

The Industrialization Of Clinical Research

Clinical research has become an industry of its own, one that warrants careful scrutiny to protect human research subjects.

by Richard A. Rettig

PROLOGUE: The brave new world of clinical research has sprung up so quickly and has become so vast that neither policymakers nor private-sector pioneers have been able to stay ahead of the complicated business, ethical, and regulatory issues that have accompanied the exciting developments in this new enterprise. With for-profit entities now dominating both the pace of and the market for clinical research, the question of oversight has become a critical one.

As Dick Rettig points out in this paper, the business of clinical research has largely been a response to a science that is “ripe for exploitation,” but it is not clear that the proper structures are in place to keep the business and the science in balance. As leaders in both sectors stake their claims on this new industry, perhaps they would do well to follow the credo of an earlier business pioneer, John D. Rockefeller. No stranger to the politics of industrialization, Rockefeller stated in a 1941 speech, “I believe that every right implies a responsibility; every opportunity, an obligation; every possession, a duty.”

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ABSTRACT: Recent controversies over the protection of human subjects, payment of physicians for recruiting patients to clinical trials, Food and Drug Administration (FDA) removal of approved drugs from the market, and reporting of results of clinical trials have highlighted important facets of clinical research. Less visible has been the industrialization of clinical research, and especially of clinical trials, that is, its emergence as a “line of business” of substantial magnitude and rapid growth. The growth of drug-industry outsourcing of clinical trials and the concomitant rise of a contract research industry are described in this paper, which argues for greater transparency in the conduct of both publicly and privately sponsored clinical trials.

SEVERAL HIGH-PROFILE CONTROVERSIES have recently opened a window on some important aspects of the organization and conduct of clinical research. First, in 1998 the inspector general of the Department of Health and Human Services (HHS) issued a critical report of the institutional review board (IRB) system.¹ In May 1999 the Office for Protection of Research Risks (OPRR) briefly suspended the multiple project assurances (MPA) for all human subjects research at Duke University as a result of IRB deficiencies; this halted all federally sponsored research involving human subjects there until an acceptable corrective action plan was instituted.² The OPRR and the Department of Veterans Affairs (VA) deactivated the MPA at the West Los Angeles VA Medical Center in March 1999, thus suspending all research; the VA has since instituted two new initiatives to ensure the protection of research subjects, but the OPRR deactivation remained in effect in December 1999.³ The OPRR also deactivated the MPA for the west-coast IRB of the Friends Research Institute in February 1999, reinstating it after corrective action; it also suspended all federally supported research at the University of Illinois at Chicago until all projects are reviewed by the local IRB. The U.S. Food and Drug Administration (FDA) suspended all research at the University of Colorado involving FDA-regulated trials that had not been reviewed by its IRB within the past twelve months; the OPRR concurred with the FDA without taking formal action.

Second, in May 1999 the *New York Times* raised questions about paying physicians to recruit patients for clinical trials, disclosure of financial interests of physician-investigators, and compensation of patients for participation in trials.⁴ Another story the next day focused on one physician’s high standard of living made possible by research that involved the fraudulent submission of clinical trial data.⁵

Third, in response to charges that recent removals of drugs from the market for safety reasons reflected negatively on speedier review times, FDA officials concluded that this was not the case. They

cautioned, however, that “the increased rate at which drugs are entering the market, the higher consumption of medicines by the population, and the use of pharmacologically active ‘alternative medicines’...increase the probability of misprescribing and adverse reactions...Given these realities, the FDA’s postmarketing surveillance system will become even more active and essential in ensuring drug safety in the coming decade.”⁶

Finally, numerous problems with the reporting of clinical-trial results have been identified in recent years, including efforts by a British pharmaceutical company to suppress trial results that did not support its claims of superiority over a competitive product; differential interpretation of clinical trial results as a result of affiliation with drug-company sponsors; ghost authorship of clinical-trials papers by nonresearchers; and multiple reporting of the results of a single trial in several peer-reviewed journals.⁷

Less visible than these controversies has been the emergence of an entirely new industry, the contract research industry, that is engaged mainly in the management of clinical trials for the pharmaceutical industry but that also includes biotechnology and medical device firms as clients. Driven mainly by drug firms’ outsourcing of clinical trials, this industry reflects the rapid increase in the magnitude of clinical research over the past decade. In this paper I describe some of the major changes in clinical research represented by this new industry and suggest some of their implications.

Why should health policy analysts care about clinical research? First, clinical research is central to translating the promise of biomedical research into improved clinical practice—the “neck of the scientific bottle” through which all advances in biomedicine must flow before they can benefit the public.⁸ Innovation in medicine affects health care financing and delivery.

Second, the National Institutes of Health (NIH) budget is projected to double in the near future, spurring further rapid scientific advance. The fiscal year 1999 NIH budget of more than \$14 billion increased 14 percent over FY 1998. The FY 2000 budget increased 14.7 percent, to \$17.9 billion.⁹ A large portion of that budget will be directed to clinical research, including clinical trials. Ensuring that these funds are spent wisely argues for policy oversight and research.

Third, pharmaceutical industry research and development (R&D) has also grown rapidly and now exceeds the NIH budget (Exhibit 1). Moreover, the boundaries between publicly funded and privately sponsored clinical research are no longer sharply defined, and the activities themselves are more dependent on one another than ever before. Consequently, clinical research takes on increasing importance as public and private research support broadens and

EXHIBIT 1

Research And Development (R&D) Spending At The National Institutes Of Health (NIH) (By Fiscal Year) And In U.S. Research-Based Pharmaceutical Companies (By Calendar Year), Millions Of Dollars, 1986-1998

Fiscal year	NIH R&D	Calendar year	U.S. R&D
1998	\$13,648	1998 (est.)	\$17,223
1997	12,750	1997	15,517
1996	11,928	1996	13,627
1995	11,300	1995	11,874
1994	10,956	1994	11,102
1993	10,336	1993	10,477
1992	8,922	1992	9,312
1991	8,277	1991	7,929
1990	7,576	1990	6,803
1989	7,145	1989	6,021
1988	6,667	1988	5,234
1987	6,328	1987	4,504
1986	5,401	1986	3,875

SOURCES: National Institutes of Health, History of Congressional Appropriations, for fiscal years 1988-1998, www4.od.nih.gov/ofm/CJ99/page66.stm; National Institutes of Health, Source of Funds, Medical and Health Related R&D, Fiscal Years 1986-1995 (for fiscal years 1986-1987), www4.od.nih.gov/ofm/PRIMEER97/page6.stm; and Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Survey, 1999*, in *PAREXEL's Pharmaceutical R&D Statistical Sourcebook, 1999*, 3.

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deepens the growing scientific base for medical innovation.

Are existing organizations for “managing” this enterprise adequate from a policy standpoint? Clinical research challenges the NIH on priority and resource allocation; academic medicine regarding infrastructure support and professional reward of faculty; the FDA in the evaluation of new therapeutics and postmarket surveillance; IRBs regarding the protection of human subjects; health services research in assessing outcomes and effectiveness in early-stage therapeutic developments; and third-party insurers in evaluating coverage of new therapies. Evidence suggests that all parties are under stress and that prudent steps toward greater transparency are warranted.

The Dimensions Of Change

Clinical research is understood today as being the bridge between laboratory science and clinical practice.¹⁰ A distinction now is made between laboratory-oriented research and patient-oriented research, the latter requiring direct physician-to-patient interaction. Some patient-oriented research is translational, a deliberate effort to apply laboratory research results to a small number of patients in a clinic setting. Much of it consists of clinical trials in humans of new diagnostic or therapeutic products (drugs, biologics, medical devices), regulated by the FDA as Phase 1, 2, 3, and 4 trials.¹¹

■ **Sponsors.** Clinical trials involve four parties: sponsors, manag-

“The nation’s sustained investment in biomedical research has created a science base ripe for exploitation.”

ers, investigators and sites, and patients. Pharmaceutical clinical research must be viewed in the context of the large, rapidly growing sales of pharmaceuticals, both in the United States and worldwide, which have more than doubled in the past decade. Sales from 1970 to 1999 increased an average of 11 percent per year in the United States, 10.8 percent in the rest of the world, and 10.8 percent overall. Estimates are that 1999 sales will increase by 13 percent over 1998 levels for the United States and by 7.6 percent worldwide.¹²

Worldwide pharmaceutical R&D also has grown rapidly. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that \$20 billion of R&D will be conducted in the United States in 1999 and another \$3.9 billion in the rest of the world, a 14.1 percent increase over 1998.¹³ R&D expenditures as a percentage of industry sales have risen from 11 percent to nearly 21 percent in the past twenty years. Drug firms’ R&D budgets are expected to grow in the next few years by at least 10 percent per year. When biotechnology is included, worldwide pharmaceutical R&D for 1996 is estimated by one source at \$44 billion, one-third for basic research and two-thirds for development.¹⁴ The major firms in both industries spend heavily on R&D. In 1994 seven of the top-ten drug companies spent more than \$1 billion on R&D, and six firms spent an estimated \$2 billion each in 1999. R&D expenditures for the top-ten biotechnology firms ranged from \$52 million to \$324 million in 1994 and from \$77.6 million to \$630.8 million in 1997.¹⁵

A functional breakdown of U.S. drug R&D spending shows that the bulk of the funds are devoted to the development of specific compounds. For 1997 this breakdown was as follows: synthesis and extraction, 11.8 percent; biological screening and pharmacological testing, 14.9 percent; pharmaceutical dosage formulation and stability testing, 8.5 percent; clinical evaluation (Phases 1–3), 26.5 percent; clinical evaluation (Phase 4), 5.8 percent; process development for manufacturing and quality control, 10.0 percent; regulatory, 4.3 percent; bioavailability, 2.1 percent; and other, 10.6 percent.¹⁶ A slightly different breakdown for major biotechnology companies for 1994 was as follows: research, 38 percent; Phase 1, 17 percent; Phase 2, 33 percent; Phase 3, 9 percent; and new drug application (NDA) review, 3 percent.¹⁷ Biotechnology invests heavily in early-stage research; in time, greater Phase 3 investments will occur.

What is driving the growth in pharmaceutical clinical research? A

major factor is that the nation's sustained investment in biomedical research has created a science base ripe for exploitation. Indicative of this, the pipelines of drug firms are full of potential new therapeutics. Approximately 5,000 new compounds were in preclinical development worldwide in 1997, of a total estimated 7,000 compounds in the drug development pipeline.¹⁸ Moreover, biotechnology firms are bringing a growing number of new compounds to the regulatory-approval stage before introduction to the market, and this is expected to increase. The growth of clinical research in the drug industry appears to be a corollary of increasing scientific opportunities.

In addition, FDA review of new drugs has shortened greatly in the past decade and is no longer the main bottleneck in the development cycle. The enactment of the Prescription Drug User Fee Act in 1992, reauthorized in the Food and Drug Administration Modernization Act (FDAMA) of 1997, has led to markedly reduced FDA review times for new drug approvals (NDAs). The median NDA review time, once thirty months, has fallen below fifteen months.¹⁹ This change reflects a major shift in the philosophy of drug evaluation from one of avoiding premature release of new drugs until safety has been decisively established to one of facilitating rapid access to the benefits of new therapeutics. Shorter FDA review times reduce an unpredictable external cost element in the drug development cycle, provide firms with an incentive to submit NDAs to the FDA for consideration, and thus stimulate industry clinical trials.

Traditionally, drug firms have both sponsored and managed clinical trials. Indeed, trial management remains an internal function for some firms, and most use a mix of internal and outsourced clinical trial management. In the traditional mode, drug firms have been responsible for trial design and for recruiting investigators and patients, all organized to support an NDA submission to the FDA.

In the past decade, an increasing amount of clinical trial work has been contracted out. Exhibit 2 presents various estimates for several years, each with a slightly different focus. On the basis of these estimates, however, it is safe to say that at least \$5 billion and perhaps as much as \$8 billion of R&D is currently going to contract research organizations (CROs).²⁰ The contract drug development market is estimated by Covance (one of the big-three CROs) to grow 18 percent per year.²¹ Another source estimates outsourced R&D growth at 15–20 percent annually and increasing CRO penetration of total drug development research from 15 percent to 22.1 percent between 1995 and 2000, for year-to-year growth slightly over 20 percent.²²

A number of factors are driving the outsourcing of clinical trials. First, government and private-sector cost containment and market-

EXHIBIT 2**Estimates Of Outsourced And Contract Research Organization (CRO) Pharmaceutical Research And Development (R&D)**

Estimate	Year	Outsourced R&D amounts	CRO R&D amounts
Covance	1996	\$8 billion	\$4-\$5 billion
CenterWatch	Unknown	-	\$3.5-\$5 billion
PhRMA (clinical evaluation; phases 1-4)	1995 2000	\$2.050 billion \$5.143 billion	-
PhRMA (R&D outside firms for human use drugs)	1997 1998	\$5.3 billion \$6.1 billion	-

SOURCES: Covance, "Corporate Fact Sheet, 1998" (Princeton, N.J.: Covance Inc., 1998); *An Industry in Evolution* (Boston: CenterWatch, 1997 and 1999); and Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Survey, 1999*, in PAREXEL's *Pharmaceutical R&D Statistical Sourcebook, 1999*.

place globalization pressures on drug prices have generated an intensive search for efficiencies in the drug development cycle, which has not shortened, even though FDA review times are shorter.²³ Industry has concluded that some bottlenecks can be managed more effectively by external than by internal resources. Second, pipeline management may pose a problem when the number of new compounds approaching market approval is large. Firms may find contract research an attractive way to escape the limits of existing organizational capacity. Third, industry consolidation may also be a CRO stimulus, as merged companies seek to manage costs by reducing jobs, centralizing R&D, and outsourcing to reduce fixed costs.²⁴ It may be easier for a merged company to outsource clinical trials than to integrate two R&D units.

Fourth, biotechnology firms, with great scientific competence, often lack the internal resources and experience (capital, equipment, and staff) to conduct preclinical and clinical research. A number have chosen to outsource rather than to create these capabilities *de novo*. Fifth, as the market for new drugs has become increasingly global, the concurrent harmonization of U.S., European, and Japanese drug evaluation procedures has created opportunity for drug firms to seek regulatory approval in various national markets simultaneously rather than sequentially. Coupled with an increase in multinational trials, international CROs often are better able than a drug firm's central regulatory affairs unit is to provide expertise about the regulatory requirements of a specific country and can help to tailor clinical trials accordingly. Finally, as clinical trials have become more complex in response to chronic disorders and life-threatening conditions, CROs with particular therapeutic expertise become attractive to drug firms with promising research but limited experience in a given therapeutic area.

■ **Clinical trial managers.** Outsourcing of clinical trial manage-

ment to CROs is no more than two decades old.²⁵ This industry is highly fragmented, consisting of hundreds of small firms providing highly specialized “niche” services and several large, full-service firms. The 1999 *CenterWatch Industry Directory* lists more than 550 U.S.- and foreign-based CROs. In 1998 the seven largest CROs in net revenues were Quintiles Transnational Corporation, Covance Inc., PAREXEL International Corporation, Pharmaceutical Product Development Inc., Phoenix International Sciences Inc., Kendle International Inc., and ClinTrials Research Inc.²⁶ Stock prices for major CROs are tracked by *CenterWatch Weekly* (the big-three CROs are Quintiles, Covance, and PAREXEL).

Quintiles, incorporated in 1982, became publicly held in 1994.²⁷ It grew from a contract biostatistics and data management group of ten people in a single office to more than 18,000 employees in more than 130 offices in thirty-one countries by July 1999. Dennis Gillings, its chairman and chief executive officer, saw drug development as an information management problem, not a medical research problem. Focusing on FDA approval as the goal of drug development, he saw that information technology (IT) could manage clinical trial data as one large database. He aspired “to create an IT infrastructure that would accept data from multiple sources, in different disciplines, working at different locations and in different languages.”²⁸ Quintiles reported net revenue of \$1.19 billion for 1998—the first CRO to breach the billion-dollar level—up 39 percent over 1997. Net income was \$84 million, up 50 percent from the prior year.

Covance became an independent, publicly traded corporation as of 31 December 1996.²⁹ Formerly Corning Pharmaceutical Services Inc., it was created by a series of acquisitions over the prior decade. It includes competence in preclinical drug safety assessment and Phase 1 clinical research; Phase 2 and 3 clinical trials; pre- and postapproval studies; clinical laboratory services; pharmaceutical packaging; health economics and outcomes research; and the manufacture of biologics. In 1998 net revenues were \$731.6 million, up 23.9 percent from 1997; net income was \$48.6 million. Covance, in its 1997 annual report, argued that in addition to safety and efficacy, the “other important questions” in drug development were whether a new drug would be the first of its kind to reach the market; the cost-effectiveness of a new compound compared with alternative treatments; ease of manufacturing; acceptance by providers and patients after regulatory approval; and whether “government and private healthcare insurers agree to pay for the drug.”³⁰

PAREXEL, founded in 1983, had grown by acquisitions and internal growth to approximately 4,200 employees in forty-five locations in twenty-nine countries by August 1999.³¹ It reported net revenue of

\$348 million for the fiscal year ending 30 June 1999, up 22 percent from the prior year. Income from operations was \$20.6 million, and net income was \$15.6 million. Acquisitions in 1998 and 1999 included firms engaged in multinational contract research, regulatory affairs consulting, and contract marketing services in Europe.³²

September 15, 1999, was a financially dark day in the CRO world. Quintiles announced that its third- and fourth-quarter earnings would be below expectations, based on the loss of major clinical trial contracts. Its stock fell 42 percent as a result.³³ Covance had announced losses of \$50 million the week before, as a result of Phase 3 shortfalls and contract cancellations.³⁴ CenterWatch reviewed the general situation in October 1999.³⁵ The scientific and clinical uncertainties of drug development were once again revealed, underlining the fact that the economic forces acting on sponsors are prime determinants of CROs' economic prospects.

CROs' services can be grouped under drug development, related resources, and marketing. Drug development services include pre-clinical services (pharmacology, drug metabolism and pharmacokinetics, and toxicology and pathology); pharmaceutical sciences (formulations development and manufacturing, analytical chemistry, and quality control); and drug packaging, labeling, and distribution (both to support trials and to market approved drugs). Quality control concentrates on compliance with international Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP) regulations, and International Standards Organization (ISO) 9000 quality system standards.

Clinical trial management services for all phases include project management, study and protocol design, case report form development, clinical database design, data entry and verification, data management, statistical analysis and reporting, investigator and site selection, healthy volunteer and special population recruitment, investigator meetings, clinical monitoring, centralized clinical trial laboratory, bioanalytical and clinical chemistry laboratory services, pharmacokinetics and pharmacodynamics, expert report writing, and regulatory applications.³⁶

Regulatory services deal with complying with FDA requirements in this country and those of relevant non-U.S. authorities. These requirements include drug safety surveillance; regulatory support of clinical trials; preparation of regulatory documents; interaction with regulatory authorities; submission strategies; training for GLP, GCP, and GMP; and determination of national and international regulatory requirements, including data evaluation requirements.

Related resources include studies of outcomes research, pharmacoeconomics, quality-of-life analysis, and patient satisfaction stud-

ies. The Lewin Group, for example, is a wholly owned health services research subsidiary of Quintiles. Similarly, Health Technology Associates was a 1996 Covance acquisition, giving the parent company health services research capabilities as well.

Not all clients are large pharmaceutical firms. Quintiles, in its Emerging Companies Institute, deals with all phases of drug development related to smaller biotechnology and drug firms and has the equivalent of a mini-CRO for medical devices in its Medical Technology Consultants. Similarly, Covance's biomanufacturing services are designed for the needs of biotechnology companies, which often lack the capability to meet FDA-required GMP standards.

■ **Investigators and sites.** The conduct of clinical trials requires investigators and patients, which has led to the creation of another market segment: site management organizations (SMOs). One commentator defined SMOs as "centrally managed groups of multiple investigative sites that work on behalf of biopharmaceutical companies or contract research organizations and focus on the front-end aspects of clinical studies."³⁷ These include marketing investigative sites (to sponsors or CROs), negotiating contracts, obtaining IRB approval and handling regulatory documents, enlisting clinical investigators, training investigators and coordinators, recruiting and enrolling patients, and improving and standardizing sites and practices.

The top-three centrally owned and managed SMOs are Clinical Studies of Raleigh, North Carolina; Hill Top Research of Cincinnati, Ohio; and Affiliated Research Centers of Gurnee, Illinois. Clinical Studies, a division of Phymatric, a physician practice management (PPM) organization, has thirty-five owned sites in the United States and site-management contracts with several large health care providers.³⁸ Hill Top owns twenty-two sites in the United States and Canada, has more than 650 employees, and conducts Phase 1-4 trials in a variety of therapeutic areas. It advertises its goal as accelerating clients' drug development programs by quickly and efficiently enrolling and randomizing patients; conducting studies according to sponsors' protocols; and delivering clean, high-quality data consistent with FDA reporting requirements. Affiliated Research Centers, an investigator-owned SMO, specializes in gastroenterology, internal medicine, neuroscience, and urology. With more than 150 community-based sites across the country, it recruits, evaluates, and enrolls patients in Phase 2-4 studies.

SMO forms include CROs that have contracted with SMOs; PPMs that have entered (and often exited) site management; some health plans that have begun to exploit their patient populations and affiliated physicians for the clinical trial business; and hospital chains that have created clinical research subsidiaries or dedicated

clinical research sites.³⁹ For example, Omnicare, a leading geriatric pharmaceutical care company providing services to nearly 470,000 elderly residents in more than 5,700 long-term care facilities in thirty-seven states, recently purchased IBAH, a previously independent CRO, as a way to offer drug firms access to elderly patients for clinical trials.⁴⁰ Also, some physicians now maintain a “clinical practice” and a “research practice,” the latter to pursue drug firms’ clinical trial business.⁴¹

■ **Patients.** Patient recruitment and enrollment in a trial is a central management function for all of those engaged in clinical research. Recruiting delays can have a major impact on the speed—and thus the costs—of drug development. Not surprisingly, major CROs and SMOs advertise their patient recruitment capability prominently. Also specialized organizations focused primarily and often exclusively on patient recruitment have sprung up.

Before patients can be entered into a clinical trial, however, they must provide informed consent. Federal regulations require that the protocols and procedures of a clinical trial be reviewed by an IRB for their adequacy in protecting human subjects of research. However, there are effectively two IRB systems in the United States: one of local IRBs, the other of central or independent IRBs. Local IRBs are found at all universities and not-for-profit institutions that conduct federal government-sponsored research involving human subjects. Several thousand local IRBs constitute the loosely coordinated, mostly university-based network overseen by the OPRR.⁴² The OPRR regulates institutions through multiple project assurances. The institutions, in turn, protect human research subjects through their IRBs. In addition, the NIH requires academic institutions receiving NIH funds to use their own local IRB if they wish to remain eligible for support.

A sponsor of drug clinical trials, such as a drug company using its own funds, does not fall under OPRR or NIH requirements. It does fall under FDA regulations, as do all parties engaged in clinical trials of drugs or devices; these regulations permit the use of central IRBs.⁴³ An estimated fifty or sixty such entities now exist in the United States, of which perhaps fifteen to twenty review informed-consent protocols for most industry-sponsored clinical trials. These independent (usually for-profit) organizations are dedicated exclusively to reviewing research protocols for compliance with FDA regulations regarding protection of human subjects. Sponsors are interested in central IRBs because they consolidate in a single entity the process of reviewing protocols, sites, and investigators for a multisite trial. A multisite trial based in academic health centers (AHCs), by contrast, must deal with as many local IRBs as there are

“The emergence of new contract research organizations displaces AHCs from a previously unchallenged central position.”

study sites. Central IRBs also normally provide one- to two-week turnaround for protocol review and approval, compared with much longer times at AHCs.

Not surprisingly, there are divided opinions about the use of central IRBs. Are proprietary, central IRBs, working for either a drug firm or a CRO with market-share and bottom-line objectives, more vulnerable or susceptible to ethical lapses than are local IRBs in AHCs? A recent report by Public Responsibility in Medicine and Research presents a balanced view of the issue: “There is no evidence that the quantity or force of pressures [for protocol approval] is systematically greater for any specific review board type [local or central]. No empirical evidence exists to suggest that different types of review boards deal better or worse with such pressures.”⁴⁴

Policy Implications

Industrialization of clinical research fundamentally constitutes the emergence of clinical research—and especially clinical trials—as a large, rapidly growing “line of business.” Although this is occurring mainly in drug development, it appears also in biotechnology and medical device development. Industrialization also reflects an intensified search for efficiency throughout the product development cycle, especially in the organization and conduct of drug clinical trials. It generates competition for market share in clinical research among new organizational players, such as CROs, SMOs, central or independent IRBs, providers with “research practices,” and traditional organizations such as AHCs. The emergence of these new contract research organizations displaces AHCs from a previously unchallenged central position. This in turn, is forcing AHCs to reexamine their role in clinical research.

The industrialization of clinical research has had relatively low visibility. It is poorly understood by many in academic medicine and government research agencies. At minimum, this development calls for greater recognition that clinical research is quite different today than it has been in the recent past.

The private sector is clearly pressing the clinical research envelope in the name of increased efficiency of clinical trials. However, private-sector activity is not as transparent as public-sector activity is. Moreover, the entire clinical research enterprise is no longer anchored firmly in the public sector. Neither the NIH, the OPRR, nor

academic medicine is as central to clinical research as it once was. The FDA is the first line of defense of the public interest in dealing with the industrialization of clinical research. The question must be raised, then, whether public institutions, policies, and procedures are sufficient to cope with a rapidly unfolding future.

■ **Role of AHCs.** About a decade ago, AHCs began to lose drug industry-sponsored clinical trials market share to CROs because they had longer patient recruitment times, higher error rates in data collection and reporting, and higher costs.⁴⁵ AHCs have responded by creating centralized clinical trial offices to promote ease of interaction with industry sponsors: Columbia, Pennsylvania, Duke, Emory, Michigan, Pittsburgh, New York, and Rochester universities have done so. In addition, both sponsors and academics have rediscovered the market value of academic “leadership” in drug development. It is highly advantageous in the launch of a newly approved drug to have the results of the critical clinical trial be published coincidentally in a major medical journal in a paper authored by a prominent academic. AHCs also have attempted to form consortia, but here the record is mixed. A ten-year effort by the University HealthSystem Consortium to promote the changes among its members that would make them competitive with CROs recently folded. The Association of Professors of Medicine in 1999 established the Academic Network for Clinical Research (ANCR), a joint venture with the U.S. subsidiary of Canadian Medical Laboratories. It is too early to tell whether this entity will succeed. Finally, some AHCs have created alliances with CROs; Emory and the Cleveland Clinic Foundation have signed cooperative agreements with Quintiles; and Georgetown has a contract with PAREXEL for Phase I studies.

The open question is whether AHC leadership in the new world of contract research will be exercised in support of all industry trials, in providing leadership only in major trials, or in promoting academic values and perspectives that are independent of industry. Will competition for “market share” of industry-sponsored trials drive financially hard-pressed AHCs, or will they carve out a distinct role for investigator-initiated, hypothesis-driven trials?

■ **Protection of human subjects.** This is clearly the focal point of public concern for the conduct of clinical research. Among reasons identified in the past for slower AHC patient recruitment times was lengthy IRB approval times. Turnaround times of two and three months for academic IRBs were not uncommon, even at major research institutions. The incentives existed for the development of a private, for-profit, non-university-based IRB network, especially for multisite clinical trials; and indeed, one emerged.

The attention of the HHS inspector general, the OPRR, and the

National Bioethics Advisory Committee, however, has been focused mainly on the federally funded medical research reviewed by local IRBs. This local IRB system is overburdened and increasingly under stress, so public preoccupation is understandable. Moreover, legal authority over central IRBs is exercised almost exclusively by the FDA, not by the OPRR and the NIH. However, more patients are being entered in multisite trials through the central IRB system, about which rather little is publicly known.

Although informed consent is at the heart of the system for protecting human research subjects and the principal concern of IRBs, other issues affect human subjects. These include the compensation of physician-investigators, bonuses for rapid completion of enrollment targets, disclosure of the financial relations between investigators and sponsors of trials, and the payment of subjects (volunteers and patients) for participation in clinical trials.⁴⁶ These issues also deserve attention, regardless of clinical trial sponsorship.

■ **Transparency.** This concern links all questions in the clinical-research domain. Concerns have been raised about suppression of research results by drug firms, bias in interpreting inconclusive research as a function affiliation with nonprofit or for-profit institutions, multiple reporting of the results of a single trial, and ghost authorship of articles, especially among nonacademic investigators for whom publishing is not a strong incentive.

Among the remedies suggested, the most significant is the proposal to register all clinical trials at inception, whether governmentally or privately sponsored.⁴⁷ Drummond Rennie has further argued that journals require that the trials they publish be registered.⁴⁸ Resistance to such action has traditionally come from the drug companies, which fear giving an advantage to competitors by indicating their research initiatives. But there are signs that the situation may be changing. The FDA conducted a survey of 128 drug firms to find out why more were not submitting clinical trial data to Physician Data Query (PDQ), a public-access database maintained by the National Cancer Institute. They found that many firms were unaware of PDQ and that awareness was the greatest predictor of data submission. Furthermore, concern about release of confidential information “did not appear to be a significant barrier.”⁴⁹ Schering Health Care and GlaxoWellcome have committed themselves to voluntarily registering information about Phase 2–4 clinical trials.⁵⁰

Independently, and driven mainly by patients’ demands for information, a provision of FDAMA was adopted that requires the secretary of health and human services, acting through the director of the NIH and in consultation with the FDA commissioner and the director of the Centers for Disease Control and Prevention, to “establish,

maintain, and operate a data bank of information on clinical trials for drugs *for serious or life-threatening conditions*" (emphasis added).⁵¹ Early in 2000 the National Library of Medicine (NLM) was expected to announce the establishment of a single database of all NIH trials, going beyond the requirement of the law. At approximately the same time the FDA was to have published a guidance document for industry that explains the statute and regulations and how drug firms may submit their clinical-trial data to the NLM Web site. This effort builds on a decade of experience with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) trials and cancer trials. Hopeful signs exist, then, about movement toward a more transparent system.

THE INDUSTRIALIZATION OF CLINICAL RESEARCH has been accomplished without a major train wreck. However, evidence accumulates of smaller-scale problems scattered across the vast clinical research enterprise. Concerns arise because of the rate of increase and magnitude of clinical research, the growing dominance of for-profit entities, and the limited transparency of the enterprise. It is prudent that we should at least understand these developments better so as to judge their benefits, anticipate their problems, and deal with them in advance. Simply put, it is in everyone's interest to avoid pouring new wines into old wineskins, given the high stakes associated with clinical research.

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11. Phase 1 trials seek to establish the safety of a new drug, including the safe dosage range, and typically involve a small number (twenty to eighty) of normal, healthy volunteers. Phase 2 trials constitute the initial evaluation of a drug's therapeutic effectiveness and involve larger numbers, in the range of 100 to 300 volunteer patients having the disease of concern. Phase 3 trials are done to confirm effectiveness and identify adverse effects and may involve 1,000 to 3,000 patients when the comparison is the drug against a placebo or more when the comparison is to another drug. Phase 4 trials are done after a drug is approved for marketing, sometimes in response to an FDA request for monitoring safety, often because the sponsoring firm wishes to obtain understanding of a drug in widespread clinical use, or to compare two approved drugs in order to establish the superiority of one of them.

All Phase 1, 2, and 3 clinical trials are conducted under an investigational new drug (IND) application to conduct studies of a drug in humans. The FDA requires that all of those conducting such studies file this application. Strictly speaking, an IND is not the compound itself but the application, although popular use often applies the term to the drug. Phase 3 trials provide the evidence supporting a new drug application (NDA), which the FDA must approve before a drug is introduced to the market. An NDA is a sponsor's application to the FDA for approval of a new drug for a specific clinical indication. It includes the results of all preclinical and clinical studies and is

- the basis on which the FDA decides whether to approve a drug for introduction to the market. FDA regulations governing sponsors and contract research organizations are found at 21 *Code of Federal Regulations (CFR)*, Part 312.3; those governing investigators, at 21 *CFR*, Part 312.60.
12. Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Survey, 1999* (Washington: PhRMA, 1999), 106, Table II. For the complete survey, see www.phrma.org/publications/industry/profile99/index.html.
 13. *Ibid.*
 14. Covance, "Corporate Fact Sheet, 1998" (Princeton, N.J.: Covance Inc., 1998)
 15. *An Industry in Evolution* (Boston: CenterWatch, 1997), 15; and *An Industry in Evolution*, 2d ed. (Boston: CenterWatch, 1999), 63.
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 18. Covance, *1997 Annual Report* (Princeton, N.J.: Covance Inc., 1997).
 19. D.A. Kessler et al., "Approval of New Drugs in the United States: Comparison with the United Kingdom, Germany, and Japan," *Journal of the American Medical Association* 276, no. 22 (1996): 1826-1831.
 20. See Covance, "Corporate Fact Sheet, 1998"; "The Evolving CRO Market," *CenterWatch* (1 September 1998); and *PAREXEL's Pharmaceutical R&D Statistical Sourcebook, 1999*, 9.
 21. Covance, "Corporate Fact Sheet, 1998."
 22. *PAREXEL's Pharmaceutical R&D Statistical Sourcebook, 1999*, 15.
 23. Covance Inc., Form 10-K, Annual Report Pursuant to Section 13 or 15(d) of the Securities and Exchange Act of 1934, for the fiscal year ended 31 December 1997, submitted to the U.S. Securities and Exchange Commission.
 24. *Ibid.*
 25. Industrialization is not confined to clinical trials management. It also involves firms on the leading edge of changes in trial design, such as computer-assisted trial design and clinical trial simulation software. At the other end of the pipeline, increasing contract work deals with marketing of new drugs.
 26. Covance Inc., Form 10-K, annual report for the fiscal year ended 31 December 1997.
 27. Quintiles Web site, www.quintiles.com, for 12 January and 20 April 1998 and 11 February, 22 July, and 13 August 1999.
 28. Quintiles corporate description, 11 February 1999.
 29. Information obtained from various sources, including Covance Inc., Form 10-K, annual report for the fiscal year ended 31 December 1997; a packet of Covance materials prepared for prospective investors; Covance, *1997 Annual Report*; and the Covance Web site, www.covance.com.
 30. Covance, *1997 Annual Report*.
 31. Information obtained from various documents, especially press releases and financial statements, available online at www.PAREXEL.com.
 32. On 29 April 1999 Covance and PAREXEL announced an agreement to merge, which would have vaulted the new company into first place in this growing industry. On 25 June the companies announced jointly the termination of their merger agreement.
 33. R. Ho, "Quintiles Issues Earnings Warning; Stock Plunges 42 Percent," *Wall Street Journal*, 17 September 1999, B9.
 34. *Health News Daily*, 9 September 1999.
 35. "Correcting the Public CRO Market," *CenterWatch* (1 October 1999), 1.
 36. Centralized clinical laboratory services allow consistency of laboratory methods, reagent manufacturers, and clinical trial reference ranges; equipment calibration, and standardized reporting of data.

37. B.L. Maloff, "Partnering for Success—Performance Measurements for Sponsors, Contract Research Organizations, and Site Management Organizations," *Drug Information Journal* 33, no. 3 (1999): 656.
38. "PPMs Revisited," *CenterWatch* (1 April 1999), 1; and "SMOs Chalking Up Mixed Results," *CenterWatch* (1 June 1998), 1.
39. "Ingenix Expands Worldwide Pharmaceutical Services with Acquisition of ClinPharm International" (Press release, 16 March 1999). See also www.ingenix.com/news/releases/3-16-99.html or www.unitedhealthgroup.com.
40. "Omnicare to Acquire IBAH" (Press release, 31 March 1998, available at www.businesswire.com/webbox/bw.033198/64775.htm).
41. As this paper was being revised, a colleague at then-AHCPR received a "Dear Colleague" letter (24 November 1999) from MedStar Research Institute of Washington, D.C., the research subsidiary of MedStar Health System (a merger of the Medlantic Healthcare Group with Helix Health of Baltimore), informing her of their "even stronger, more robust basic and clinical research program."
42. The OPRR was located in the Office of the Director, NIH, until July 1999, when it was moved to the Office of Public Health and Science, Office of the Secretary of Health and Human Services.
43. The Health Industry Manufacturers Association (HIMA) lists seventeen commercial IRBs on its Web site, www.himamet.com/irb.htm.
44. Public Responsibility in Medicine and Research, *Demystifying Central Review Boards: Current Options and Future Directions* (Report of the proceedings of a meeting, "Central IRB Review of Multi-Site Trials," Boston, 1999).
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46. N. Dickert and C. Grady, "What's the Price of a Research Subject? Approaches to Payment for Research Participation," *New England Journal of Medicine* 341, no. 3 (1999): 198–203. See also Letters, "What's the Price of a Research Subject?" *New England Journal of Medicine* 341, no. 3 (1999): 1550–1552.
47. R. Horton and R. Smith, "Time to Register Randomised Trials," *Lancet* 354, no. 9185 (1999): 1138–1139.
48. Rennie, "Fair Conduct and Fair Reporting of Clinical Trials."
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