CLINICAL RESEARCH

A Radical Proposal: Integrate Clinical Investigation into the U.S. Health Care System

Richard A. Rudick[1,2]* and Delos M. Cosgrove[3]

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The health of the public depends on a healthy clinical research enterprise, and a healthy clinical research enterprise cannot develop if it is disconnected from the clinical care enterprise. The integration of a robust clinical research enterprise into the U.S. health care system is now, more than ever, a national priority, and a completely new approach is desperately needed.

Even in the face of the politically polarized U.S. health care debate, there is near-universal agreement among policy-makers regarding the importance of health promotion and disease prevention, the use of evidence on which to base health care decisions, and the translation of innovations and new knowledge emanating from the nation's biomedical research enterprise. Advances in these areas are driven by academic medicine and by the clinical investigator who, despite new training programs, remains the endangered species described by Wyngaarden 30 years ago (*1*). This deficiency did not arise because potential new investigators are uninterested in research—training opportunities have been well received. Here we argue that the clinical investigator remains endangered because (i) our academic medical centers have no clearly defined, formal career track for these individuals, and (ii) the clinical research enterprise is, by and large, divorced from the clinical care enterprise, creating innumerable complex barriers to clinical investigation.

THE IMPORTANCE OF CLINICAL INVESTIGATORS TO OUR HEALTH CARE

Clinical investigation is that component of biomedical, social, and behavioral science that is performed in order to understand human disease, prevent and treat illness, and promote health (Fig. 1). It is a continuum that involves patient populations and clinical materials and includes studies of disease mechanisms, detection, diagnosis, and natural history; epidemiology; experimental therapeutics (including clinical trials); disease prevention; health promotion; behavioral sciences; health services research; treatment effectiveness research; and health economics. Translational research refers to research that moves across boundaries and has been traditionally defined as "bench-to-bedside" research, in which findings from the laboratory are applied to research subjects. More broadly defined, translational research represents a variety of studies that move across traditional boundaries; for example, from the laboratory to the clinic, or the reverse; from medical center patients to the community; or from epidemiology to health policy.

For research that involves patients or healthy control individuals, clinical investigators are the crucial final link between research and clinical care. Clinical investigators have knowledge and experience in dealing with medical conditions and wellness, but they also need expertise and skill sets related to the discipline of clinical investigation (Table 1). The difference between the expert clinician and the clinical investigator was recognized by the U.S. National Institutes of Health (NIH) when it created the Clinical and Translational Science Award (CTSA) program, which includes postdoctoral career development for clinical investigators. Indeed, one of the main reasons why NIH launched the CTSA program in 2006 was to spur the development of clinical investigation into a distinct career specialization that crosses professional and medical disciplines (*2*).

Clinical research is the engine that drives progress in medical practice, and a vigorous and effective clinical research enterprise is a necessary prerequisite for better understanding of health and disease and for effective application of the rapidly expanding knowledge bases in the biomedical and social sciences to human populations. Thus it seems self-evident that the health and well-being of our nation critically depend on the vitality of our clinical research enterprise. At a time when the United States is expending more than $2.4 trillion per year on health care, expenditures are rising rapidly, and the nation is contemplating changes to the health care system, it is essential that we include a vision for a strong clinical research enterprise as a major component in our planning.

CHALLENGES FACING THE CLINICAL INVESTIGATOR

Despite its fundamental importance, the clinical research workforce has been in jeopardy since 1979, when Wyngaarden documented a dramatic decline in the number of M.D.s entering postdoctoral research training and a steady decline in the percentage of research grants led by principal investigators with an M.D. degree (*1*). Since then, the NIH Directors Panel on Clinical Research (1995), the Association of American Medical Colleges (AAMC) Task Force on Ensuring the Future of Clinical Research (2000), the Institute of Medicine's Clinical Research Roundtable (2003), the NIH Roadmap Initiative (2004), and the AAMC Task Force II on Clinical Research (2006) have studied these problems and recommended solutions.

The AAMC Task Force II on Clinical Research emphasized the lack of research curricula in predoctoral and medical school programs (*3*). They recommended that the Liaison Committee on Medical Education require training in translational and clinical research for medical school accreditation and that the Accreditation Council for Graduate Medical Education add competency in clinical research to other competencies required for postdoctoral specialty training. These recommendations were adopted in 2008 with the goals of inculcating an appreciation for clinical research within medical training itself, and in many instances, accelerating clinical research training for students interested in a clinical research career. This is important, because the length of clinical training and the advanced age at which clinical investigators begin research careers have been noted repeatedly. As Dickler *et al.* pointed out, even for students not interested in a research career, research training is crucial in order to prepare clinicians to read and interpret the medical literature, communicate with clinical investigators, ex-

[1]Department of Neurology, Cleveland Clinic, Cleveland, OH 44195, USA. [2]Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH 44195, USA. [3]Cleveland Clinic, Cleveland, OH 44195, USA.
*Corresponding author. E-mail: rudickr@ccf.org

plain clinical and translational research to patients and refer them for clinical trials, advocate for clinical and translational research to the public, and generally participate in clinical research programs (*4*).

The funding challenges facing clinical investigators have been repeatedly emphasized and are especially worrisome. As clinical revenue margins have contracted, clinical investigators have faced an increase in clinical demands, and academic medical centers have been less able to shift revenues from clinical operations accounts to research projects. Investigators are faced with the daunting challenge of funding their research careers project by project through applications to public and private research funding organizations. This has occurred at a time when competition for research funding is fierce and when clinical investigation is at a competitive disadvantage. As Dickler and colleagues report (*5*), over the past 40 years, physician-scientists with only an M.D. degree have been significantly ($P < 0.05$) less successful than their Ph.D. counterparts in obtaining an initial R01 grant. Of those M.D. investigators who were successful, they were significantly ($P < 0.05$) less likely to obtain a subsequent R01. This finding is especially alarming because M.D. investigators are much more likely to propose clinical research in their grant applications than are their Ph.D. counterparts, and first-time M.D. applicants proposing clinical research are less likely to receive funding than first-time M.D. applicants proposing basic, nonclinical research (*5*). These findings suggest a systemic imbalance in funding for physicians proposing clinical research projects. As a result, many well-trained clinical investigators leave the research field for clinical practice or to enter industry.

Additional factors thought to threaten the clinical research workforce include a dearth of clinical research mentors, ever-increasing clinical demands, significant debt after finishing medical school, an ever more complex regulatory environment, concerns about conflicts related to the relationship between academic investigators and industry, and loss of talent to the pharmaceutical industry.

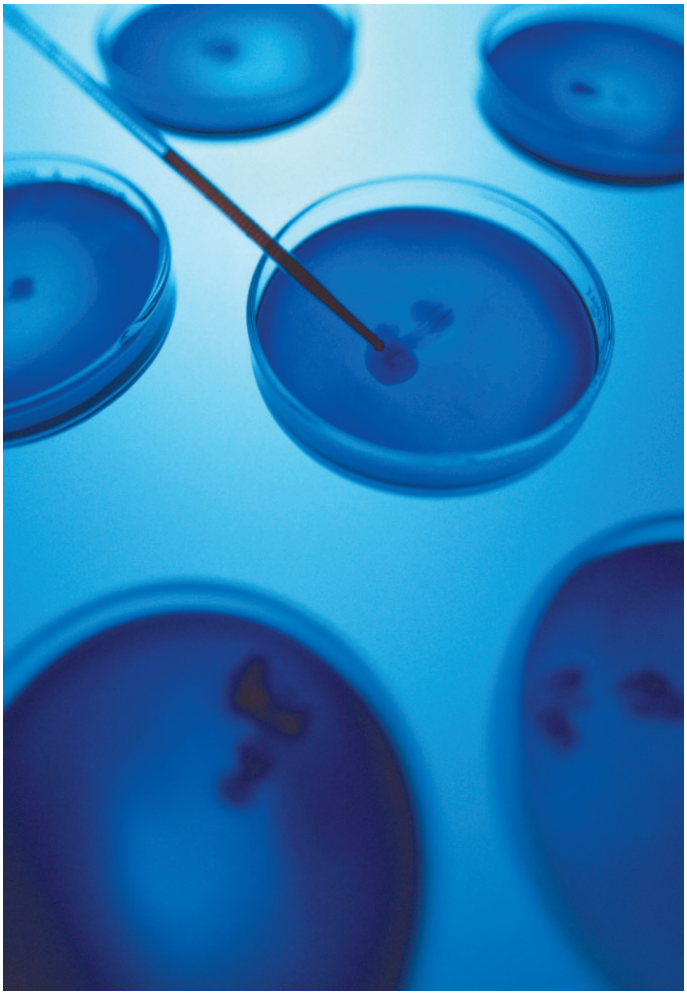

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Fig. 1. Better than an apple a day: A robust clinical research enterprise.

THE RESPONSE AND OPPORTUNITIES CREATED

Much of the response to concerns about the clinical investigator has focused on building the clinical research workforce. New initiatives include the physician loan repayment program, which partially alleviates an economic disincentive for physicians to enter research careers (*6*). The Clinical Research Curriculum Award [the NIH K30 program (*7*)] established clinical research education and training programs at medical centers across the United States, leading to many master's-level degree programs in clinical research. The Mentored Patient-Oriented Research Career Development Award (the NIH K23 program) and the MidCareer Investigator in Patient-Oriented Research Award (the NIH K24 program) were designed to train clinical investigators (K23) and to provide support for mentors (K24). Between 2000 and the present, many clinicians have dedicated 5 additional years of their careers to serious clinical research training through these programs.

Re-engineering of the clinical research enterprise was a key focus of the NIH Roadmap for Medical Research (*8*), and central to that effort was development of the clinical research workforce of the future. The Roadmap emphasized the need for a multidisciplinary clinical research workforce that includes physicians, dentists, nurses, dieticians, epidemiologists, and biostatisticians and informatics specialists, among others. It also emphasized multidisciplinary team-oriented research and dissemination of the research enterprise at the community level (*9*). One particularly important consequence of the NIH Roadmap was the development of the Multidisciplinary Clinical and Translational Research Training Program (the Roadmap K12 Program), which was later incorporated into the larger CTSA program.

In parallel to the growth of the clinical research workforce, knowledge has exploded in genetics, imaging, systems biology, bioengineering, nanotechnology, and many other fields. Electronic health record technology (*10*) is developing rapidly, and the interface with electronic research records will not be far behind. A comparative effectiveness agenda has begun to emerge that the federal government has recognized as being key to both improving the nation's health and reforming health care: $1.1 billion was authorized for comparative effectiveness research as part of the American Recovery and Reinvestment Act. Comparative effectiveness research is badly needed. Patients commonly receive expensive tests and treatments despite a lack of data that show the value of the test or treatment. On the other hand, commercial

Table 1. Areas of expertise required for the clinical investigator.
Ability to formulate clinical research topics that focus on important, testable questions
Ability to review and synthesize the literature
Ability to design feasible research studies to address the questions
Ability to implement research protocols
Ability to recognize and avoid sources of error
Ability to manage large volumes of clinical data
• acquisition
• storage
• quality control
Ability to appropriately analyze, interpret, and report research results
Knowledge about ethical and regulatory issues, including but not limited to
• informed consent
• protection of vulnerable research populations
• adverse event monitoring and reporting
• compliance with research billing
• conflicts of interest
• standards of authorship

insurance often rejects coverage for educational programs or other multidisciplinary treatment approaches simply because data demonstrating effectiveness are not available. Clinical research is the only way to answer questions of effectiveness. Some have called for a new clinical research science that is aimed at defining "value" in health care (*11*).

The programs described above have resulted in an emerging workforce fully capable of addressing the crucial questions of effectiveness and value and of introducing new knowledge and technologies into medical practice, but major barriers remain to implementing such developments to improve the public health.

WHAT ARE THE BARRIERS?

Despite the opportunities and urgent need for a robust national clinical research enterprise, this endeavor is threatened for two reasons. First, there is no stable career path for the clinical investigator within our teaching hospitals and medical schools. The appointment, promotion, and tenure systems recognize and reward individual scientists who conduct basic biomedical research in preference to team-based clinical investigators, and there is no defined career track with secure funding for the clinical investigator within the health care system itself. Clinical investigators must meet the challenge of seeking funding for clinical research, project by project, while simultaneously navigating the numerous complex systems related to clinical research. The funding challenges for clinical investigators have been discussed repeatedly, but no proposed solutions have been implemented.

Second, the clinical research enterprise and the clinical care enterprise have evolved along largely separate pathways and are consequently disconnected at numerous levels, creating near-insurmountable obstacles for the clinical investigator. We have developed separate accreditation mechanisms, human protection mechanisms, medical and research record systems, adverse and sentinel event reporting methods, compliance offices, billing offices, contracting offices, and financing structures (Table 2). The result is that we have two completely separate enterprises. This is unfortunate, because the patients are the same people as the research subjects, the health care professionals are the clinical investigators, and clinical and research visits often occur at the same time and in the same room, but the clinical and research visit "events" are completely separated at multiple levels administratively and procedurally.

Academic medical centers have dealt with this problem by creating separate research offices, which generally have little to do with hospital or medical practice administrative offices. Some have segregated clinical research to research units within hospitals or to separate floors or research buildings. The clinical investigator can be bewildered by two separate sets of rules and regulations, two separate sets of administrative offices, and minimal administrative help on the clinical research side.

There is little doubt that just navigating the byzantine interface of the clinical research administrative infrastructure discourages those seeking a career in the field. Not only does the clinical investigator have to dedicate increasing amounts of time to funding his or her research career while also meeting increased patient care demands, but the investigator must also devote tremendous amounts of time to addressing the administrative maze of the clinical research and patient care structures.

A RADICAL PROPOSAL

We need a national plan in the United States to effectively integrate the enterprises of clinical research and patient care at every level. Integration could minimize or even eliminate a major disincentive for those who want to pursue a career in research. Clinical investigators must become central to the mission of health care, and we must create a culture of analysis and continuous improvement. We need a new model in health care—one that is much more efficient and effective and is constantly evolving based on evidence that is produced by the system itself. We need continuous introduction of incremental and innovative treatments, powered by data concerning the delivery systems, insurance coverage methods, effectiveness, and costs and benefits of care. This can only be accomplished by establishing an attractive career for clinical investigators within the health care system and by integrating research and care at the financing, regulatory, and administrative levels. The

Table 2. Separate infrastructure for clinical research.
Accreditation bodies and standards
Research record systems
Human protection methods
Adverse event–reporting methods
Compliance programs and offices
Research billing offices and procedures
Research contracting offices
Research financing and accounting
Conflict of interest procedures

two systems cannot operate effectively as two separate worlds, because the quality of care provided by the U.S. health care system critically depends on the health and vitality of U.S. clinical research, and vice versa.

This fundamental problem has received almost no discussion, although some have alluded to it. The AAMC Task Force I on Clinical Research stressed that "clinical research lies at the interface of the medical school and its affiliated clinical delivery system" and emphasized how academic health systems must have a strategic plan for integrating clinical investigation into the medical education and health care delivery enterprises, noting that the organizational complexity of health care systems is a barrier that has to be overcome (*12*). For the most part, such integration has not occurred.

Horig *et al.* (*13*) recommended "radical change in the practice of health care delivery … so that the public can benefit from modern, interactive and educated approaches to personalized health care," but did not specify what the radical changes might be. Others have suggested national bodies for biomedical research policy and the promotion of clinical and translational investigation and, in particular, new funding strategies (*13*–*17*). However, these efforts principally address investigator-funding issues and do not address the need to integrate clinical research with the health care system. Crowley *et al.* suggested that 0.25% of the budgets from health care stakeholders would be adequate to support a public/private partnership—the National Clinical Research Enterprise—and would enable the creation of the national infrastructure needed to transform clinical research into a national enterprise that would serve the public health (*14*). This idea comes closest to a mechanism to integrate clinical research with the health care system.

We propose that the U.S. Congress commission the Institute of Medicine to study the issue of clinical research and health care integration and make specific recommendations. These directives should include approaches to harmonizing the regulatory environments, creating a financing system for investigators, and developing methods for setting research priorities and funding high-priority projects. Without radical change leading to effective integration, clinical investigators will continue to struggle, and opportunities to improve human health will go unfulfilled. Indeed, clinical research may remain "a fragmented cottage industry … with no overarching vision, no cohesive organizational framework, and at times not even a common forum for dialogue or active collaboration" (*14*). Effective integration and financing can position the U.S. clinical research enterprise to serve the health needs of the public by providing a rapid mechanism for the application of new knowledge and technology to human populations, and for the gathering of evidence on which to base crucial decisions about the effectiveness of health care interventions, health care delivery systems, and the myriad medical services currently available.

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