Clinical Research in the United States at a Crossroads
Proposal for a Novel Public-Private Partnership to Establish a National Clinical Research Enterprise

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FOR OUR NATION’S HEALTH, THE NATIONAL health of the United States, it is simultaneously the best and worst of times. As promised, the Human Genome Project is regularly delivering remarkable insights into human disease that are now driving accelerated development of novel therapies. Doubling the budget of the National Institutes of Health (NIH) has restored its productivity from the slowed momentum due to relative underinvestments in the 1990s. Public expectations are increasing with the hope that the translation of these new basic insights into the public’s health care is imminent. On the other hand, 44 million US citizens have no health care insurance. According to the recent surgeon general’s report on oral health in America (2000), 108 million US individuals do not have dental insurance. Increasing state deficits force reductions in public investments in health care for the poor, and academic health centers (AHCs), which deliver a disproportionate share of their care, are under major economic stresses. Health care costs continue to increase at double-digit paces accompanied by in-

The clinical research infrastructure of the United States is currently at a critical crossroads. To leverage the enormous biomedical research gains made in the past century efficiently, a drastic need exists to reengineer this system into a coordinated, safe, and more efficient and effective enterprise. To accomplish this task, clinical research must be transformed from its current state as a cottage industry to an enterprise-wide health care pipeline whose function is to bring the novel research from both government and private entities to the US public. We propose the establishment of a unique public-private partnership termed the National Clinical Research Enterprise (NCRE). Its agenda should consist of informed public participation, supportive information technologies, a skilled workforce, and adequate funding in clinical research. Devoting only 0.25% of the budgets from all health care stakeholders to support the NCRE would permit adequate funding to build the infrastructure required to address these problems in an enterprise fashion. All participants in the US health care delivery system must come together to focus on system-wide improvements that will benefit the public.

JAMA. 2004;291:1120-1126 www.jama.com

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creasing economic uncertainties.\textsuperscript{7} Influential scientific leaders are now demanding radical solutions to these impending problems.\textsuperscript{7,8} Amidst all this turmoil, the translation of basic research to public health (i.e., the clinical research process), with its implicit promise of alleviating human suffering, is increasingly emerging as a bottleneck in the national health of the United States.\textsuperscript{9,10}

During the past 3 years, the Clinical Research Roundtable (CRR) of the Institute of Medicine has had an ongoing dialogue about these issues. This article, authored by likeminded members of the CRR, represents our interpretation of these ongoing deliberations. Recently, we conceptualized the challenges facing the clinical research of the United States as 2 translational roadblocks and ascribed the solution to various health care system stakeholders (Figure 1).\textsuperscript{9} The first is the traditional “bench-to-bedside” transfer of basic discoveries into human testing. The second is the difficulty implementing therapeutic advances proven effective in large well-conducted trials into the daily practice of medicine.\textsuperscript{11-13} The first block, traditionally a domain of the NIH, research universities, and human translational programs within AHCs, biotechnology, and pharmaceutical arenas, has improved with the doubling of the NIH budget. Reengineering clinical research is one of the top priorities of the new NIH director.\textsuperscript{14}

The NIH’s heightened awareness of these problems has set a new and hopeful tone. More problematic, however, is the lack of a clear system-wide plan to address the second translational block that is so deeply embedded within the US health care delivery problems and that currently has limited infrastructure.

As a result of some of the past 3 years of CRR activities, we conclude that the clinical research effort in the United States must be seen for what it is—a fragmented cottage industry constituted of multiple stakeholders, some of whose funding is derived from governmental sources and others from industry, with no overarching vision, no cohesive organizational framework, and at times not even a common forum for dialogue or active collaboration. The current poorly articulated and highly compartmentalized components of the existing nonsystem are inefficient and often redundant. Hence, they diminish effectiveness and increase costs of translating basic research to patient care while often not contributing materially to its safety or efficiency.

Most importantly, this existing but outdated infrastructure, put in place nearly 40 years ago to support a much narrower and less professional spectrum of clinical research activities, is currently functioning on overload. The US capacity to translate basic science into improved health care for its population is rapidly being exceeded by the burgeoning scientific opportunities at hand. Basically, the “clinical research grid” is failing.

On the other hand, this is precisely the moment that a cohesive and coherent national clinical research enterprise could be an unimagined, powerful, and empowering mechanism to bring basic science more quickly into the everyday management of disease. The potential contemporary ability to alleviate human suffering through clinical research, integrate many disciplines into this noble endeavor, and make it broad-based and inclusive of the growing minority populations and scientists is simply an unparalleled biological opportunity born from the successes of the Human Genome Project, among other advances. A new and vigorous mechanism for improving the national health care must be devised.

These problems, particularly the second translation block, which prevents the rapid transfer of well-proven therapeutic interventions into routine medical care, are not owned by anyone, yet they are clearly enmeshed within the complexities of financing the nation’s failing health care delivery system. Only a well-functioning, fully integrated, efficiently standardized, safe, and highly

\textbf{Figure 1. Two Translational Roadblocks on the Way Toward Improved Public Health}

Clinical research can be viewed as encountering 2 separate roadblocks on the way toward improving public health. These 2 translational blocks have different factors creating each but whereas the National Institutes of Health has been consistently targeting the bench-to-bedside block, no one is taking responsibility for the second, which is integrally tied with the funding of the health care delivery system.
Figure 2. Organizational Chart of the National Clinical Research Enterprise

Figure 3. Proposed Interrelationships Between the National Clinical Research Enterprise and Health Care Stakeholders

To be effective, the National Clinical Research Enterprise must interact with and respond directly to representatives from the full spectrum of health care stakeholders.

collaborative human research system will overcome these 2 looming translational blocks, an ideal we refer to as the National Clinical Research Enterprise (NCRE). In keeping with recent requests for radical solutions, we propose to reinvigorate the US clinical enterprise to serve our nation’s current and future needs.55 We intentionally put forth a provocative proposal to raise awareness of our calamitous view of this problem, stimulate discussion, elicit reactive actions, and hopefully move the public dialogue forward toward more viable solutions.

Establishment of an NCRE and a Board of Directors

We envision a new entity, the NCRE, constituted as a unique public-private partnership and designed to address the following mandates: (1) to provide a unique national forum for participatory discussions, integrated deliberations, and most importantly collective actions involving all governmental and private stakeholders in clinical research; (2) to set and maintain national standards to improve the safety and efficiency of clinical investigation simultaneously—goals that are not only compatible but also mandatory to address in parallel; and (3) to coordinate activities, create incentives, and directly fund construction of an up-to-date, seamlessly integrated, and continuously improving national clinical research infrastructure to sustain efficient and safe transfer of basic research into practice to improve the future health of our nation (FIGURE 2).

Establishment of a Unique National Forum

To accomplish this task, participants in the NCRE and its executive board of directors (FIGURE 3) should include representatives from the full spectrum of both governmental and for-profit health care stakeholders, not just participants from AHCs and conventional government organizations. Ideally, these should include AHCs; allied health care professionals, including nurses, biostatisticians, behavioral biologists, clinical investigators, dentists, community health organizations, and individual community representatives; government representatives from Agency for Healthcare Research and Quality, Department of Constitutional Development, Centers for Medicare and Medicaid Services, Department of Defense, Food and Drug Administration, NIH, and Department of Veterans Affairs; health care payers, including traditional deliverers; industry representatives from biotechnology, device, and pharmaceutical industries; information technologists; nongovernmental foundations interested in clinical research; professional societies representing practicing clinicians, clinical investigators, or both; and most importantly, patients and disease advocacy organizations.

Before the establishment of the CRR by the Institute of Medicine, no forum existed for such collegial discussions
and potential collective actions. However, all current participants are now impressed by the CRR’s ability to convene, educate, dialogue, and alter relatively fixed opinions by careful analysis and thoughtful advocacy within parent organizations. Ultimately, these deliberations have resulted in several individually authored publications that have defined the problems and suggested solutions to the current roadblocks in clinical research. Thus, the CRR can be a model for the NCRE.

**Functions of a Board of the NCRE.**
An executive committee of the full board of the NCRE could be established to coordinate and execute all NCRE efforts (BOX). Accordingly, both the full board and its executive committee need to be equitably constituted of representatives from the stakeholders in a fair and rotational basis. The NCRE board should bring to its task an integrity derived directly from its neutrality, equity, and objectivity. It should demonstrate cogent and thoughtful policy analysis and an articulate advocacy for changes in the system’s clinical research. However, analysis and advocacy go only so far; the NCRE would need to act (ie, to fund systematic improvements in the system directly). To do this, new funding is required that is additive to and noncompeting with already existing traditional funding sources.

Actively engaging busy leaders from all health care organizations is difficult but should follow from one central truth. Acting individually, no participant organization has been able to solve the current problems; only collective action offers a chance to effect the types of overarching, dramatic changes that are necessary. Participation in any cooperative organization uniformly involves some sacrifice of individual autonomy. Presumably, such a loss of autonomy will be outweighed by a unique national leverage obtainable only through collective action. For example, fostering collaborative establishment of national standards for clinical research vocabulary, databases, and information technologies in clinical research is currently not possible and would be a logical starting point for an NCRE board. Secretary of Health and Human Services Tommy G. Thompson recently announced a National Healthcare Information Initiative designed to standardize health care information technology that he believes could save at least $100 billion a year. This announcement represents an outstanding example of an initiative in which an NCRE, if it existed, could easily graft onto a clinical research infrastructure with benefit to all at marginal additional costs.

**Accountability.** The NCRE would need dual accountability both to the public and to its constituent member organizations to be successful. Although public accountability would be a unique driver of involvement in any collective action, responsiveness to individual parent organizations will be necessary to ensure continued authority and resources to provide the needed leverage to change the status quo. The constituency and functioning of the current CRR is an example of how such a multidisciplinary board can function. All participants accommodated to the collective insights derived from the other individual members’ perspectives, needs, and concerns. This consensused-driven dialogue has been essential groundwork for the more significant changes we envision in proposing this unique public-private partnership.

**Agenda.** The NCRE should target only those issues critical to the enterprise’s success that require multiple stakeholders for a solution. In broadest terms, these are 2 distinct areas: overseeing and integrating the nation’s diffuse and inefficient investments in clinical research, and channeling adequate funding into peer-reviewed projects to implement changes necessary for a safer, more efficient, and self-sustaining NCRE. We recently outlined 4 distinct areas that would prove a worthy agenda for such a public-private partnership: (1) increasing public understanding, confidence, and participation in clinical research; (2) developing an adequately trained and diverse workforce and maintaining the individuals in an environment that nurtures their ongoing career development; (3) improving the US biomedical informatics base for clinical investigation; and (4) funding this innovative clinical research enterprise.

The public’s participation in clinical research is threatened by concerns over

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**Box. Vision of the National Clinical Research Enterprise (NCRE) Board**

**Structure**
The NCRE board should represent all entities and organizations performing and benefiting from clinical research.

It should have the independence to ensure that the needs of all stakeholders are considered.

Its activities should be funded in an equitable manner across all system stakeholders.

It should be formally connected to accountability mechanisms within all stakeholder groups.

**Function**
The NCRE board should actively catalyze, facilitate, and fund cross-sector collaboration that addresses the 2 translational blocks: translation from laboratory bench to clinical trials and translation from clinical trials to community issues of public confidence in clinical research.

Facilitate development and standardization of informatics approaches to data gathering, adverse event reporting, and public access.

Address clinical research workforce needs.

Ensure effective stewardship via a 0.25% investment in clinical research from across the entire health sector.
understanding safety, privacy, and conflicts. Building a more efficient, patient-oriented, and safer clinical research infrastructure is clearly a necessary change that will require all stakeholders to agree on standards, to integrate them into their workflow, and to sustain them over time. Funding proper public service advertisements about involvement in clinical research and promulgating clear information on its safety are examples of important initiatives that could be funded by the NCRE. A vibrant NCRE could also ensure a sustainable pipeline of well-trained clinical researchers by catalyzing novel funding partnerships between the public and private sectors, in part by providing a unique forum for ongoing discussions between these groups and in part by direct funding of gaps that exist between other organizations.

Developing new integrated clinical research training programs, which incorporate private sector participation, establishing new shared core facilities, constituting and rewarding multidisciplinary teams, and incorporating outcomes research into clinical trials are all examples of long-term objectives that are currently difficult if not impossible to achieve to a substantial degree, yet could be catalyzed by the NCRE. The convening power of the NCRE board could also assemble the public and private sectors to design new favorable mechanisms for evoking further investments in clinical research from its for-profit members, such as tax incentives.

Funding: The 0.25% Solution. The accurate estimate of the cost of this innovative agenda of revitalizing the US clinical research infrastructure is not known. However, any national investment in an NCRE should be commensurate with the expectations of our nation’s population for improved health as a result of their sustained investment in basic biomedical research, incremental in nature during a 5-year period, and contingent on demonstrable progress toward agreed-on stated goals.

Given the long underinvestment in clinical research infrastructure in the United States, an additional 0.25% of the total current national health care budget is approximately the estimated magnitude of investment needed to address the NCRE’s agenda. This level of investment assumes that the National Healthcare Information Initiative of the Secretary of Health and Human Services is funded at the levels that were suggested as a foundation for the changes proposed.9 Such investment is not without national precedent. It is analogous in direction if less in magnitude to Canada’s remarkably successful 1% commitment to reinvigorate that nation’s biomedical research efforts.23 In addition, this benchmark investment would bring the health sector in line with research and development investments made by other US industries and with investments in basic biomedical science. For example, major chemical companies spent more than 3.6% of sales on research and development in 2000, although pharmaceutical companies spend a significantly higher percentage (approximately 17%).24

Although there is no widespread agreement among CRR members on the mechanism by which such an investment would be mandated, several suggestions could be considered. Contributions to this “0.25% solution” could be both in-kind as well as through direct support of training and infrastructure in areas of high priority to individual stakeholders with the provision that they must benefit the entire enterprise. Investments could be rewarded through tax credits to deliver competitive advantages to its participants.

Some organization members already expend more than 0.25% of their budgets on clinical research and its infrastructure and thus might not be required to add additional moneys. Presumably, they would still be eager to participate in the NCRE to synergize and leverage their existing heavy investments with other participants. For example, the NIH and Centers for Disease Control and Prevention currently devote substantial percentages of their budgets to clinical research. However, these governmental agencies and their investments currently have little influence on nor ability to effect the requisite changes in the private sector essential to ensuring that their findings can translate and impact as broadly on patient care as they wish.

Other organizations (eg, Centers for Medicare and Medicaid Services) currently have no existing mechanisms to make such a contribution whereas others (eg, health care providers and health maintenance organizations) view such a commitment as a “user tax” making them noncompetitive and adding to the escalating costs of health care. However, all organizations need to calculate their annual expenditures attributable to the current inefficiencies of the system and compare them with these proposed investments. Such ongoing “costs of non-investment” probably substantially exceed 0.25% of their budgets. However, recognizing the legitimacy of many of these fiscal concerns, it may well take new mechanisms to enable full involvement by all participants.

Potential Problems Requiring Further Dialogue and Resolution Participation. Wary of more layers of regulation or the opportunity costs involved, some stakeholders favor a voluntary partnership funded by members that would move more slowly toward a mutually agreed vision. Other stakeholders argue that if such a self-assembled entity were to form, it would have been accomplished by now given the magnitude of the problems. Citing the dearth of successful voluntary efforts to address issues of this magnitude, other stakeholders favor a model involving government oversight. The authors reject such a notion believing it unlikely that any exclusively governmental model can ever engage the full spectrum of private sector changes needed to effect major changes, even within the NIH. During the first 3 years of CRR deliberations, most organizations who provided testimony expressed dissatisfaction with the current system and thus it is likely that participation could be easier to expand than anticipated.
**Governance.** The proposed NCRE would represent both government and private sectors so that its recommendations/standards could trigger industry-wide action addressing the 2 translational blocks. If all stakeholders were convinced of both the merit of such a vision and assured of its operational capabilities, the task of the NCRE would be much easier. Nonetheless, given the unique structure of such a public-private partnership, its governance is problematic because few previous models for such a structure exist. However, the National Academies of Sciences (or some other independent organization with similar neutrality and scientific/medical expertise) represents a logical, nongovernmental, and respected base for such an organization as the NCRE.

A recent report from the National Academies of Sciences on reorganizing the NIH approaches a part of this problem by recommending the creation of a new position of deputy director of the NIH for clinical research. This position would coordinate and centralize leadership, funding, and management for the NIH portion of its clinical research portfolio combining several intramural and extramural programs. The authors applaud this recommendation and believe it will improve NIH's ability to respond to and participate in the current challenges facing that portion of clinical research presided over by NIH funding. Our recommendations should not detract from the excellent momentum and bold national vision for clinical research contained in the new roadmap plans of the new NIH director, Dr. Elias Zerhouni. However, we believe that these novel clinical research efforts of NIH would be greatly enhanced by establishment of an NCRE.

The National Academies of Sciences report also mentions that several NIH officials told the committee that for decades the NIH has had difficulty in funding clinical research and population-based studies involving major diseases harbored under the aegis of individual NIH Institutes. For the clinical research enterprise to function effectively, better understanding, coordination, and collaboration among stakeholders is required. The NCRE board could be the mechanism to facilitate such coordinated stakeholder action and potentially anneal these important NIH initiatives with those of the for-profit section to address the 2 translation blocks in clinical research in a fashion not currently possible.

The challenges to be performed by the NCRE board will be daunting, time-consuming, and expensive and will require great political and scientific skills to succeed. Particularly problematic will be achieving the funding required to effect the substantial changes that will be required system-wide. Furthermore, there are no guarantees that this new arrangement will work any better than what exists. On the other hand, no alternative currently exists in our complex health care system capable of achieving the desired results. The NCRE's agenda was uniformly requested by nearly all of the health care participants testifying before the CRR during the past 3 years. Therefore, the various elements of this proposal are simply a reflection of the needed areas of progress that we uniformly heard from the clinical research, federal, industrial, payer, and provider communities involved in and governed by the current system.

**Conclusion**

The clinical research infrastructure of the United States is currently at a critical crossroad. Fragmented, outdated, and ailing, it is rapidly emerging as a rate-limiting step in transferring novel basic research into improved patient care. To efficiently leverage the enormous biomedical research gains made during the past century and those which are coming at an ever-increasing pace in this century, a drastic need exists to restructure and coordinate the inchoate system into a coordinated, safe, and more effective enterprise equipped to deal with these future opportunities. To accomplish this task, clinical research must first be viewed for what it is, a currently fragmented and out-dated national system initially established 50 years ago to support a cottage industry. Its functioning must be envisioned and dealt with for what it has now become, an enterprise-wide health care pipeline whose function is to bring the novel research from both government and private entities to bear on the disease burden of the US public and harvest our nation's impressive investment in discovery into an implementation phase.

To correct these problems, we propose the establishment of a unique public-private partnership termed the NCRE. Its agenda should consist of informed public participation, supportive information technologies, a skilled workforce, and adequate funding in clinical research. Devoting only 0.25% of the budgets from all health care stakeholders to the support of the NCRE would permit adequate funding to build the infrastructure required to address these problems in an enterprise fashion. Only timely, integrated, and system-wide investments can deliver the tacit promises of improved health care to our nation that attend our rapid basic science advances; marginal investments in the already poorly functioning and overloaded system will not.

Public expectations for the delivery of basic biomedical research discoveries from the sequencing of the human genome, new device developments, and biological breakthroughs to improved health care are accelerating. This impending shortfall of delivery from our biomedical research threatens both basic and clinical research, requires coordinated attention by both biomedical research communities, and arrives at a particularly inopportune moment. To avoid disappointing these increasing national expectations, all participants in the US health care delivery system must come together to focus on system-wide improvement in the NCRE that will benefit the public. Our nation deserves nothing less.

**Funding/Support:** The meetings referred to in this article were supported in part by the Institute of Medicine.

**Role of the Sponsor:** The Institute of Medicine did not participate in the preparation, review, or approval of the manuscript.

**Disclaimer:** The views expressed in this article are those of the author(s) and do not necessarily represent the official position of the Institute of Medicine or the National Academies of Sciences.
of the authors and do not necessarily reflect the opinions of the Institute of Medicine, the Institute of Medicine’s Clinical Research Roundtable, or the Roundtable’s sponsoring organizations.

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Freedom of expression is the matrix, the indispensible condition, of nearly every other form of freedom.
—Benjamin N. Cardozo (1870-1938)