful with no offsetting benefits; and some treatments may be more costly but equally as effective (along all relevant dimensions) as others. It should be easy to agree that such treatments should not be paid for. However, most cases are not so clear cut. Many treatments can be useless in some cases, but useful in others in others; or harmful in some cases and helpful in others. It is sometimes necessary to have a considerable amount of clinical information in order to determine whether a particular treatment is likely to be "beneficial," and it will be difficult for payors to clearly define the conditions under which some treatments will be paid for without developing an administrative structure that absorbs much of the savings. This is particularly true for many of the diagnostic tests.

Even more important, treatments can be very beneficial, somewhat beneficial or marginally beneficial. Again, some treatments may have positive impacts on some health status indicators but have no impact on other measures. PORTs will provide a considerable amount of information about the effectiveness of treatment. However, in order to use some

of this information the payors will have to make decisions about *what* it is they want to pay for.

Discussion

The PORTs initiative is of great importance. They are the most visible symbol of a new way of looking at health care in the United States. PORTs are being funded because it is hoped that they will provide information that will lead to an improvement in the quality of medical care delivered in the United States, and that they will promote the delivery of cost-effective care.

I believe that the research conducted by PORTs will, indeed, lead to improvements in the quality of health care provided and will promote the delivery of more cost-effective care. However, I am concerned that the effectiveness of this initiative will be judged by the Congress by whether it has had a *measurable* impact on the cost of health care in the United States, and I do not think that it will have a *measurable* impact on costs.

Costs have not been increasing because the amount of ineffective care provided has increased, but rather because of the spread of new diagnostic testing methods and treatments. Henry Aaron has said it this way, "There is no indication that the technological creativity that has been largely responsible for the very rapid growth in medical outlays is abating. Scientific imagination that has given us various kinds of transplants and the new methods of treatment and diagnosis that have been driving up expenditures, is likely to push even harder in the future." Others would argue that the increase in the number of physicians, per se and the increase in the number of specialists has an independent effect on costs. If these are major sources of growth of medical expenses, it is highly unlikely that the findings of PORTs will be powerful enough to have an impact on that trend.

The myth at the moment is if only we could get rid of "inappropriate" care, we would have enough resources to pay for all effective care. Consider a familiar example—the per capita cost of medical care is higher in Boston than it is in New Haven, and there are no data to suggest that this difference has resulted in different health outcomes. However, it is not clear that if one carefully examined the practice patterns of individual physicians in Boston that they would be found to be any more "inappropriate" than the practices of individual physicians in New Haven, although they would be found to be different. We do not know how to use payment policy to make providers in Boston practice medicine in the same way as they do in New Haven.

Conclusions

The PORT program is an important initiative for the field of health services research. Not only should it lead to an expansion of the capacity in the field, it ought to result in research that will result in significant methodological strides. In turn, the research should generate findings about the effectiveness of treatments and the relative effectiveness of different treatments for the same conditions so that one can assess their cost effectiveness. Since the researchers are charged with developing methods to disseminate their findings, the initiative should lead to improvements in the quality of health care and in the efficiency with which care is provided. However, many of these changes will be quite subtle, and it may be difficult to measure them.

There is some likelihood that PORTS will be evaluated on the basis of their impact on the overall level of health care costs in the United States. If this is the case, then PORTs will be doomed to failure. There are many factors contributing the rising costs; given the current level of funding, it is highly unlikely that PORTs will have a significant impact on those factors.

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APPENDIX D3. THE EVOLUTION AND CURRENT STATUS OF CONFLICT OF INTEREST REGULATION IN BIOMEDICAL SCIENCE

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and

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Introduction

This effort to formulate guidelines regulating conflicts of interest arising in connection with the Patient Outcomes Research Teams (PORTs) coincides with a temporary lull in a rising clamor of public and regulatory concern in this area. The problem, as succinctly stated recently by the Executive Council of the Association of American Medical Colleges, is the fear that "financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research."[1] A well-documented increase in the number and importance of academic-industrial relationships over the last decade[2] has added to concerns that the excellence of American academic science might become a casualty of these new financial influences, or as Rep. Ted Weiss bluntly frames the question, "Is Science for Sale?"[3] This concern is particularly intense in relation to clinical medicine, in which the implications of scientific innovation for public health, welfare and safety are more obvious and immediate.

A review of recent developments in the regulation of conflicts of interest in biomedical research suggests that the workshop may wish to surpass the minimal standards currently mandated by the federal agencies and most institutions as well as those proposed by clinical and educational consortia. These standards indicate that at a minimum, the workshop should recommend a policy of full confidential disclosure by all PORT participants of financial interests in businesses in a position to profit from products or procedures under examination ("interested businesses"). Recent developments in regard to self-regulation by investigators in clinical trials also suggest the wisdom of a self-denying rule whereby all key scientific participants in PORTs would forego financial ties to interested

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businesses during the course of such studies and for a period of time afterwards.

Historical Overview

Over a twenty-five year period, the recurrent theme in regard to conflict of interest has been self-regulation in anticipation of standards imposed by Washington. At the height of federal support for academic research in the mid-1960's some agencies, notably the Atomic Energy Commission, sought to deter conflicts arising from undisclosed financial interests in connection with research paid for by the government, e.g., the purchase of equipment from, or the orientation of research to benefit, a private firm in which the faculty member had an interest. At that time, stringent government-wide regulation was forestalled when research institutions through their consortia (the American Association of University Professors and the American Council on Education) resolved to adopt individual institutional standards providing advice and guidance to faculty in planning outside relationships.[4]

Within a short time, most major research institutions adopted policies which rejected "comprehensive and detailed codification" while providing very general guidelines by which faculty were to determine the existence of a conflict. Many delineated activities which were "clearly permissible," such as receipt of nominal honoraria and publication royalties, from those which, while requiring some degree of review, were generally allowable with disclosure, such as most faculty consulting. A third category consisted of activities thought "likely to involve conflicts," including, for example, the assumption of executive responsibilities with a for-profit company. It was a characteristic of most of these early policies that they vested in faculty discretion to decide when a conflict existed, in which case there was to be disclosure to the departmental chair or supervisor, who would consult with the dean in appropriate cases.

This structure survived with minor alterations until the early 1980's, when the rise of biotechnology led to a new era of academic-industrial cooperation as business, particularly in the life sciences, turned to academe for scientific expertise.[5] These relationships brought enormous benefits for both sides and for the public, which the Congress recognized in enacting federal legislation intended to foster such collaborations by permitting academic institutions and scientists to benefit financially if their federally-sponsored research led to commercial products.[6] At the same time, the spiraling growth in the costs of biomedical research began to outpace federal funding for such activities, requiring universities and hospitals to seek new sources of support.

These developments were greeted with concern in some quarters, and in 1981 the Oversight Subcommittee of the House Committee on Science and Technology called on the American Association of Universities (AAU) to develop ethical guidelines for university-industry collaboration, pointing with alarm to "the metamorphosis of our scientific research force from educators to entrepreneurs . . . "[7] After considering the Subcommittee's report, the AAU Committee on University-Industry Relations concluded that uniform guidelines were unnecessary but agreed to facilitate the sharing of information on research collaboration among universities, industry, government and the pubic, and established a Clearinghouse on University-Industry Relations for this purpose in 1983.[8]

Many institutions moved at this time to revise existing policies. Some, such as Yale, commenced institution-initiated disclosure in the form of an annual report of the level of commitment and the organizations involved in all non-university professional work, including consulting, equity, board memberships and managerial positions.[9] Others, such as Harvard, retained faculty-initiated mechanisms, but sought to refine and improve policies regulating university-industry sponsored research agreements and concomitant bilateral agreements between such companies and faculty.[10] Such policies were intended to insure:

(1) the priority of the institution's commitment to education and training and to the development of basic knowledge in preference to commercial applications;
(2) the intellectual integrity of the appointments process;
(3) the openness of agreements and relationships and a disfavor of secrecy; and
(4) the unfettered freedom of faculty to choose the direction of their research and whether and when to publish.

Throughout this period, institutions continued to stress voluntary disclosure and avoided *per se* prohibitions.

The regulation of academic conflict of interest was also affected in the 1980's by the rise of state laws governing this area. In a number of states local laws applicable to public university or hospital employees will consequently dictate conflict of interest rules for public institutions. Hence university employees are sometimes forbidden to participate in an official capacity in, or receive extra compensation in connection with, a transaction between the university and a business entity in which the employee has a substantial interest. Public university scientists are often also precluded from accepting employment which might impair their independence of judgment in the performance of their university duties and from having investments in a business entity which would create a

substantial conflict between their private interests and their university responsibilities.[11] Such statutes are diverse, and state court decisions interpreting them are generally few in number and more likely to deal, for example, with issues such as participation by professors in state agency proceedings.[12] Certainly a state university or hospital employee must carefully consider any applicable state statute in planning outside relationships.

It should also be noted that since the mid-1980's some federal agencies have prohibited "organizational" (as opposed to "personal") conflicts of interest, in which the institution's self-interest could be thought to interfere with its obligations as a government contractor.[13] By this means, such agencies seek to avoid practices such as "wired bidding," whereby a contractor designs a request for proposals on which it subsequently bids. While these rules appear to be rather narrowly focused, their definitions are sometimes broad enough to reach some personal conflicts, e.g., a "relationship . . . whereby . . . a contractor (including chief executives, directors, proposed consultants or subcontractors) has interests which (1) may diminish its capacity to give impartial, technically sound, objective assistance or advice. . . . "[14] Although there is currently no Public Health Service (PHS) rule regarding institutional conflicts, the workshop may wish to consider at least a mechanism to prevent wired bidding on subcontracts. One possibility would be to include on the proposal form for subcontracts a question, "Did you participate in the preparation of this RFP?" An affirmative answer would require the AHCPR to consider whether it wished to waive the conflict in appropriate cases.

Recent Concerns Regarding Clinical Studies

Concern about conflict of interest has intensified in the last two years as a result of a few egregious cases receiving great attention. One such case involved a medical researcher, Dr. Sheffer Tseng, who undertook direction of a clinical study at the Harvard-affiliated Massachusetts Eye and Ear Infirmary (MEEI) on a therapeutic agent, the rights to which he had assigned to a company, Spectra Pharmaceutical Services, Inc., in which he subsequently became a major shareholder. [15] The FDA-approved protocol, which was designed to assess the effectiveness of topical treatment with a Vitamin A analogue (tretinoin) for the "dry eye" syndrome, was funded by Spectra and supervised by Dr. Kenneth Kenyon of MEEI, who also acquired stock in Spectra after commencement of the study. In the course of the study, Dr. Tseng deviated significantly from the protocol without approvals and failed to report discouraging results of his research for a number of months. When these results were publicly

announced by the company in 1987, the stock price fell significantly. It has been reported that Tseng had sold his holdings by this time and realized a large profit. An institutional review at Harvard Medical School concluded, *inter alia*, that "a significant conflict of interest developed after the clinical study began, (that] proper safeguards were not in place to protect the study from potential bias; and that Dr. Tseng was improperly supervised."[16]

The Tseng case sharpened the focus of discussion with respect to conflict of interest upon the particular problems associated with clinical medicine. During 1989, articles appeared in the *Wall Street Journal, New York Times, Boston Globe* and other publications, pointing to the increasing frequency of financial interests, particularly equity stakes, held by researchers in firms whose products they evaluated. [17] Among the situations reported:

(1) activity by a prominent scientist in publicizing and promoting a major new drug while simultaneously holding options to acquire a significant stock interest in the manufacturer of that drug;
(2) receipt by one researcher of stock options from the sponsor of his work on an antiviral preparation with a portion of the options contingent upon FDA approval of the drug;
(3) a NIH study on the efficacy of antibiotics on ear infections in children conducted while the principal investigator received private research grants, speaking honoraria and travel expenses from companies that manufactured the tested drugs;
(4) concern that consulting and stockholder relationships between a small pharmaceutical company and the Dean and four of five department heads of a College of Pharmacy could have influenced the evaluation by the institution's researchers of claims of toxicity with respect to company products developed by one of the stockholding scientists; and
(5) questions concerning the possibility that equity or option-holding scientists could have delayed or minimized data about potential complications of their company's drug.

The subject was seized upon in Congress by Representatives Ted Weiss (Chairman, House Government Operations Committee's Subcommittee on Human Resources and Intergovernmental Relations (the oversight committee of the Department of Health and Human Services]) and John Dingell (Chairman, Energy and Commerce Committee and Chair of its Subcommittee on Oversight and Investigations). Rep. Weiss held hearings in September 1988 at which witnesses testified that some investigators in Phase II clinical trials of anti-blood clot medications (the TIMI or "Thrombolysis in Myocardia Infractions" trials) held stock or options in the

company manufacturing one of the drugs (Genentech and TPA).[18] Weiss has continued to be vocal, holding a second round of hearings in 1989 and publishing several articles, of which the following excerpt is representative:

> One recurrent finding has been that universities can be surprisingly blind to potential conflicts of interest; they are adamant that consulting fees and other forms of remuneration will not affect the impartiality of their faculty members . . . *When the federal government is paying for the research*, that research should not be tainted by any possibility of bias due to financial conflict of interest."[19]

NIH Activity in the Area

As the principal funding support for the biomedical scientific community, the National Institutes of Health (NIH) inevitably stepped into this debate, beginning in 1987 with an amendment of the PHS Grants Administration Manual. This new rule on "Standards of Conduct for Employees" required grant recipients to "establish safeguards to prevent" the use by investigators of their positions for purposes "that are, or give the appearance of being," motivated by a desire for private financial gain.[20] Grantee institutions were also required to implement "written policy guidelines on conflict of interest": (1) indicating proper and improper relationships; (2) providing for notice of such conflicts by investigators to a grantee official; and (3) specifying possible sanctions. This development was greeted quietly since the agency had not attempted to prescribe substantive standards and was only requiring what most research institutions had already had in place for some time.

In the wake of the Tseng case, a further step followed in January 1989, when an amendment to the *NIH Guide to Grants and Contracts* stated the agency's "expectation" that participating investigators "will not have financial interests in organizations that produce drugs, devices, or other interventions studied in a controlled clinical trial."[21] In June, NIH jointly sponsored with the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) a two-day meeting on conflict of interest including representatives of academe, industry, independent research institutions and government.[22] This was followed in September by the publication for comment in the *NIH Guide* of a far-reaching but highly ambiguous document entitled "Proposed Guidelines for Policies on Conflict of Interest." ("Proposed NIH Guidelines").[23]

These guidelines would have required, in essence, the avoidance of *any* prospective financial conflict of interest in connection with an NIH award. Specifically prohibited were:

(1) receipt by investigators of equity or stock options in any company that would be "affected" by the outcome of NIH or ADAMHA research or whose product or equipment was being evaluated in such research;
(2) receipt by investigators of honoraria or fees from, or engagement in a management position by, a company if the recipient were involved in any NIH or ADAMHA project evaluating or testing that company's product;
(3) disclosure of agency-funded research results to any company "with which a conflict exists" until such results are "publicly available."

Waivers to these rules would have been permitted only where the financial interest involved was "insignificant" and there existed no "potential of influencing research results." The proposal would also have required the awardee institution to obtain full financial disclosure of outside relationships at the time of the proposal and annually thereafter and to notify the agency if a waiver were proposed to be granted or if a conflict were detected after the award.

Vehement protests during the ninety-day comment period from some seven hundred representatives of the research and industrial communities led Department of Health and Human Services (DHHS) Secretary Louis Sullivan to withdraw the draft guidelines on December 29, 1989.[24] Secretary Sullivan has promised a new proposal but indicates that it will be published in the *Federal Register* for notice and comment, rather than in the more informal and legally dubious format of the *NIH Guide*. Representative Weiss has publicly warned DHHS not to be deterred by criticism from the research community[25] and has threatened to add conflict of interest standards to the NIH authorization bill this year.[26]

Recent Self-Regulation in Clinical Studies

Public discussion of this topic has led to two notable instances of self-regulation in connection with clinical trials and to calls from within the biomedical community for more of the same. One case involves the Post Coronary Artery Bypass Graft Surgery (Post-CABG) Clinical Trial, a seven-year multi-center randomized trial study of the impact of cholesterol reduction and anti-thrombotic treatment upon the development of atherosclerosis in patients who have undergone coronary artery bypass graft surgery. After noting that the trial will evaluate the efficacy of pharmaceutical

products of three U.S. corporations and that the study's results could affect the profitability of these products, the principal investigators announced in April of last year that they would not buy, sell or hold stock or stock options in companies providing medications for the study, nor would they serve as paid consultants to such companies. [27]

This ban will last from the commencement of patient recruitment through termination of the investigator's (or institution's) involvement in the study and will extend to the investigator's spouse and dependents. All "key investigators" are covered, excluding persons providing "primarily technical support or who are purely advisory," i.e., without direct access to the trial participants or data, unless they are "in a position to influence the study's results or have privileged information on the outcome." Each person subject to the policy will be required to file with the trial's coordinating center a conflict of interest statement and to update it annually. In a similar move, the Phase III team for the TIMI clinical trial referred to above has also adopted guidelines which will provide comparable restrictions and has taken the further step of prohibiting financial ties with involved companies for a year following the conclusion of the study. [28]

A number of commentators within the biomedical community have expressed approval for the self-denying approach taken by the Post-CABG and TIMI trial teams while urging even more extensive steps to curtail the acquisition by researchers of financial interests in the new drugs and clinical devices they are studying. *New England Journal* Editor Arnold Relman called in April 1989 for disclosure of all financial ties between researchers and the products and procedures they are investigating both to sponsors and to publishing journals.[29] He also recommended policy reviews by all institutions sponsoring clinical research or employing clinical investigators, leading to "a broader and more institutionalized approach." Dr. Arthur Caplan, director of the Center for Biomedical Ethics at the University of Minnesota, has also called for a flat ban on financial stakes of any kind in clinical trials: "These people should divest their ownings or disqualify themselves if they have a stake in the outcome. . . . The standards for human research have to be higher than those of other studies." [30]

Recent Moves by Consortia and Individual Institutions

Under the impetus of these suggestions and with a determination to insure continued public confidence in the integrity of the biomedical research enterprise, the major professional consortia have reviewed the subject and promulgated new recommendations to their memberships, and

some institutions have revised their own policies. Such reviews have grappled with two questions: (1) should present provisions for disclosure be intensified, and (2) are any situations of potential conflict so dangerous that they should not be allowable? Recent reports by the Association of Academic Health Centers (AAHC) and the Executive Council of the Association of American Medical Colleges (AAMC) have answered the first question affirmatively while deferring to institutional discretion as to the second.

The AAMC paper calls on its members to develop procedures for "full disclosure to the institution, and to the interested public, of financial and professional interests that may influence, or may be perceived to influence, research activity or other scholarly responsibilities. . . ." This disclosure is to occur at least annually and would include all relevant personal interests, e.g., equity stakes, outside professional positions and salary, gifts, honoraria and loans, of the faculty member as well as immediate family members. Cases should be reviewed by supervisors, and if there is "any reasonable question of conflict or legitimacy regarding the situation, then all relevant information should be passed on to a designated institutional committee." The policy expresses the hope that an institutional common law may develop as this committee gains experience.[31]

The AAHC similarly endorses regular disclosure by faculty, researchers, staff and students for themselves and their immediate family members of "significant financial, personal or professional relationships that raise a potential conflict of interest between their academic role and outside interests."[32] With respect to sponsored research, the report also calls for disclosure of "[s]ignificant financial, persona, or professional relationships that raise a potential conflict of interest. . . . in all speeches, writings, advertising, public communications, or collegial discussions" relating to the research. [33]

At the institutional level, Johns Hopkins last November joined a number of schools in intensifying disclosure requirements and instituted a flat ban on the ownership by investigators of shares in companies sponsoring their work.[34] According to *Science*, however, Stanford University School of Medicine has so far resisted *per se* prohibitions but has begun "spot auditing" of its annual disclosure forms and has added questions on an investigator's financial ties to its human subject review protocol.[35]

Existing rules have also been extensively revamped at Harvard Medical School, where the Faculty Council and the thirteen-institution consortium of affiliated teaching hospitals recently approved a new policy. This document includes a broader, more precise definition of conflict of interest (any outside financial interest touching in any way upon faculty responsibilities,

e.g., teaching, research, patient care or administration), mandatory written financial disclosure not less frequently than annually and a much elaborated set of guidelines (with detailed definitions) identifying the most common sensitive situations.[36]

What is new in the Harvard policy is a category of outside activities to be subject to maximum scrutiny, focusing upon faculty who conduct clinical research and those who own stock in companies sponsoring their work. The policy mandates intensive review by a standing faculty committee on conflict of interest for every case in which a faculty member proposes to participate in any way in clinical research (including FDA or other committees reviewing such research) on technologies or drugs in circumstances of possible financial benefit. This rule covers all equity interests and consulting income but *excludes* salary and royalty income paid through sponsored research relationships. Also subject to mandatory committee review will be every case in which a faculty member proposes to have research support from a company in which he owns stock. Research support is broadly defined to cover equipment, biological materials and drugs as well as cash. This rule also covers basic as well as clinical research.

Other high-scrutiny situations under the Harvard policy include:

(1) the assumption of executive positions with outside for-profit businesses;
(2) clinical referrals to a business in which the faculty member has a financial interest (but excluding school-or hospital-affiliated institutions and individual or group private practice plans); and
(3) circumstances in which a faculty member expects to receive financial returns from businesses competing with the school or the employing hospital.

Finally, Harvard faculty will also be expected to disclose in conjunction with any published or formally presented research results any financial interest relating to those results.

Conclusions and Applications to the PORTs

Emerging standards in conflict of interest regulation suggest a number of common themes to be considered in formulating guidelines for PORTs:

(1) an increasing reliance on regular, detailed, mandatory financial disclosure that includes relevant information with respect to spouse and dependents;

(2) maximum scrutiny of financial relationships with organizations producing drugs, devices or other interventions which the financial stakeholder is studying, especially a the research approaches the clinical trial stage;

(3) greater concern with respect to equity relationships, with other ties, such as consulting and management positions, increasingly suspect as the research comes closer to evaluation or testing of actual or prospective products;

(4) the possibility that disclosure, supervisory controls and monitoring may be sufficient to allow some conflict relationships to continue, provided:

(a) monitoring mechanisms are stringent and provide reasonable and publicly acceptable assurances that research will be free from bias;

(b) there is no early, financially advantageous disclosure of research results; and

(c) any reference to the relevant research in speeches, writings, advertising or collegial discussions is accompanied by disclosure of the relationship.

(5) notwithstanding (4), a trend in clinical trials towards a self-denying rule whereby key scientific participants agree to forgo financial ties to interested businesses during such studies.

Conflict of interest guidelines for PORTs investigators should also take into account several specific features of these studies. These considerations relate to the composition or study teams, to subsequent dissemination of the results, to expertise developed in the course of the study, and to funding sources. Depending upon the financial arrangements involved, these features may pose particular risks of conflict of interest for study investigators.

The breadth of expertise in the individual PORTs teams will lead to increased credibility for the research results, likely far greater than that achieved by any single publication or study. Seldom in clinical research do groups consist not only of subject-matter experts and biostatisticians but also of decision analysts, epidemiologists, meta-analysts and economists. In many cases, National Advisory Bodies further enrich the PORT. Thus, there will be many requests for information and opinions from the PORTs. These will take the form of informal conferences or lectures on the results as well as on general methodologic issues. In addition, as part of the experimental design itself, there will likely be formal dissemination of research results to specific groups of physicians. The ability to influence large numbers of students, physicians, patients and policy makers will be great.

In the course of executing its research strategy, each of the teams is likely to become expert, perhaps uniquely so, in a number of areas of interest to investigators in other aspects of health services research or health policy. Expertise might include development of any of the following: specialized software and/or hardware for analysis of claims data; instruments or survey tools for assessing outcomes; approaches for assessing utilities; educational programs describing alternative treatments; and miscellaneous software programs. In the absence of a regulatory framework, this expertise could lead to the unmonitored formation of businesses (either for-profit or not-for-profit) in which members of the PORT have a financial interest.

Funding for PORTs is another vehicle by which conflicts of interest may arise. Currently, although the funding level is approximately $1 million (direct plus indirect) yearly, the breadth of problem areas within the purview of any PORT and the depth of investigation possible within a given area are larger than can be adequately covered by that amount of money. The ready-made group of investigators and study sites makes PORTs an attractive vehicle for funding by industry; in addition, the possibility of supplemental funding by industry is obviously desirable for the teams themselves. Currently, it would appear that industrial funding would be used primarily for support of clinical research activities.

A further consideration is the desirability of reasonable uniformity. It is important to note that whatever conflict of interest guidelines are recommended for PORTs, investigators will also be obligated to abide by those of their university or hospital. Because the more stringent of the two will control in any given situation, it is possible that not all PORTs would be subject to the same guidelines. This undesirable possibility is perhaps another consideration arguing for reasonably stringent standards at the funding level.

Notes

1. "Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research," adopted by the Executive Council of the Association of American Medical Colleges, February 22, 1990, p. 6.
2. See, e.g., D. Blumenthal, M. Gluck, KS. Louis, D. Wise, "Industrial Support of University Research in Biotechnology," Science, Vol. 231, 17 January 1986, p. 242, and C. Sims, "Business-Campus Ventures Grow," New York Times (December 14 1987).
3. "Is Science for Sale? Conflicts of Interest vs. the Public Interest," Hearings to the House Committee on Government Operations, Subcom

mittee on Human Resources and Intergovernmental Operations, 101st Congress, 1st Session June 13, 1989.

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APPENDIX D4. THE STRUCTURE AND METHODS OF PORTS: SOURCES OF BIAS

John Wennberg, M.D.[1]

I want to thank the Institute of Medicine for hosting this Workshop on Potential Conflicts of Interest in Patient Outcomes Research Teams. Some five years ago, the John A. Hartford Foundation provided our research group with the support to undertake an evaluation of the practice-style related reasons for variations in treatment rates for benign prostatic hypertrophy or BPH, a common condition that affects most men after age 65. We knew from previous research that the rates for one BPH treatment, namely prostate surgery, varied such that in some communities in Maine over 50% of men received a prostatectomy by age 80, while in others the rate was as low as 15%. We undertook a series of research studies to identify the causes of variation, focusing on the discovery and testing of the different treatment theories that might explain the large differences in practice patterns. It is in the evolution of our experience with the evaluation of alternative treatments of BPH we learned one version of the PORT mission.

Recognizing that at least some of our concerns over conflict of interest are idiosyncratic to the mission as we have discovered it and that they may seem foreign or remote to those who have different versions in mind—I want to raise them for your consideration, to show how important the interpretation of the mission is to understanding of the potentials for conflict of interest.

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PORT Mission

In my opinion, the PORT mission is to achieve a non-regulatory solution to the failure in the past to undertake the systematic evaluation of all treatment options available to treat a particular condition such as BPH, cataracts, stable angina or a heart attack. The Food and Drug Administration (FDA) has provided a strong regulatory focus for causing new drugs to be evaluated before they reach the medical market. But the FDA evaluation paradigm has been narrowly conceived—restricted in the theories it causes to be evaluated, in the outcomes it considers relevant, and in the pressures it places on the profession and industry to evaluate. The treatment theories actively evaluated involve only drugs versus placebos, even though in most clinical situations the options for treatment are much broader. For example, in the case of stable angina the options include use of surgery (coronary artery bypass), a device (coronary artery angioplasty), diet (low fat diets) and other life-style modifications.

The FDA approach is further limited in that it is not concerned with new uses made of drugs once they are on the market. For example, physicians have learned to use certain anti-hypertensive drugs to treat the symptoms of BPH, even though these drugs have not been evaluated for this purpose. The outcomes considered relevant by the FDA are often changes in biochemical or physiologic parameters, and they do not necessarily include those outcomes that are relevant to patients such as relief of pain, improvement in functional status, and avoidance of complications. (For example, they may include improved coronary artery blood flow or improvement in the flow of urine, but not changes in symptoms, the occurrence of side effects or changes in functional status.)

The failure to systematically evaluate all treatment theories relevant to a particular condition, to use outcome measures that capture the events that are relevant to patients and to make the results of assessments available to physicians and patients in ways useful in choosing treatment options results in systematic flaws in the scientific and ethical basis for clinical decisionmaking. The flaw in federal science policy that irrationally restricts evaluations is not likely to be repaired, however, by extending regulatory mandates. I say this not simply to echo a disfavorable attitude toward regulation, but for structural reasons. The required focus is on the evaluation of all relevant treatment theories. Much of medical theory emerges from the exigencies of clinical problem solving, as part of the ongoing practice of medicine. For example, much of surgical innovation is really a modification of traditional treatment strategies which do not involve novel equipment or new drugs that could be easily withheld from practice until evaluations have been made.

Some of the most expensive "medical theories" emerge in the building of hospitals or other facilities. One of the major theories of interest to outcome research is whether the availability of hospital beds at the rate of 4.5 beds per 1,000 produces better outcomes to the population served than availability at a rate of 2.9 per 1,000.

The mission of the PORTs, then, is to become the focus for extending the mandate to evaluate to all relevant treatment theories for a particular condition or problem. It must do this without regulatory gate-keeping authority and without the firm (and confining) bases in administrative law that protect its members from corruption through the elaborate client-judge protocols that routinize the relationships of the FDA. PORT members must actively engage in the give and take of the marketplace of ideas. They must become known to and directly engage the originators of ideas and the innovators of new technologies. Ultimately, they must set the rules that cause ideas to be evaluated. I use the phrase "set the rules" in the sense of pointing to the examples for good research based on appropriate methods, identifying the relevant outcomes, establishing processes for evaluating and synthesizing research and reaching conclusions on the status of specific treatment theories. I also use the word "cause to be evaluated" to make clear that the PORT's mission is not to do all of the evaluation itself, but rather to move the profession (and patients) to accept the ethic of evaluation on the basis of good science.

PORTs follow a professional, not a regulatory model. I want to give you some examples of what they do based on our own experiences with the evaluation of alternative treatments for BPH, so you may see the nature of some of the interactions between PORTs, physicians and patients as well as industry. I will then turn to consider some features that could lead to conflict of interest or corruption of the process.

Experiences of the Dartmouth Assessment Team

As I mentioned, the entry into the problem of alternative treatments for BPH was the discovery and follow-up of the variations in rates of prostatectomy among communities in Maine. We met with physicians from high and low rate communities across the state of Maine. Initially, the arguments were between our group and the clinicians; very soon, however, the debate was among the clinicians in Maine, as they began to discuss their opinions on the treatment of BPH. It soon became apparent that the clinicians divided roughly into two camps, one camp subscribing to the preventive theory, the other to the quality of life theory of surgery.

Under the preventive theory, surgery early in the course of BPH is called for, because for most people the disease will progress to the point

where surgery is required to save patients from the serious complications of bladder or kidney failure. If surgery is delayed, patients will be older and sicker when they require it; overall, life expectancy was thought to be higher if one operates early. Physicians who subscribed to the quality of life theory were much less pessimistic about the natural history of the disease, believing that in most people it does not progress to the point where life is threatened. For most people, surgery is of value because it reduces symptoms and improves the quality of life. The decision to undergo surgery should therefore be based on symptoms, their anticipated relief and the willingness of patients to undergo the risks of surgery in order to secure its benefits.

We used Hartford Foundation funds to recruit an international team of urologists, epidemiologists, biostatisticians, decision analysts, social psychologists, sociologists and computer scientists to undertake a series of studies to test these two treatment theories. Putting together information from the medical literature, claims data analysis, interview studies, and decision analysis, we could show that the preventive theory was in error. Using a wide range of possible assumptions, we could find no evidence that people would live longer if patients with BPH were operated upon to prevent subsequent development of bladder or kidney obstruction. As an assessment team, we drew the conclusion that the preventive theory was not a valid reason for early prostatectomy.

The data we obtained from an interview study of patients who underwent surgery also showed a "slam bang" effect of the operation on symptoms, with outcome probabilities for symptom relief that were much more favorable than watchful waiting. However, this relief could only be obtained by risking certain complications, the probabilities for which were also documented by our study. Moreover, we could see from the data that there was no strong correspondence between patients' medical histories and their symptoms and the choices individuals would prefer to make between watchful waiting and surgery. We thus came to the further conclusion that rational choice in the decision to undergo a surgical procedure or to watchfully wait depends on patient preferences; these can only become known by actively engaging the patient in the decision process—by asking him what he wants. Values and attitudes are key because they provide the logical, rational reasons for undertaking the surgery.

We therefore could conclude that the practice-style reasons for the variations we had observed in Maine derived from an incorrect professional theory about the value of early surgery and from the entanglement of patient preferences for treatments with those of the advice-giving physician. The ethical and the scientific conclusions thus lead in the same direction. The need was to communicate the message of choice to doctors

and patients in ways that would help them base choice more firmly on the preferences of patients. I will return to describe how we have handled this dissemination process a little later because the conveying of information that effects individual choice is a focus for conflict of the PORT mission.

It was while undertaking the evaluation of surgical outcomes in Maine that we first noted differences in patient survival, depending on which type of prostate operation they underwent. Subsequently, we studied the phenomenon in Denmark, the United Kingdom and Canada, consistently finding an excess mortality in the five years following surgery among patients who underwent the transurethral prostatectomy (TURP), compared to those undergoing the open prostatectomy. A similar excess in mortality appeared when TURP was compared to other operations, such as cholecystectomy or hernia repair. We went back to the medical records, abstracting data on case severity and co-morbidity and were unable to explain the result on the basis of differences among patients. We also found a report in the literature of a small randomized clinical trial of open versus TURP that was consistent with the hypothesis that TURP, somehow, has a deleterious long-term effect on survival. However, neither our group nor consulting urologists could come up with any convincing mechanisms as to how this effect might occur. Left with this uncertainty, we concluded that a large scale randomized clinical trial would be required.

The publication of the results of the open versus TURP studies opened a new phase in the development of our assessment team. The result was not a welcomed one for either patients or urologists, who in the United States perform nearly 400,000 TURPs a year. We appreciated an editorial in the *Lancet* stating that someone had rolled a boulder in the quiet pond of urology. We appreciated it because it did not dismiss the result out-of-hand, but rather called for thoughtful response of the urology community to the challenge. The major breakthrough for the mission of our PORT, however, has been the response of the leadership of American urology, in particular the officers and senior membership of the American Urological Association (AUA).

We have been at work now for a year with the AUA, helping in the design of a large scale randomized clinical trial to test the hypothesis of excessive mortality following TURP. As the work has progressed, the focus of the AUA effort has widened to include a focus on new treatment theories as well. When our assessment team began its work four years ago, the field of urology was indeed like a placid pond. Other than surgery and watchful waiting, there were no serious options for the treatment of BPH. Not so today. The last few years have seen a plethora of new BPH treatment theories, some involving balloon dilation of the prostate gland, new drugs, microwave diathermy, and others involving

urethral stents and new ways of surgically affecting the prostate gland. Under traditional science policy, these new treatments would enter routine clinical practice without benefit of systematic evaluation. This is no longer the case. The AUA, working with our PORT team, is establishing a network of some 20 centers to undertake the protocol that will bring each of these new treatment theories under active assessment. Our PORT team is providing scientific direction on study design and help in managing the data collection procedures.

The recent completion of the planning and grant writing phases and the initiation of a six center pilot study funded by the AUA brings the story to the present. A PORT mission has been defined which includes (1) explicating the causes of practice variations; (2) testing the underlying conflicts in practice theory; (3) establishing relationships with the leadership of the practice community to promote systematic evaluation of new as well as widely used technology; (4) the synthesis and integration of the results of assessments, including estimates of the probabilities for various outcomes; (5) the demarcation of the role of patient values in decisionmaking; and (6) the dissemination of results of the assessments, with a focus on communication about treatment options in a form useful to patients and physicians for clinical decisionmaking.

Vulnerability of PORT Mission to Conflict of Interest and Corruption of Purpose

Let me now examine the vulnerabilities of this mission to conflict of interest and corruption of purposes. I have noted four areas of concern: economic conflict of interest, ideological corruption, existential corruption, and corruption of discursive practices.

Economic Conflict of Interest

This is perhaps the easiest to deal with because the problem is well understood and certainly not unique to the PORT. The background reading and the scenarios for discussion at this conference represent this concern well. I do not want to deal with details, but it is worth noting that the mission outlined above requires active relationships between stake holders and the assessment teams. The latter's judgments concerning the relative advantages and disadvantages of a specific stake holders particular treatment theories have obvious economic consequences.

PORT teams can expect active interest from industry in their activities and numerous opportunities for consulting fees and honoraria. PORT

teams also have the potential for access to insider information on the prospects for profit of technologies which affects their qualification to own stock in the companies they stand to influence. Policies to prevent the appearance and actuality of conflict of interest will be needed. In the case of our own group, we have chosen to forego any honoraria and consulting fees and not to own stock whose value is affected by urologic treatments.

Economic interest cut into the mission of the PORT in another way in the case of drugs or devices that have not yet received FDA approval. On more than one occasion, our group has been asked to help in the planning of the evaluation of new drugs, prior to FDA approval. While the rational interests of efficient evaluation are promoted by this involvement (for example, making certain that phase II and III drug trials include evaluations of the probabilities for each of the outcomes that matter to patients), secrecy and exclusivity requirements of the drug industry, designed to protect proprietary interests, have gotten in the way of some collaborations. These barriers not withstanding, we have been gratified by the efforts to cooperate by the drug and the device industries as well as their respect of our interpretation of the PORT mission.

We have also been impressed by the willingness of manufacturers to contribute directly to the costs of outcomes research. For example, the balloon manufacturers are contributing resources to the AUA pilot study mentioned above. However, such direct financial dealings between manufacturers and PORTs or its collaborators raises red flags and should be avoided. If we can learn to harness the energies of industry, to help them in their need to have their products developed, the outcomes research agenda can be accelerated. One suggestion is for an institute that can serve as a depository and distributor of industrial (or perhaps third party payor) funds to outcomes research which would avoid the need for a direct relationship between PORTs and their evaluatees.

Ideological Corruption

PORTs may be susceptible to another kind of conflict, one I have chosen to label "ideological". This is the way I label a tendency to lose objectivity that a member of a PORT may experience if he or she becomes invested in a specific treatment theory rather than in the ethic of evaluation. A temptation we all experience as researchers is to believe that somehow we have gotten hold of the truth, that we know the answer. In our determination, we can loose sight of the role of the PORT which is to manage the process of evaluation. There is probably no specific remedy that guards against this temptation; it comes from ingrained recesses in minds and souls. However, PORTs can protect themselves

from its consequences by virtue of the fact that assessment teams are multidisciplinary, that they engage in ongoing dialogue and membership is replaced and refreshed.

Existential Corruption

The mission we have defined for the PORTs is one that challenges the conventional wisdom and raises intellectual barriers to the influx of new, underevaluated medical theory. This is an inherently conflict-ridden role, one susceptible to what, for want of a better label, I call existential corruption. It is the bad faith that comes from fear of ostracism, of career instability, and other unfortunate outcomes that befall those who are whistle blowers, who challenge optimistic assumptions that all forms of medical technology lead to progress. To understand this problem in one extreme, imagine the possible fates of the evaluative scientist who shows that it is safe and in the public interest to close 700 beds in Boston. We need to worry about how to make it possible to provide stable careers to those who want to work in the evaluative sciences, to permit intellectual freedom to reign as the primary ethic driving the evaluative processes. A good deal of the needed protection may rest in the commitment of the federal government to ongoing funding in the area of the evaluative sciences. This, in turn, works to advance the evaluative sciences into the tenured faculty ranks, to make them and the ethics of evaluation central to the mission of the academic medical center.

Corruption of Discursive Practices

These are the biases that become introduced in the act of communicating and are the least well understood of all. I first became aware of the problem when we struggled to learn how to disseminate the results of our BPH assessment in a way that could help physicians and patients make decisions that more closely reflected the patient's own preferences for outcomes and attitudes toward risk. You will recall that one conclusion was the need to ask the patient what treatment he wanted, based on a detailed sharing of information about the outcomes of watchful waiting and surgery. We worked out a strategy based on the use of interactive videodisc technology. In developing the program, we encountered a number of problems concerning the adjudication of differences in opinion on the "fairness" of a given representation of a medical decision problem. (By making one version of the communication process "objective", the debate over fairness emerged for the first time; here-to-fore,

communication on options had occurred in the black box of the physician's office, unobserved, uncriticized and uncontroversial.) We worked out these conflicts through debate and argumentation, within the context of "focus groups" that sought to narrow the range of disagreement and to arrive at an overall judgment that the presentation was "as fair as it could be." The acceptability of the version we produced has withstood several test in clinical practice where both patients and physicians have found it helpful.

I anticipate that other PORTs, as a result of their assessments, will come to similar conclusions concerning clinical practice: for many (probably most) medial conditions, there is no single "correct" or "appropriate" treatment; what is right for one patient—the treatment that best fits his or her preferences for outcomes and risks—is not the same treatment that is right for another patient faced with a similar situation. The PORTs are thus fated, if they follow this mission, to engage patients and physicians in a new discourse, the discourse of shared decisionmaking. The structuring of the institutions that produce and sustain the flow of information, and establish and maintain the rules of discursive practices are perhaps the greatest challenge of all. We are now taking steps to develop a not-for-profit corporation, the Foundation for Informed Medical Decision Making, which we hope can meet the challenge.