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Linking Scientific Discovery and Better Health for the Nation: The First Three Years of the NIH's Clinical and Translational Science Awards

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Abstract

A comprehensive system for translating basic biomedical research into useful and effectively implemented clinical diagnostic, preventive, and therapeutic practices is essential to the nation's health. The state of clinical and translational research (CTR) in the United States, however, has been characterized as fragmented, slow, expensive, and poorly coordinated. As part of its Roadmap Initiative, the National Institutes of Health instituted the Clinical and Translational Science Awards (CTSA), a sweeping and ambitious program designed to transform the conduct of biomedical research in the United States by speeding the translation of scientific discoveries into useful therapies and then developing methods to ensure that those therapies reach the patients who need them the most. The authors review the circumstances of the U.S. biomedical research enterprise that led to the creation of the CTSA and discuss the initial strategic plan of the CTSA, which was developed from the first 3 years of experience with the program and was designed to overcome organizational, methodological, and cultural barriers within and among research institutions. The authors also describe the challenges encountered during these efforts and discuss the promise of this vital national health care initiative, which is essential to creating a pipeline for the scientific workforce needed to conduct research that will in turn provide a rational evidence base for better health in the United States.

Clinical and translational research (CTR) is vital to linking scientific advances to improved health. Its difficulties, however, are well known:¹ the U.S. approach to CTR has been fragmented, slow, expensive, and poorly coordinated,² while accelerating scientific progress continues to widen the gap between the current state of CTR and its potential.

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In addition, the cadre of clinical-translational researchers is largely trained in our nation's academic health and science systems (AHAS), where intellectual, cultural, and physical barriers between CTR investigators and researchers focused on basic science,^{3–11} have hindered translation of discoveries into a framework for improving the nation's health. There has also been a critical shortage of translational scientists working at the interface of basic and clinical research, and the interchange of intellectual properties between academic centers and the industry that develops technologies and medications is cumbersome and difficult to navigate. In addition, community-based research is maturing as information-based learning health systems¹² are becoming technically feasible, but a committed, trained cadre of researchers is needed to implement this vision.

Finally, CTR depends on interactions among our AHAS and multiple entities (many of them commercially driven) that develop medical products and, in the case of practicing physicians and other providers, deliver the bulk of patient care. This interface, however, has been beset by concerns that threaten the viability of public-private collaboration. The net effect of these issues is that CTR has been widely perceived as failing to deliver on its promise.

The NIH Response

Under the leadership of Dr. Elias Zerhouni, the National Institutes of Health (NIH) took these shortcomings seriously. After a series of focus groups and outreach sessions, the NIH Roadmap Program was announced in 2002.^{13,14} The Roadmap was initially characterized by three themes: (1) new pathways to discovery (for more efficient conduct of big science); (2) research teams of the future (emphasizing multidisciplinary and interdisciplinary research); and (3) re-engineering the clinical research enterprise. As the program has progressed, it has taken on new challenges and broadened in scope.¹⁵ After completing several pilot programs, the NIH announced in 2005 the Clinical and Translational Science Awards (CTSA), intended to foster the national transformation of CTR.¹⁶ The genesis of the CTSA effort was a growing view that piecemeal effort would not accomplish the goal of transforming clinical and translational research, because the structural and policy issues involved were fundamental and deeply embedded in AHASs. As of September 2009, 49 AHAS, including three minority institutions, have been chosen through competitive peer review and funded by a CTSA cooperative agreement.¹⁷ The NIH's stated goal is to grant 60 awards, with total steady-state funding to reach \$500 million annually—the largest single dedicated CTR program in U.S. history. The majority of this funding for infrastructure was recovered from the phase-out of the General Clinical Research Center program (GCRCs), which focused largely on bench-to-bedside investigation. Additionally, the NIH-funded K30 clinical research training program and the non-categorical career development award program of the National Center for Research Resources (NCRR) were folded into the CTSA.

CTSA: The First Three Years

Institutional transformation

The first three years of the CTSA program provided significant learning experiences. A patchwork institutional legacy of funded programs with interwoven departments, centers,

and institutes (with correspondingly complex internal and external relationships) created a daunting environment in which to attempt sweeping transformations.¹⁸ Chief among these challenges was the engagement of a broad spectrum of researchers capable of creating a coordinated infrastructure for CTR. Discovery science in AHAS has typically rewarded individuals rather than the teams needed for effective CTR. Moreover, researchers working in the clinical setting have powerful financial incentives for focusing on efficiency and productivity in patient care, making it difficult to carve out time for careful conduct of research in the clinical setting. The CTSA effort therefore seeks to implement a systematic approach to CTR that is complementary to (and not competitive with) excellent discovery research efforts and high-quality patient care at these institutions.

Each CTSA institution has focused on overcoming historical and cultural barriers to CTR. The expert community devoted to the integration of CTR is small, leading to practical challenges in projecting the initiative's importance across institutions and limiting rates of progress. Established administrative systems and processes pertinent to clinical research are typically inefficient and overly risk averse. The siloed nature of academic institutions can render fundamental communication among researchers difficult, while modern institutional infrastructure (financial systems, communications, databases, human resources), which hitherto resided in individual laboratories, departments, or schools, is often lacking. In particular, the discipline of informatics has had difficulty exerting significant influence, slowing the uptake of methods and technologies that could expedite collaborative efforts within and across institutions.

Each institution has also had to accommodate the phasing out of the GCRCs. At the time the CTSA program was announced, a network of more than 70 GCRCs supported patient-oriented research by providing dedicated research space, staff, biostatisticians, core laboratories, pilot and educational programs, and informatics support in a manner similar to the CTSA, albeit on a smaller, more focused scale. Nevertheless, the GCRC mechanism was criticized for providing intensive support to a limited number of investigators and for almost exclusively emphasizing bench-to-bedside translational research. Prior to the CTSA program, many GCRCs were developing evolutionary plans to support broader ranges of research and investigators, efforts that were limited by restrictive program regulations. However, the NIH has catalyzed the transformation of these centers to meet its new vision for CTR by implementing the CTSA program while simultaneously announcing the termination of the GCRC funding mechanism in 2010.

The integration of established GCRCs into the broader CTSA structure is a core strength of the program. Each site has a mandate to transform its CTR program while maintaining the flexibility needed to innovatively pursue institutional goals. Accordingly, CTSA sites can transform any aspect of their GCRC, including scientific focus, resources, administrative structure, physical plant and budget, thus providing a venue for interdisciplinary human subjects research.

These plans generally reflect institutional missions and priorities. For example, AHAS emphasizing bench-to-bedside research have centered their CTSA programs on their transformed GCRCs, while sites focused on population-based research and multisite trials

can reduce or eliminate traditional GCRC functions. Innovative hybrid models that assign priority to community- and practice-based multidisciplinary research can flourish, and public-private partnerships involving technological development or community groups have also emerged. Thus, the CTSA program is far broader in scope and includes the entire spectrum of clinical and translational research, whereas the GCRC program was much smaller and more focused within each institution.

Working as a consortium

The intense efforts demanded by this transformation have challenged sites to strike an appropriate balance between supporting translational facilities and research consonant with previous GCRCs, and developing other aspects of their CTSA program. Historically, GCRCs have been connected in a loose network with limited cross-institutional initiatives, but this new national consortium, characterized by a continuous exchange of ideas between and among the NIH and CTSA institutions and funded through a cooperative agreement mechanism, will link investigators in a robust network for sharing best practices and implementing national, trans-CTSA initiatives.

Given the internal issues involved, progress toward common goals must overcome the attenuation of investigators' energy. A naïve observer might assume that not all institutions are equally gifted in all areas of CTR, and that a grand economy of scale could be achieved by mandating sharing of key technological resources and research clusters. However, given the critical role of AHAS in training researchers and practitioners, creating a consortium that leaves core institutional systems intact requires intensive planning, and the breadth of each institution's investments in CTR has to be considered. After prolonged discussion within a broad, inclusive committee structure (www.ctsaweb.org), the NCRR leaders and the CTSA principal investigators (PIs), through a joint planning exercise, developed a consensus set of strategic goals considered most deserving of consortium resources for the purpose of translating scientific discovery into improved health; these goals (which are described in detail in a companion article in this issue of *Academic Medicine*¹⁹) directly address the most pressing system needs described above.

Strategic Goals

Research management

All who engage in CTR have endured the frustrations of redundant paperwork and complex negotiations that have become inherent to clinical research.²⁰ The combination of institutional review board (IRB) review, contracting, and budget negotiations can consume over 6 months for each protocol in typical American AHAS; much of this activity is useless or redundant.²¹ This is compounded by complex payment schemes for care and services provided to research subjects. While efforts such as those embodied in the Centers for Medicare and Medicaid Services (CMS) policy on reimbursement for clinical trials have established the important principle that research participants should not be penalized by withholding standard-of-care payments to their providers, ambiguities in the voluminous regulations have given rise to cumbersome, expensive enforcement bureaucracies.²¹

This problem is a complex systems issue comprising multiple interacting (and sometimes competing) interests and subsystems that must be synchronized; as such, rectifying it is more complicated than merely reducing delays or pruning excess bureaucracy. Indeed, the intricacies of liability and payment for services have made contracting even more fraught than IRB review.

The extreme risk aversion present in most AHAS ultimately leads to acceptance of additional complexity as necessary for compliance, while proposals for streamlining are heavily scrutinized for legal and reputational risk. Unsurprisingly, many researchers believe these safeguards are on balance harmful, denying patients access to clinical studies and hindering accumulation of evidence relevant to their care.²² Inordinate amounts of perceived risk and institutional expense and time are blamed for declining numbers of U.S. health professionals who are willing to conduct research²³ and for the migration of research from the United States to countries that offer lower costs.²⁴ Even the NIH is now offshoring a significant amount of clinical research, as demonstrated by several recent NIH trials that have included more non-U.S. than U.S. patients, such as the National Heart, Lung and Blood Institute's STICH and OAT studies.^{25,26} In light of these issues, much will be gained from a national streamlining effort that identifies administrative elements that truly enhance patient protections and ensure research validity. Despite the centrality of quantitative evidence in applying CTR findings, there is no such evidence to support this proliferation of regulations and systems, often triggered by public awareness of a problem in research conduct and promulgated without assessment of effectiveness.

The CTSA Consortium seeks to transform this ineffective system by developing metrics to assess the length of the process at individual institutions and by creating common approaches to contracts and shared IRB considerations, thereby avoiding redundancy in multicenter studies and accelerating the start-up phase of clinical research. Another major effort will enlist business and engineering schools and health science disciplines to develop detailed process maps. Evidence regarding the relative merits of process elements will then be collected so that useless items are eliminated, deficient ones improved, and useful ones fortified, unifying disparate subsystems into a functional system within and across institutions. All CTSA institutions have agreed to work toward openly displayed quality metrics for research processes and will collect data on the behavior of research sponsors to ensure accountability for maintaining efficiency and quality. As the system becomes more efficient, standards for phenotyping disease and health will also be addressed.

Training and sustaining the next generation

The nation's AHAS are vital to nurturing successive generations of practitioners, researchers, and leaders. But while many issues regarding the training of discovery scientists and clinicians could be debated, the pathway for these critically important professionals is clear compared with that of CTR investigators, whose endeavors often span multiple domains. Training programs for the coming interdisciplinary environment are not well established and must overcome complex departmental and institutional barriers. Institutional T and K training programs funded by the NIH have yielded encouraging results, but NIH and AHAS policies and programs that define clear, secure, mentored training paths of

sufficient duration are still needed to produce and sustain an outstanding national CTR workforce.

Because the CTSA program will encompass most research-intensive AHAS, it can develop best practices, foster economies of scale, and encourage innovation in training. There is a consensus that defining core competencies for CTR and sharing effective curricula would have the enormous benefit of helping institutions avoid duplication of basic material. This is not envisioned as a monolithic national curriculum; rather, institutions may develop notably effective approaches that should be widely shared, thus promoting rapid diffusion of advances in quantitative methods, interdisciplinary team conduct, research ethics, community-based research, human systems biology, and application of genomics and related technologies to therapeutic development and evaluation. Accordingly, committees have been fine-tuning a comprehensive set of competencies for the wide variety of researchers interested in this type of research. Another critical dimension of career development and sustenance is careful attention to the lifespan focus of researchers, with major support of investigators working on issues relevant to the health of children and the elderly.

National resource inventory, research networking, and data sharing

The CTSA PIs endorse the concept of sharing among institutions in three dimensions: big technologies; new tools and expertise; and fundamental capability. The first assumes that there are elements of biomedical technology so expensive that only certain institutions can afford them. Thus, establishing systems that allow investigators at institutions with limited means (including those without CTSA Cooperative Agreements) to access such resources when appropriate (e.g., genomic technologies; large-scale clinical trials coordinating centers) will be a key priority. First-rate IT and informatics expertise could permit widespread access, although the necessary human systems must be developed and emplaced. Several major supplemental grants have been funded to develop an interactive inventory of core technologies.

The second dimension assumes that clusters of investigators will develop excellence within individual institutions and across small groups of institutions. The intellectual and social chemistry needed for innovation cannot be dictated, and useful tools often emanate from focused multidisciplinary groups intent upon particular problems. Thus, within the Consortium, institutions are encouraged to differentiate based on interests and missions, while benefiting from complementary efforts by other Consortium members. As useful tools are developed, the ability to share them efficiently will be a major asset.

The third dimension is establishing fundamental levels of knowledge and operational systems in all CTSA program domains in order to provide the necessary substrate for modern biomedical education and training. For example, while not every institution may invest in cutting-edge informatics, genomic or proteomic technologies, or large clinical trials coordinating capabilities, each must have the basic expertise and systems investment to be able to use these tools appropriately. This means that institutions will need to assess whether their faculty can provide the minimum necessary teaching and mentoring capabilities to trainees.

There is, however, a strong consensus that the complex infrastructure for networking investigators needed to accelerate progress in CTR is presently lacking. While younger generations are adept with new modes of communication, many faculty remain wedded to old-fashioned networking methods. Creating effective networking tools to span investigator generations will be a significant challenge, and the Consortium is focusing on developing tools that will expedite the networking of people, resources, and data both within and outside of CTSA institutions.

Community engagement and evidence to inform policy

Enormous disparities in health outcomes (now measurable with great precision), coupled with broad acceptance of the importance of disease prevention, have made community engagement a critical facet of CTSA activity. Most academic health centers have now become academic health systems with complex ecosystems characterized by interdigitated networks for primary and specialty care; an increasing number incorporate large primary care networks and alliances with public health delivery mechanisms. By recognizing and respecting the needs of the communities they serve, CTSA recipients seek to improve community health by collaborating on the evaluation of methods for implementing strategies shown in focused clinical trials to be effective.

Additionally, with major changes on the horizon for the U.S. health system, the CTSA Consortium is mindful that these changes should be based on evidence whenever possible. As the CTSA Consortium seeks to leverage the expertise of research-intensive AHAS and engage communities, the generation of systematic evidence to inform effective policies on technology assessment and health services will be a lynchpin of this strategic goal. Given this focus on combining research expertise with community engagement, the CTSA program will be uniquely suited to respond to the new national emphasis on evaluating comparative effectiveness and eliminating disparities in health access and outcomes.

The T1 investigator

After initial priorities were developed, a consensus developed among Consortium members that bench-to-bedside-and-back research was in a state of jeopardy. This problem seems to stem from the complex financial and cultural circumstances of AHAS, circumstances marked by the shift of capital out of clinical departments and into health systems. These investigators have difficulty covering all of their expenses and often cannot compete with full-time clinicians when seeing patients because of distractions from ongoing research. The Consortium is thus focusing on methods of institutional support for this “endangered species” and developing best practices to encourage multi-institutional T1 projects.

IT and informatics: Key integrative forces

As biomedical science evolves into an information-intensive discipline characterized by sophisticated, robust quantitative measurement and analysis, a mature approach to IT and bioinformatics will be vital for connecting research and practice. Unfortunately, these specialties have been underdeveloped at many AHAS. Moreover, the best path forward may not be clear, while necessary investments are often substantial. Most investigators and institutions would be delighted to use off-the-shelf technologies and informatics platforms:

the continuum of expertise required to deploy purchased software is easily grasped compared with that needed for developing new bioinformatics capabilities. The issue is further complicated by the common confusion within institutions about the gray area between IT and informatics inherent in the iterative nature of innovation and deployment.²⁷

Fortunately, CTSA programs can ameliorate these problems through group learning and sharing. Different AHAS have expertise in different areas of informatics; the ability to develop a new approach to data reduction in unbiased proteomics experiments is different from the ability to articulate a clinical trials management system or disease-specific ontology. As institution1 specific innovations are developed, the CTSA Consortium will provide a venue for identifying successful approaches and rapidly disseminating best practices (particularly if underlying infrastructure is harmonized), thereby accelerating propagation and uptake of improvements and standards.

Interacting with the National Institutes of Health

Biomedical research support at the NIH is complex and dependent on the strategic plans of 27 component institutes and centers, most of which receive funding through specific Congressional authorizations. The CTSA program is funded through the recycling of GCRC, K30, and select K12 and T32 funds, as well as a special allocation to the NIH director, set at a predefined level and managed by the Office of Portfolio Management and Strategic Initiatives, and allocated to the NCRR for administration of the cooperative agreements. Since the CTSA program is designated for general institutional infrastructure, its funds typically are not deployed within institutions in a manner specific to therapeutic areas, except for pilot projects.

This matrix, in which the CTSA specifically supports infrastructure for NIH-sponsored research, while funding from other NIH institutes supports disease-specific projects, should create economies of scale and foster synergy among NIH institutes. In order to realize this promise, the national CTR infrastructure must overcome legacies of Institute-specific programs that can inhibit interdisciplinary resource sharing. As technological costs continue to outpace NIH budgets, much can be gained by eliminating these redundancies. Innovative, flexible funding mechanisms will encourage rational sharing of resources; likewise, institutional leaders must provide local incentives and credit to investigators for cooperation.

External partners

Most CTSA applications include multiple external partners (e.g., academic institutions, government agencies, community physicians and hospitals, community and patient advocacy organizations, and pharmaceutical and medical products companies). These consortia are built on the concept that funding and in-kind services will be shared to achieve common goals, such as creating a technology development core or community intervention project. In some cases, multiple AHAS collaborate on basic CTSA applications, creating regional or statewide consortia. These coalitions, however, are fragile and could falter if the efforts needed to maintain collaborations across distance and administrative barriers, or to deal with conflicts of interest and rules governing public-private partnerships, are not

sufficiently encouraged. Likewise, interactions with similar consortia now developing within many countries will be critically important as well.

Funding constraints

The U.S. economy is undergoing extraordinary stress. Further, biomedical research has suffered years of declining funding relative to inflation, including an abrupt major reduction in funds available to CTSA institutions after the program was initiated. The AHAS understand the challenges of securing support for biomedical research, especially when so many aspects of the U.S. enterprise are ailing. Nonetheless, this sudden change in support caused grave concern, given the imperative for CTSA institutions to transform internally while simultaneously committing to Consortium activities. The CTSA PIs believe that restoring the original commitment of resources to support the CTSA program is not only vital for achieving the transformational goals of the program, but is also critical to redeveloping the scientific infrastructure essential to our economy's long-term success.

A Bold Plan that Must Succeed

The CTSA program has a bold plan to transform a CTR system widely regarded as outmoded, inefficient, and failing the public. Success in this difficult task is absolutely essential, as failure would signal the continuing decline of the U.S. biomedical research enterprise. Success in these transformative efforts will require creativity, patience, and continuing dedication across the spectrum of researchers. Institutional officials must reward CTR activities that creatively deploy resources to foster efficiency. Those who thrived within the old culture of AHAS must support needed changes; at the same time, CTSA institutions must carefully preserve the many successes that do not need reform. The NIH should develop funding mechanisms that reward collaboration and reduce barriers among its own institutes, which could in turn markedly enhance the value of these investments. Continuous improvement of suboptimal elements and reinforcement of effective systems will be central to this undertaking. Ultimately, success of the CTSA effort is critical to the well-being of our biomedical research enterprise and to the health of our nation.

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