The Right Infrastructure Can Help You

Attract Clinical Trials to an AMC

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One university's academic medical center attracts industry-sponsored research with an infrastructure created specifically to meet the needs of both academic researchers and the pharmaceutical industry.

During the early 1990s, academic medical centers conducted most industry-sponsored clinical trials of new drugs and medical devices. In the ensuing decade, the situation changed fundamentally. Now only a minority of new trials are conducted in academic centers.[1] This change, and the reasons for it, have been the subject of numerous commentaries.[2–6]

Perhaps the most important force driving this shift away from academia is the increasing pressure on trial sponsors to bring products—with a limited patent life—to market ever more quickly. Academic centers, with their varied missions and ponderous bureaucracies, have been slow to respond to the increased emphasis on speed. At the same time, however, physicians in the private sector began to enhance the quality of their practices, to benefit their patients by offering promising new treatments, and to add a new revenue stream to incomes diminished by managed care.

Academia took note and launched various initiatives to address the problems and concerns cited by industry sponsors.[7–8] This article reports on one university's comprehensive attempt to build an infrastructure that enables it to conduct industry-sponsored clinical trials in an academic setting—and to do so efficiently and effectively.

Traditionally, academic centers and their leaders took a permissive attitude toward industry-sponsored clinical trials. That is, they *permitted* and occasionally *encouraged* such studies, but rarely supported them with institutional resources. To justify moving new institutional assets to directly assist faculty participation, it is important to articulate a compelling case. The Reasons box presents a partial list of important reasons for institutional support of industry-sponsored clinical trials.

We contend that the nature of clinical trials, indeed of clinical research in general, is at the very core of the mission of an academic health center. No other single activity integrates the various missions of a medical school—research, education, and patient care—as completely as clinical research. Clinical research enhances collaboration between laboratory-oriented, patient-oriented, and population-oriented scientists. Thus it facilitates the application of new discoveries to the treatment of human disease. By its very nature, clinical research is usually practiced by clinically active faculty. That helps strengthen the teaching and patient-care missions of the school.

Indeed, it could be said that it is specifically clinical research and teaching that distinguish a medical school from a research institute on the one hand and from a patient-care clinic on the other. For many faculty members, industry-sponsored clinical trials are the major form of clinical research activity. Ensuring their continued participation in such research is important to them, to many of the patients they seek to serve, and thus, to schools of medicine.

Challenges to participation

Although AMCs have cogent reasons for academic participation in industry-sponsored clinical trials, they must meet several challenges, including competition, quality control, bureaucratic inefficiencies, and academic credibility.

Competition. The past decade has brought a great increase in new therapeutic agents ready for testing and additional money to support their evaluation in FDA-mandated, multiphase clinical trials. So it is no surprise that the number of investigators filing FDA Form 1572s for these trials has also grown—by one estimate—more than 300% in the last half-dozen years.[9] Even so, most investigators conduct fewer than two trials per year. As many as one-third never conduct another trial after their first year—evidence of the need for additional professionalization of clinical trial investigators. Filling that need would seem to be the natural province of academic institutions. Yet, professionalization requires focus—a challenge for institutions that must also continue to perform research and to provide teaching, training, and patient care.

Quality control. The breadth of faculty expertise at most academic centers, both in terms of interest and sheer numbers, makes them potentially attractive as a site for one-stop shopping. But, in keeping with traditions of free speech and academic freedom, the governance of most

academic centers is highly decentralized. Recent experiences exposed the weaknesses of that system, resulting in the kind of notoriety all centers would rather avoid.[10–11] If a center, *as an institution,* is to support or advocate additional clinical trial activity, then it must assume greater institutional responsibility for ensuring public confidence in the clinical research process.

Various regulatory agencies have created—and are creating—new policies and procedures for the scrutiny of clinical research activity.[12] By their very nature, the new policies have had, and continue to have, the greatest impact at academic centers. To respond, centers will have to provide new programs for teaching and training faculty and staff—programs that neither government nor industry is currently funding.

Inefficiency. The inherent inefficiency of large bureaucratic and decentralized institutions are a drawback. From the pharmaceutical industry's standpoint, time is money. Sponsors see major disincentives in spending excessive time on such necessities as negotiating contracts and budgets and on institutional review board (IRB) review of protocols and consent documents.

Academic credibility. Perhaps the greatest challenge, however, is internal. That is, academic credibility for faculty participation in industry-sponsored clinical trials can be weak.[4–5] For decades, clinical research has taken a back seat to basic research. Federally financed investigator-initiated research is more prized than research initiated by industry—or, for that matter, by the National Institutes of Health. Also highly valued are faculty members with special clinical expertise—say a new procedure of one sort or another—that helps distinguish the institution as a center of excellence. Faculty are rarely recruited for their expertise in clinical research *per se.*

Attitudes are changing, however, fueled in part by the promise of translating the discoveries of basic investigation into new treatments. At the forefront of this translational research are the drugs and devices provided by industry. To maintain, even enhance, their traditional role of demonstrating the way discoveries should be applied to human health, academic centers must make themselves attractive venues for industry-sponsored clinical trials.

Reasons for Support of Industry-Sponsored Trials

An AMC's faculty, hospital, and patients (potential subjects) all have their own reasons for seeing industry-sponsored clinical research as an asset.

The faculty has academic, clinical, training, strategic, and fiscal reasons:
- Trials are sometimes the best way to test biological hypotheses
- Faculty members may wish to participate in trials that test drugs based on their own work
- Faculty could enjoy enhanced industry-academic interactions
- Other units in the institution (biostatistics, for example) can be involved
- Access to cutting-edge therapeutics
- Opportunities for trainees (including funding)
- Opportunity to collaborate with hospital partners
- Additional (discretionary) income

The hospital's reasons for supporting industry-sponsored clinical research include
- Marketing access to cutting-edge therapeutics
- Marketing facilities
- Added value for part-time (private) faculty
- Quality control

Patients, who are potential subjects, are interested in
- Access to cutting-edge therapeutics
- Altruism
- Access to premium care
- Reduced health care costs

Washington University School of Medicine recognized both the importance of and challenges to clinical research. In 1996, it began a comprehensive redesign of the way it supports industry-sponsored clinical trials. As the program has grown and evolved, five domains of activity have emerged, involving operations, subjects, alliances, sites, and education (Figure 1).

Center for Clinical Studies

The operational arm is the Center for Clinical Studies (CCS). It occupies 4500 square feet of space at the heart of the medical center and employs about 28 FTEs (full-time equivalents); half of those employees are clinical research coordinators. Subject exam and waiting room space occupies about 1200 square feet, primarily for subjects there for specific follow-up visits by coordinators, not physicians. The new outpatient Center for Advanced Medicine, to be opened around December 15, will occupy an additional 3500 square feet of clinical space.

CCS is organized as shown in Figure 2, which diagrams its five major functions and their programs.

Business. An important—and unusual—feature of the infrastructure is that all business contracts for industry-sponsored clinical trials are routed through the CCS, and eventually signed by CCS staff. At most academic centers such contracts are usually handled by the office charged with managing NIH grants. In many cases, contracts must also be reviewed by legal counsel. The CCS, in contrast, employs two paralegal contract managers who review contracts using a matrix of conditions set out by WU's legal counsel. As long as terms can be negotiated within the matrix, the CCS director or business manager can sign the contract on behalf of the university. Instances in which such terms cannot be readily negotiated are referred to legal counsel for additional review.

Our unique arrangement has resulted in a 50% reduction in contract turnaround time. Fewer than 5% of contracts require

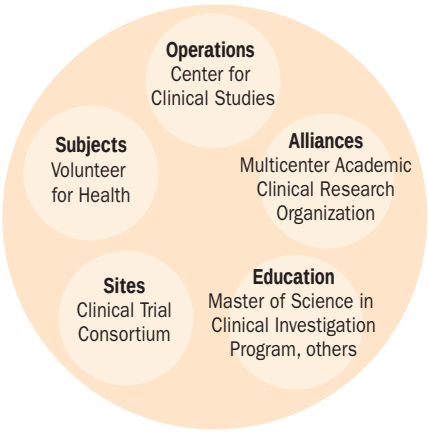

Figure 1. Domains of activity within the Center for Clinical Studies (CCS).

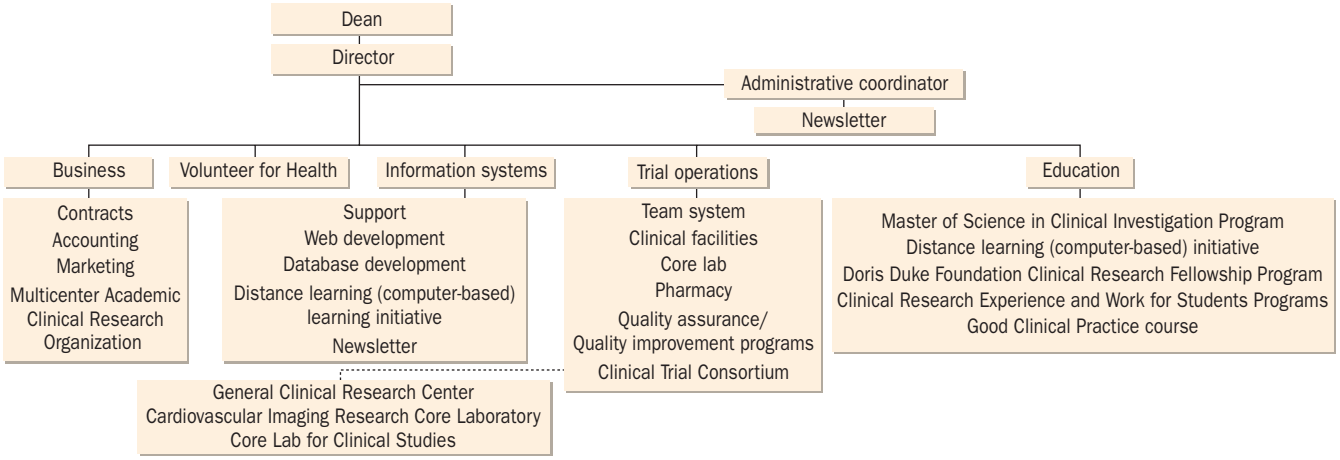

Figure 2. Organizational chart of the CCS, showing major activities of the different organization units.

consultation with other institutional offices (such as the Office of General Counsel).

Equally important, processing all contracts through the CCS allows us to develop and maintain a robust database of the types of trials we perform, and with whom. Indeed, significant effort has gone into developing a highly integrated set of databases (Figure 3). To support the day-to-day operations of the Center for Clinical Studies and its marketing, contracts, research coordinators, accounting, and management groups, the Information Systems (IS) group built a number of programs and databases.

The marketing group uses computer applications and a database to store information about clinical investigators and their clinical interests and about sponsors' therapeutic specialties and contact information. The information is used to generate reports that help target marketing to specific clinical specialties. The marketing group uses another application and database to store and track information on potential studies. As we get information on potential studies from various sources, the group adds it to the database. The information can then be shared with the contracting group when a study is selected.

The contracting group uses computer applications and databases to store all essential aspects of an agreement with a sponsor. Once a contract is signed, members of the contract group fill in the account numbers; then research coordinators use yet another application to track billable hours. Likewise, the contracts group enters information about the billing terms of a contract so that invoices can automatically be generated each month. The accounting group uses information from almost all of the databases to maintain ledgers.

Finally, all members of the management team use information from all the databases to get performance reports, financial reports, and study status reports.

Thus, the operations portion of the Center for Clinical Studies provides a comprehensive service and support program to promote and conduct clinical research at Washington University. Services cover a wide range of needs and encompass all stages of executing a protocol. CCS services can be categorized as those offered to sponsors, to the institution as a whole, and to individual investigators involved in specific trials (see CCS Services box).

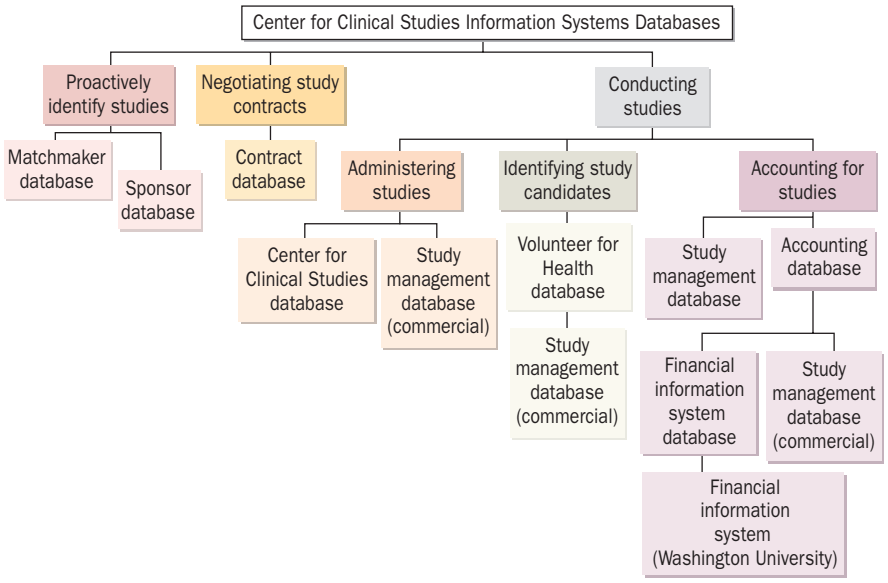

Figure 3. Integrated series of databases developed by the Information Systems group within the Center for Clinical Studies

Clinical trial operations. Prestudy services include pre-initiation site visits to review the protocol, assess the feasibility of the study, and ensure that tools and systems are in place to conduct the study according to the protocol. Site visits include reviews of budgeting, preparation and submission of IRB and regulatory documents, and attendance at investigators' meetings. The center provides many services that relate to the direct conduct of the study, including identifying and recruiting subjects, screening and enrolling candidates, coordinating re-

CCS Services

Sponsor-oriented
- Single point of contact
- Preferred-provider arrangements
- Master contract agreements
- Ancillary resources (such as GCRC, biostatistics)
- Web site
- Investigator database
- CRA-friendly facilities

Institution-oriented
- Marketing
- Physician networks
- Patient registries
- Uniform laboratory/radiology pricing
- Contract negotiations

Investigator-oriented
- Single point of contact
- Pre-initiation services (IRB submissions, visits, for example)
- Execution (coordinator services, for example)
- Patient exam/waiting areas
- Storage
- Accounting
- Web site: http://ccs.wustl.edu/

quired protocol procedures, developing source documentation, and completing case report forms. In addition, study drug accountability, storage, and administration can be provided. Coordinators can make arrangements for specimen collection, processing, packaging, and/or storage. Poststudy services include both short-term and long-term record storage.

The CCS offers clinical space dedicated to industry-sponsored clinical trials. Exam rooms are furnished with all the standard equipment needed for subject visits. In addition to the clinical space, the CCS offers a long-term subject waiting area, a VCR for teaching purposes, and such equipment as a portable EKG machine and IV infusion pumps.

Clinical trial operations management has a team structure. A team leader supervises approximately four or five clinical research coordinators (CRCs). The team leader is responsible for the initial training of new CRCs, for ongoing quality assurance and quality improvement, and for fiscal oversight of the staff and study protocols.

In addition to providing comprehensive support for specific studies, CCS staff play a major role in helping sponsors identify qualified faculty investigators, regardless of whether they require additional trial support (Figure 4). Indeed, a faculty member may choose some or all of the services that we provide (CCS Services box). This flexibility has been a major factor in the faculty's broad acceptance of the CCS.

Subject recruitment. In 1998, we established Volunteer for Health (VFH). That CCS unit helps university investigators with volunteer contact and recruitment. The stated goals of the program are to match interested volunteers with appropriate clinical studies within the university, and to provide information to the local community about clinical research activities at the university.

The first priority for Volunteer for Health was to recognize its role in the research process. Procedures were carefully planned in conjunction with the Washington University IRB, a protocol was submitted and approved by the IRB, and new procedures, materials, and questionnaires are reviewed annually. As part of VFH standard operating procedures, the IRB must approve any information about a study that is used on the VFH Web site or in advertisements. The VFH staff obtains informed consent from each subject before collecting any demographic or medical information or sharing it with an investigator.

Key operating components of VFH include a central phone number with numerous message boxes to handle inquiries from potential volunteers, a database to capture demographic and self-reported medical information, and an interactive Web site. Using the Web, potential participants can view studies that are recruiting subjects and express their interest electronically.

Investigators who use VFH services may post a study on the Web site, request a dedicated phone mailbox with expanded capacity, and receive a list of potential participants from the existing database. Dedicated databases have been developed for groups of projects in specific therapeutic areas and for large individual projects. Investigators may use VFH staff to contact and prescreen potential volunteers, or use only the point-of-contact services with all of the screening work done by the study coordinator.

Under a cooperative agreement between the university and Barnes-Jewish Hospital—the primary teaching hospital affiliate of Washington University—the VFH office is located in the main lobby of the hospital. That central location is used to meet subjects in several large studies and to provide information to curious hospital visitors.

Through its ongoing effort to inform and involve the public, the community outreach efforts of VFH have succeeded in promoting clinical research at Washington University. Each year, VFH staff members represent the university at 10–20 health fairs, coordinate several community health screening events, and accept 10,000–15,000 inquiries about studies through VFH's central phone number. From 800 to 1200 persons submit health questionnaires through the

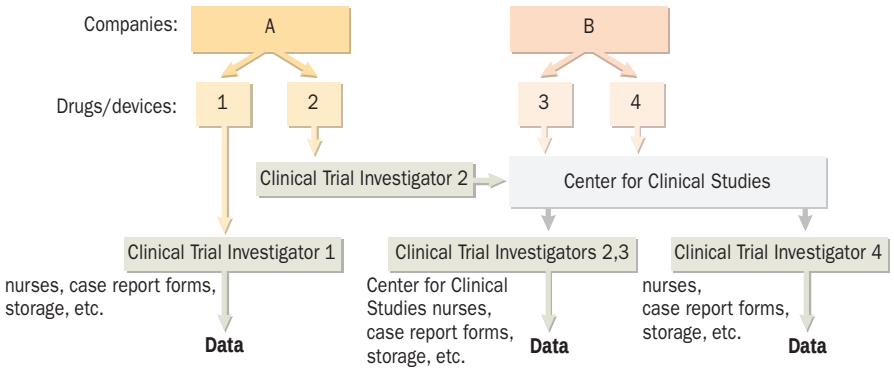

Figure 4. The CCS within the overall opportunity for sponsor-faculty interaction. Sponsor companies (A and B) have drugs to be tested (1–4) and may seek clinical trial investigators (1–4) at the School of Medicine either directly or via the CCS. The investigators may elect to use some or all of the resources available from the CCS.

Web site each year. So the VFH database currently contains information about more than 9000 potential volunteers with a variety of illnesses—including some who are willing to volunteer as a normal control. Volunteer for Health helps to recruit subjects for 100–150 clinical studies each year and directs callers and walk-in volunteers to any investigator with an IRB-approved study at the University.

The VFH program serves both the university community and sponsors of clinical trials by providing a clear message that subject recruitment is a priority at Washington University.

Education and training. More and more attention is being paid to qualifying, training, and credentialing clinical investigators and research coordinators. Each academic center's IRB is responsible for ensuring compliance with the regulations, policies, and procedures mandated by the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and the Office of Research Integrity (ORI), among others. But most IRBs are not equipped to provide the education and training programs necessary to ensure that investigators and coordinators know how to conduct research according to the applicable guidelines and regulations.

The Center for Clinical Studies at the Washington University School of Medicine helped lead new initiatives in research education and training.

At Washington University School of Medicine, the CCS helped lead new initiatives in research education and training. For instance, the CCS offers a quarterly 20-hour seminar in good clinical practice. The CCS also administers the Master of Science in Clinical Investigation Program (MSCIP). That program targets physicians just completing their clinical training who wish to get an advanced didactic experience in clinical research. Likewise, the CCS administers two programs for medical students: the Doris Duke Foundation Clinical Research Fellowship Program (DDF-CRFP, for students who are willing to spend an additional year in medical school on a mentored and supervised clinical research project), and the Clinical Research Experience and Work for Students Program (CREWS). CREWS seeks to match students with investigators who have employment opportunities in clinical research. This past year, five students were accepted into the DDF-CRFP, and more than a dozen other students found part-time work in clinical research labs. Students in both programs are required to participate in a series of lectures on the responsible conduct of research, developed by the CCS.

Clinical Trial Consortium. The latest development at the CCS is the launch of a joint venture with our affiliated health care system, BJC HealthCare Inc. Together, these entities will create a network of satellite sites in the St. Louis region. In collaboration with physicians in private practice, patients can be seen at any of these sites and recruited into trials conducted by Washington University faculty. The physician networks are organized by therapeutic area. The primary goal of this initiative is to improve the environment for conducting later-phase clinical trials, and to encourage and support those trials that are best performed in an outpatient setting. Thus, these trials can be conducted at several sites in the region, gaining access to much larger patient populations, yet requiring only a single contract, budget, and IRB review.

MACRO

Representatives of the pharmaceutical industry frequently complain that academic centers are inherently inefficient. They especially take aim at how slowly IRBs review clinical trial protocols. As various academic centers attempted to reverse the trend toward using non-academic sites, they had to confront the issue directly. Several centers, including Washington University, have begun to meet this challenge by creating the Multicenter Academic Clinical Research Organization (MACRO).[13] The other centers include Baylor College of Medicine, Vanderbilt University, the University of Pennsylvania, and the University of Alabama at Birmingham.

The original foundation for MACRO was a cooperative amendment to each institution's Multiple Project Assurance for Compliance with Department of Health and Human Services regulations for the protection of human subjects (45 CFR 46). The amendment was crafted with direct involvement by the former Office for Protection from Research Risks (OPRR) to ensure its acceptance by federal regulators. Although such amendments have been supplanted by the Federalwide Assurance (FWA) program of the Office for Human Research Protections, the original amendment still provides the basis for MACRO member interaction.

The key feature of the cooperative amendment is "limited reciprocity" between and among the member institutions' IRBs. Simply put, if one institution's IRB approves a research proposal involving human subjects through an agreed-upon process of standard operating procedures (SOPs), the IRBs of all member institutions will accept that one institution's approval. Thus, the proposed clinical research may be conducted at two or more AMCs after only one IRB approval process. IRBs at other participating institutions administratively accept the approval of the primary reviewing institution. The *limited* nature of the reciprocal arrangement is built into SOPs, which include provisions to protect the local differences and interests of each participating institution.

Advantages for research sites. Potential advantages to formalizing collaborative IRB reciprocity are clear. Reciprocity eliminates duplicated efforts. It improves the efficiency, uniformity, openness, commitment to quality, and exchange and sharing of information among the IRB members of MACRO. All of these factors enhance the protection of human subjects at each site.

Advantages for sponsor companies. A major advantage for sponsors is the ability to place a study at two or more MACRO sites with just one IRB approval process. During the first eight months

following the organization's launch, 10 industry sponsors requested placement of 12 studies using the MACRO arrangement. Eight of those trials are in various stages of processing and are slated to begin at two or more of the MACRO member institutions. Subject populations include such diverse groups as patients with acute asthma, Type 2 diabetes mellitus, pressure and venous ulcers, peridural fibrosis, hypertension, and hip or knee joint replacement or revision.

Waiting for the return on investment

The series of programs described here were developed at one medical center in response to the steady movement of industry-sponsored clinical trials away from academia. Not all academic medical centers will need or want to develop programs similar to those described here. Yet no response at all to the loss of clinical research opportunities will certainly ensure continued weakening of the role that academic centers could properly play in the clinical trial process. Such a development would serve no one well.

Our medical center made large investments in space, personnel, and funding to help secure its continued involvement in this fundamentally important activity. Whether such an investment will be paid back in full, whether industry will embrace the changes and initiatives described here, and whether academia will encourage and reward its faculty for helping promote the success of these various efforts remains to be seen.

References

1. S. Zisson, "Large Site Networks Quietly Take the Field," CenterWatch, 8, (8) 1 (2001).
2. W. Crowley and S. Thier, "The Continuing Dilemma in Clinical Investigation and the Future of American Health Care: A System-Wide Problem Requiring Collaborative Solutions," Academic Medicine, 71, 1154–1159 (1996).
3. L. Rosenberg, "The Physician-Scientist: an Essential—and Fragile—Link in the Medical Research Chain," Journal of Clinical Investigation, 103, 1621–1626 (1999).
4. D. Nathan, "Clinical Research: Perceptions, Reality, and Proposed Solutions. NIH Director's Panel on Clinical Research," Journal of the American Medical Association, 280, 1427–1431 (1998).
5. L. Shulman, "Clinical Research 1996: Stirrings from the Academic Medical Centers," Academic Medicine, 71, 362–363 (1996).
6. L. Rosenberg, "Physician-Scientists—Endangered and Essential," Science, 283, 331–332 (1999).
7. W. Crowley and S. Thier, "A Program to Facilitate Clinical Research in an AHC: The First Five Years," Academic Medicine, 76, 403–409 (2001).
8. J. Lewis and A. Lewis, "Clinical Trials in Departments of Internal Medicine: Ingredients for Success," American Journal of Medicine, 102, 323–328 (1997).
9. S. Zisson, "Anticipating a Clinical Investigator Shortfall," CenterWatch, 1 (2001).
10. G. Ellis, "Keeping Research Subjects Out of Harm's Way," Journal of the American Medical Association, 282, 1963–1965 (1999).
11. S. Kaplan and S. Brownlee, "Dying for a Cure," U.S. News and World Report (11 October 1999).
12. B. Gabriel, "New Association to Accredit Human Research Protection Programs," AAMC Reporter, 10, (9) 1 (2001).
13. D. Schuster and D. Canfield, "MACRO: A New Paradigm for Clinical Research Among Academic Health Centers," Clinical Researcher, 6, 34–36 (2001).

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