# A Historical Perspective on Clinical Trials Innovation and Leadership

## Where Have the Academics Gone?

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THE RANDOMIZED CONTROLLED TRIAL (RCT), THE GOLD standard for evaluating the balance of risk and benefit in medical therapies, first emerged as a key clinical research tool in the mid-20th century thanks to visionary leadership of agencies such as the US National Institutes of Health (NIH), the UK Medical Research Council, and academic research institutions. Since then, clinical trials activity has shifted from the NIH and academia into the purviews of the medical products industry and regulatory authorities. Recent emphasis on evidence-based medicine, patient-centered outcomes research,[1] and learning[2] and accountable[3] health care systems underscores the fact that most clinical trials fail to provide the evidence needed to inform medical decision making. However, the serious implications of this deficit are largely absent from public discourse, and a better balance between commercial interests and public health is critically needed.

In this context, the word "academic" describes a diverse group of individuals exploring scholarly questions, with motivations arising not from pursuit of profit but from an interest in the public health. The wellsprings of such activity should reside in the NIH and other federal research agencies, coupled with external grantees—most of whom work in the nation's academic health and science systems.

The primary mission of academic health and science systems, as required by their not-for-profit status, places public health interests above return on investment to specific investors. This in no way disparages the motivations of the many excellent scientists working in industry or in the US Food and Drug Administration (FDA) that regulates its products. On the contrary, the development and appropriate use of medical technologies are vital to the public health. However, it is important to remain mindful that decisions affecting for-profit research will reflect fundamentally different priorities than those of academic researchers. In a sense, the academic enterprise seeks a "return on investment" for taxpayers who grant (and support) its nonprofit status. Thus, while all researchers are bound by the same standards when conducting human studies, the fundamental questions addressed will differ, and failure on the part of academia to increase its involvement will have predictable consequences.

When fundamental trials methodologies were being developed at the NIH in the 1960s, an NIH-commissioned task force delineated recommendations for organizing and conducting RCTs.[4] One significant early example is the Coronary Drug Project,[5] a joint effort among NIH sponsors, an academic coordinating center, and a steering committee of academic leaders. In the 1970s and 1980s, the NIH often convened academic leaders to identify knowledge gaps and prioritize and conduct specific trials as funding permitted.

During the 1960s, there was scant statistical literature examining clinical trials methodologies. Researchers learned by doing trials, noting successes and failures, and iterating to advance the field. In a series of discussions in the 1970s, ideas were debated and solutions to immediate problems were proposed.[6] Throughout the 1970s and 1980s, NIH and academic biostatisticians developed many methods now in routine use, including sample size estimation, interim data monitoring, and repeated measure methods for analysis.

At the outset of this era, few large randomized clinical outcomes trials were sponsored or conducted by industry. Meanwhile, the FDA was developing biostatistical teams to support review of new drug and device applications and increasingly demanded RCTs, often with clinical outcomes end points, as the standard for approval and labeling. By the early 1990s, academia was working with industry to lead and conduct clinical trials, using a modification of the NIH organizational structure.[7] While some fields developed this hybrid model of academic leadership in industry-sponsored RCTs, most industry trials evolved in a different direction and were designed by industry scientists in concert with regulators, often with little or no independent academic input.

As the clinical trials enterprise grew, statistical principles mandated adequate sample sizes to provide power for detecting typically modest differences in clinical outcomes. Concurrently, the enterprise's rapid expansion, coupled with egregious instances of fraud or lapses in quality, resulted in the implementation of auditable data systems. This confluence of factors spurred massive increases in clinical trial costs.[8]

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Research agendas in the pharmaceutical industry were also evolving during this period. In the 1980s, an alignment of interests between science and industry meant that pharmaceutical research typically focused on diseases lacking adequate treatments, assuming that this would translate into commercial success. However, ever-increasing drug development expenses, driven partly by trial costs, drove companies to seek "blockbuster" drugs with enormous earnings potential. This in turn yielded an emphasis on highly prevalent diseases and widely applicable treatments, and "orphan" diseases were neglected as targets for drug discovery. The sales threshold for blockbuster drugs increased from $500 million to more than $1 billion,[9] setting the stage for major conflicts among the commercial goals of industry, the public health mission, and overarching needs to improve trial methodology.

As clinical research has drifted from its early public health orientation and toward RCTs as a business, trial methodologies, including statistical methods, quality-control standards, and data monitoring and analysis procedures, are now largely shaped by imperatives to develop new approved products (or increase sales of existing products) while meeting regulatory requirements. Industry now drives much of the design, conduct, and analysis of trials, while academics are often relegated to comparatively minor roles. Contract research organizations have arisen to provide efficient trials conduct according to current practices, rather than furthering innovation in trial design and conduct. In some cases, trials have been terminated by sponsors for commercial reasons, leaving public health questions unanswered.[10] In such situations, academic investigators and participants have little recourse, and a counterpoise to commercial interests is essential.

With the advent of national health care reform, payers and advocacy groups have emerged as major players. Interest in comparative effectiveness research is rapidly coming to the fore as costs increase. Soon, in addition to demonstrating effectiveness and safety, new interventions most likely will have to demonstrate reasonable costs compared with alternatives to gain approval—a requirement not currently part of NIH or FDA mandates, but inevitable as payers are increasingly constrained.

Insurance providers, private or public, have not actively participated in clinical trials and thus have missed sharing in decades of experience and methodological development. Here, then, is an opportunity for the academic community and the physicians and researchers trained in academic health and science systems—who must live with the costs of interventions in daily practice—to assert pivotal roles in the design, conduct, analysis, and interpretation of comparative-effectiveness trials.

Even greater challenges are posed by the growing congressional interest in clinical trials, the need for independent, unbiased conduct of research and evaluation of results, and the potential influence of conflicts of interest. The academic community has failed to adequately educate the public and Congress about the strengths and limitations of clinical trials—what information can be obtained reliably; the dangers of insufficiently rigorous research designs. To realize the potential of a rejuvenated clinical trials enterprise will require development of approaches to conflict-of-interest management that convince both Congress and the public that academia is acting for the public's benefit.

The NIH and the nation's academic health and science systems (and their schools of medicine and public health) should work to reinvigorate the academic clinical trials enterprise. The newly formed National Center for Advancing Translational Sciences can, through the Clinical and Translational Science Awards, leverage support for academic homes for trialists at most academic institutions, where new methods can be developed, trials can be conducted, and new generations of researchers and statisticians can be trained.

If academics do not assert leadership in clinical trials, they will remain minor players carrying out someone else's research, chairing steering committees or putting their names on manuscripts in which they have had little input. Without significant, vigorous academic involvement, critical issues may go unaddressed, diseases may be neglected, and important trials may never be conducted. The results will be needless delays in public health improvements and increased morbidity among patients whose health needs may go unstudied and unaddressed within a profit-oriented system.

**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr DeMets reported receiving compensation for consulting and for serving on data monitoring committees for many pharmaceutical, biotechnology, and device companies and for government agencies and receiving honoraria or royalties for books or book chapters. A complete listing of disclosure information for Dr Califf is available at https://dcri.org/about-us/conflict-of-interest/Califf-COI_2010.pdf. Both authors are employees of academic health and science systems.

**Additional Contributions:** We wish to thank Judith M. Kramer, MD, MS, of the Clinical Trials Transformation Initiative and the Duke Translational Medicine Institute for reviewing and making numerous valuable contributions to this article. Dr Kramer did not receive any compensation for her efforts. We also thank Jonathan McCall of the Duke Clinical Research Institute for editorial assistance with this article as part of his paid role as editor.

## REFERENCES

**1.** Clancy C, Collins FS. Patient-Centered Outcomes Research Institute: the intersection of science and health care. *Sci Transl Med*. 2010;2(37):cm18.
**2.** Olsen LA, Dara Aisner D, McGinnis JM, eds. *Institute of Medicine Roundtable on Evidence-Based Medicine: The Learning Healthcare System (Workshop Summary)*. Washington, DC: National Academies Press; 2007.
**3.** Fisher ES, McClellan MB, Bertko J, et al. Fostering accountable health care: moving forward in medicare. *Health Aff (Millwood)*. 2009;28(2):w219-w231.
**4.** Organization, review, and administration of cooperative studies (Greenberg Report): a report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967. *Control Clin Trials*. 1988;9(2):137-148.
**5.** Coronary Drug Project Research Group. The Coronary Drug Project: design, methods, and baseline results. *Circulation*. 1973;47(suppl 1):11-179.
**6.** Friedman L, Furberg C, DeMets D. *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer; 2010.
**7.** Fisher MR, Roecker EB, DeMets DL. The role of an independent statistical analysis center in the industry-modified National Institutes of Health model. *Drug Inf J*. 2001;35:115-129.
**8.** Eisenstein EL, Collins R, Cracknell BS, et al. Sensible approaches for reducing clinical trial costs. *Clin Trials*. 2008;5(1):75-84.
**9.** DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22(2):151-185.
**10.** Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. *JAMA*. 2003;289(16):2128-2131.