Development of a Conceptual Model and Assessment of the Feasibility of a National Clinical Research Associates Program

NCRA Final Report

Gery Ryan, M.A., Ph.D., Senior Behavioral Scientist

Claude Berrebi, M.B.A., Ph.D., Economist

Megan Beckett, M.H.S.A., Ph.D., Demographer

Allen Fremont, M.D., Ph.D., Co-Principal Investigator

Stephanie Taylor, M.P.H, Ph.D., Social Scientist

Michelle Cho, M.Ed., Project Associate

John Adams, M.S., Ph.D., Senior Statistician

Elaine Quiter, R.D., M.S., Project Manager

Harold Pincus, M.D., Senior Scientist and Director, RAND–U. Pittsburgh Health Institute

Katherine Kahn, M.D., Senior Scientist, Principal Investigator

Contract No. GS-10F-0275P

Katherine Kahn, M.D., Principal Investigator

Allen Fremont, M.D., Ph.D., Co-Principal Investigator

Table of Tables

		Page
Table 1:	Number of Interviews, by Stakeholder Type	3
Table 2:	Sample Interview Topics Emphasized in Early and Later Stages of the Project	4
Table 3:	Ways RAOs Help Providers Participate In NCRA	9
Table 4:	Key Infrastructural Development Tasks to Be Accomplished During Phase 1 (Years 1-3)	17
Table 5:	Estimates of NCRA Capacity, Costs, and Efficiency (Full Scale Will Support $1.9 Billion of Clinical Research Studies)	18
Table 6:	Estimates of NCRA Capacity, Costs, and Efficiency Across Cost-Reduction Strategies	22
Table 7:	Examples of Cost Sharing with Third Party Payors	24

Table of Figures

		Page
Figure 1:	Services Can Tip the Balance to Motivate Provider Participation	8
Figure 2:	NCRA Administrative NIH-Led and -Staffed Units	10
Figure 3:	Unit Infrastructural Costs for Providers and Patients	18
Figure B:	NCRA-Funded Entities Used to Coordinate and Support Services Needed by NCRA Associates	Appendix B (Page 36)

Glossary of Acronyms

ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMC	Academic Medical Centers
ARO	Academic Research Organization
CCOPs	Community Clinical Oncology Program
CMS	Centers for Medicare and Medicaid Services
CRO	Clinical Research Organization
CRU	Community Relations Unit
DCCU	Data Collection and Coordinating Unit
DIA	Drug Information Association
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
NCRA	National Clinical Research Associates
PBRN	Practice-Based Research Network
QAU	Quality Assurance Unit
RAO	Research-Associates' Organization
RAOU	Research-Associates' Organization Unit
RDD	Random Digit Dialing
ROPS	Registry of Providers and Studies
ROPSU	Registry of Providers and Studies Unit
SOU	Study Operations Unit
SSEC	Study-Specific Executive Committee
TRU	Training Unit

Executive Summary

Reengineering the Clinical Research Enterprise to Involve Clinicians

A central aim of the National Institutes of Health's (NIH's) Roadmap for Medical Research is to reengineer the clinical research enterprise in ways that will accelerate and optimize the research process and the translation of resulting knowledge into improved healthcare and health outcomes. A critical ingredient for the success of this effort is a substantial increase in the availability of community clinicians who are willing and able, in a time- and cost-effective manner, to enroll patients in clinical trials. To address the shortage and relative lack of diversity of providers and patients participating in clinical research, the Roadmap calls for the development of a new program, the National Clinical Research Associates (NCRA), that would attract an unprecedented number of practicing providers to the field of clinical research (Zerhouni, 2003). Unlike in many existing research programs, "Associates" would participate in clinical research in the community, where the vast majority of Americans receive their care. Not only would this group of practicing clinicians involve and support a larger and more representative set of patients in NIH-funded research studies, but the proposed NCRA infrastructure would also greatly support NIH efforts to more efficiently and effectively tailor its research studies and findings to the needs of healthcare providers and the patients they serve.

Goals of NCRA

The broad goals underlying the design and implementation of NCRA are to

1. Create networks and partnerships that are diverse and representative of all healthcare and clinical research stakeholders, particularly community providers
2. Improve efficiency and productivity in conducting clinical research and in disseminating new knowledge to healthcare providers (i.e., "reengineer" clinical research)
3. Promote a wide array of studies that will be applicable to a large number of patients, with results that will be available for review and dissemination by community providers as well as by scientists (i.e., providing a deeper understanding of biology and promoting interdisciplinary research teams).

To achieve these overall goals, a stable, yet flexible, infrastructure is needed to enable a large and diverse group of providers and patients to participate in a wide range of research studies. To recruit, train, and retain the necessarily large number of community providers (and patients), this new infrastructure must address the new and changing realities of clinical research and clinical practice, such as costs, liabilities, opportunities in managed care environments, and an increasingly diverse patient population. Although there are exceptions, the existing research infrastructure (e.g., subject recruitment, protocol development, equipment of administration sites) tends to be based on a traditional biomedical model that focuses on questions generated in the laboratory by the basic scientist, and the research itself often involves study designs, care settings, and patient populations that may be only partly applicable to community-based care and most of the U.S. population.

Methods

To develop our conceptual model of NCRA and assess its feasibility, we used an iterative process that incorporated input and feedback from a variety of sources and stakeholders. Data sources for our literature review included academic and trade journals, Web pages, and public- and private-sector reports. Interview data came from a diverse group of stakeholders, ranging from individual community providers not currently involved in research to leaders of large clinical research networks and national professional associations. We conducted a total of 243 interviews between September 2004 and October 2005.

We obtained cost estimates from a variety of different sources. We used detailed study costs from previously funded research that funders, researchers, and entrepreneurs generously shared with us. Additionally, we used informants who were familiar with current or past clinical research budgets, including site principal investigators (PIs) of large, NIH-funded multi-site clinical trials, clinical research project managers, and budget monitors.

Key Findings from Interviews Regarding Incentives and Disincentives Associated with Community Provider Participation in Clinical Research

Financial considerations were consistently the strongest concerns of providers and stakeholders. Although informants varied somewhat on the specific disincentives they emphasized, they almost universally agreed that economic considerations were paramount, particularly given the emergence of managed care. Providers

consistently expressed concern about the burdens associated with institutional review board (IRB) applications; report generation; communications with the principal investigator, data-coordinating center, and regulatory agencies regarding protocol design; protocol changes; IRB changes; and data quality. Providers also professed a belief that funders underestimate the administrative burdens associated with the conduct of clinical research in the community. Providers lauded the potential contributions of information systems but also expressed dismay that advances in information technology did not necessarily decrease their work burden—and sometimes increased it. Many community providers, particularly primary care providers, expressed concern that their participation was valued only for the recruitment of patients, rather than for the providers' clinical expertise or insights into important clinical challenges that could benefit from biomedical advances. In fact, some primary care providers indicated that they would not want to participate in NCRA unless a clear commitment was made to involve providers in some components of the research process beyond just recruitment of patients and data collection (e.g., creating opportunities for provider input into choice of specific study topics or design).

Despite the perceived barriers to clinical research participation, many providers were intrigued by the possibility of participating in research studies, especially if they thought that such participation could contribute to improving patient care.

How NCRA Will Achieve Its Goals

For NCRA to work optimally and provide all the suggested benefits, it needs to further the efficiency and productivity of research and the dissemination of new knowledge to healthcare providers, create networks that are diverse and representative of all healthcare and research stakeholders, and promote a wide variety of studies that can be applied to large numbers of patients. Its goal is to establish and maintain a large, diverse network of NCRA Associates, and the means to support the Associates. Once established, Institutes can use and reuse these network and support mechanisms to run multiple, large, national studies of their choosing.

NCRA should have the flexibility to accommodate various types of studies, numbers of providers, and provider specialty types and to adopt a wide range of solutions so that it can confront emerging barriers. NCRA should be designed to give providers a secure foundation so that busy practitioners are likely to risk involving themselves and their patients with clinical research and so that they are satisfied enough to be retained as long-term research participants. The proposed model of NCRA is designed to address these challenges.

Proposed Model of NCRA

The National Clinical Research Associates Program, as conceptualized, is a coordinated mechanism for bringing large numbers of community providers into the research enterprise. NCRA can be defined along three dimensions. First, NCRA is a network of providers who will participate in clinical research in the context of delivering clinical care. Second, NCRA is a well-integrated set of services designed to identify, recruit, retain and support those providers who conduct research in the clinical-care setting in a manner consistent with the high standards that characterize NIH research. Third, NCRA is an administrative and coordinating capacity that oversees the functions of NCRA and its associated stakeholders. These three dimensions work together as a tool that will further the efficiency and productivity of research and the dissemination of new knowledge to healthcare providers, create networks that are diverse and representative of all healthcare and research stakeholders, and promote a wide variety of studies applicable to large numbers of patients. In addition to the three dimensions that make up NCRA, NCRA represents a way to organize and finance clinical research and can be characterized as a flexible tool to be shared across all NIH Institutes.

As a network, NCRA is expected to scale up to 40,000–60,000 providers capable of participating in clinical research. The network will be stable, with provider retention across time and studies far exceeding the norm of today's research provider. The NCRA network has the flexibility to involve any configuration of specialty type preferred by NIH. Although initially developed for community primary care providers (e.g., family medicine, pediatric, internal medicine, and obstetric/gynecologist physicians, dentists, and nurse practitioners), NCRA is flexible enough that other community providers (e.g., medical subspecialists), other specialty providers, specialty networks, and academic providers can also make use of the NCRA mechanism. With NCRA, a system of support services for these busy practitioners of clinical care needs to be implemented to ensure that providers are aware of the research opportunities available to them and their patients.

To ensure that providers are aware of NCRA and the research opportunities available to them and their patients, NCRA will subcontract to a community-relations organization. Once providers are aware of NCRA, they need a uniform platform for registering their interests and learning about salient study opportunities. The NCRA Registry of Providers and Studies (ROPS) furnishes this service for providers as a dynamic Web-based registry. To recruit, support, and retain providers and to overcome the innumerable barriers and disincentives that providers face in participating in clinical research, NCRA will engage approximately 30 to 40 Research-Associates' Organizations (RAOs). RAOs will be incentivized to remove the barriers keeping clinical providers from participating in clinical research and to provide support to them by identifying providers likely to engage diverse patient populations and who will be eligible for specific study protocols. RAOs will recruit providers to participate and address questions and concerns providers may have. RAOs may also assist providers with NCRA registration, with refitting of their office infrastructure to facilitate research, and with patient-recruitment efforts.

Administrative structure and coordinating capacity are required to support the integrity of NCRA as it delivers services to Associate providers. The NCRA Administration is envisaged as the aggregation of an NCRA Program Office and seven units within the greater NIH, which are independent of individual Institutes. These will be the main vehicles leading the effort to make NCRA, and its potential to affect the clinical research enterprise, a reality. Although the actual delivery of services described above will be done by subcontracts, a small administrative staff will be used to manage and oversee the integration of services. The units that will provide additional infrastructure support include the ROPS Unit, the RAO Unit, the Study Operations Unit, the Training Unit, the Data Collection and Coordinating Unit, the Quality Assurance Unit, and the Community Relations Unit.

Cost Assumptions and Analyses Under Varying Scenarios

NCRA is designed to create a stable network of 40–60,000 providers, from a wide variety of practice settings, who would participate in high-quality clinical research across a broad set of study types. To ensure that the NCRA system remains flexible and robust, as well as cost-effective, NCRA's design relies on free-market principles tempered by layers of checks and balances, optimized economies of scale, and a strong but lean central administration.

The implementation of NCRA is envisioned to occur as follows. During a pre-NCRA phase, NIH allocates a budget for NCRA, endorses the basic NCRA administrative plan, and hires key personnel to staff each of the NCRA Units. During Phase 1 of NCRA (Years 1-3), the administrative and service infrastructure needed to run NCRA will be established. Key tasks to be completed during Phase 1 include the development of solicitations for ROPS, Web-based training, three model RAOs, and the community relations subcontracts; the distribution of the subcontracts; and the guiding of their development. The Study Operations Unit will begin to develop cost schedules. Pilot feasibility studies will be designed, and ten will be selected for testing in Phase 2 (Year 4). An additional 27 RAOs will be contracted. Quality- and data-management strategies will also be determined during Phase 1. Contracts for further studies will be awarded at the end of the third year. During Phase 2 (Years 4-8), NCRA will begin to recruit providers and run studies, and it will expand to its full capacity over a 5-year period.

At its peak, at Year 8, it is estimated that NCRA has the potential capacity to: (a) initiate up to 40 large multi-site studies per year; (b) support up to 100 ongoing multi-site studies per year (i.e., studies with an average of 10,000 patients); (c) enroll up to 25,000 new providers per year; (d) involve a cadre of approximately 60,000 providers per year; and (e) recruit more than 1 million patients per year. To accomplish these upper limits, it is estimated that NCRA would need the assistance of at least 40 RAOs. With these features, NCRA would have the capacity to support more than $2 billion of NIH studies.

The costs of NCRA can be divided into infrastructural costs (e.g., administration, subcontracts, and other services needed) and the costs associated with the portfolio of studies that is run through NCRA. The costs of developing NCRA's infrastructure during the first three years (Phase 1) are estimated to be approximately $20 million. The estimated infrastructural costs for running and maintaining NCRA in subsequent years ranges from $30 million in Year 4 to $48 million in Year 8.

Emerging Context for NCRA in 2006. Since NCRA and its initial scope were proposed in 2003, there have been significant changes to the NIH and the healthcare-delivery environment in which NCRA was to exist. Like many other government agencies, NIH is being asked to reevaluate and downsize many of its long-term

initiatives in the face of a weakened economy. The NIH budget, which had been steadily increasing for years, has started to decline, thereby shrinking the funds available for clinical research. In this changing environment, it will be more challenging for NIH Institutes to part from the status quo and accommodate the implementation of NCRA. A careful examination of capacity, cost estimates, and unit costs associated with differing NCRA scenarios can provide a mechanism for the Institutes and others to understand the implications of various options. Given NIH's current budget situation, it is important to determine whether the size of NCRA can be reduced.

Cost-Reduction Strategies Considered. We considered five strategies for reducing the costs of NCRA. Two seemed more appealing than others. One strategy involves NCRA continuing with the original implementation plan but ceasing expansion in either Year 6 or 7, rather than continuing expansion through Year 8. Ceasing expansion in Year 6 or 7 would reduce the number of ongoing studies from 100 to 40-60, reduce the number of providers from 60,000 to 26,000–41,000, and reduce the number of patients from more than 1 million to 310,000–610,000 per year. However, this strategy is likely to reduce the infrastructural costs by $6 to $12 million per year and has the potential of reducing the total study costs by $770 million to $1.4 billion per year. The second strategy involves a two-stage NCRA implementation, with the first stage being a demonstration project and the second stage being the full, but delayed, implementation of NCRA informed by lessons learned from the demonstration. The 4-year demonstration period would cost approximately $20 million, exclusive of study costs. If NIH decides to scale up to a larger NCRA, the investment in the demonstration study is likely to provide significant cost reductions in Phase 1 (approximately $6.5 to $8.5 million). This strategy would allow reduction in costs in the immediate years while still preserving the substantial cost efficiency expected with full NCRA implementation.

What Are the Financial Advantages of Using NCRA?

NCRA in its full capacity makes it feasible to efficiently recruit a larger number of providers at a reasonable cost relative to what it would cost for recruiting the same number of providers without an NCRA. RAND's analysis indicates that it would be extremely inefficient and probably not feasible to recruit more than 20,000 new community providers without an NCRA-like structure. NCRA is designed to engage providers in clinical research for the long term. It does so by reimbursing providers at a dollar amount commensurate with what providers would be reimbursed if that time were allocated to clinical care (*fair replacement value compensation*) and by providing support to providers and their staffs for clinical research. NCRA is designed both so that the reimbursement levels are adjusted continuously (to reflect factors external and internal to NCRA) and so that the level of support given to providers is adjusted (to reflect the individual experiences and emerging needs of providers).

NCRA's suggested infrastructure takes advantage of scale economies, as well as of the internal preservation of know-how. Like other complex mechanisms, it is expected that NCRA will have a steep learning curve and rely heavily on learning-by-doing through its implementation and consequent use. Unlike with other clinical research studies for which the infrastructure is rebuilt every time anew and any acquired know-how is largely lost, NCRA will build upon its experience. In particular, NCRA's infrastructure adjusts over time to incorporate and use the acquired knowledge while constantly moving up on the learning curve. This difference, together with scale economies, thanks to the number and size of studies that populate NCRA, will result in a more cost-effective infrastructure than a system of individual clinical research study implementations.

Why Do We Need NCRA? What Are Its Key Selling Points?

The establishment of NCRA along the lines suggested in this report will have many positive outcomes, such as meeting its NCRA goals, improving quality, and saving money. These outcomes will vary by when they are recognized, the precision with which one can attribute the outcomes to the initiation of NCRA, and the ability to predict how the outcomes will unfold with time and how they will interact with other societal developments. With the introduction of NCRA, we fully expect clinical research to become more efficient. Increased efficiency should translate into potential savings. However, it is expensive to initiate and maintain a system that will be responsive to the new expectations for clinical research that NCRA is designed to support. Accordingly, we expect that some of the savings will only become apparent in the distant future.

History suggests it would be wrong to limit decisions about NCRA to an analysis of short-term goals. Even in the longer run (which we define as 10 or more years), important outcomes should be considered in addition to potential financial savings. While some of the beneficial outcomes are easier to quantify because they are consistent with explicitly stated goals, others are more conceptual and likely to translate into highly valued

goals with time. We expect that NCRA will improve the accountability among NIH, principal investigators, providers, recruiting sites, and data-coordinating centers. The development of the NCRA Registry of Providers and Studies will allow NIH to better assess the costs and productivity of its clinical research programs. Clinical research will be conducted faster, with better documentation, improved measures of quality, and improved provider experiences. Collaboration among NIH representatives, principal investigators, RAOs, providers, and professional organizations will increase. Awareness of clinical research and the dissemination of research findings among principal investigators, providers and, ultimately, patients will increase. Participants in the research endeavor will better understand and appreciate what it costs to undertake various study designs.

One of the core features of the NCRA design described above is to increase the interactions among the different stakeholders and build a research system in which all participants in the research agenda are incentivized and rewarded for their efforts while being held explicitly accountable for the quality of their work. The other core feature of the NCRA design is to build a system to make explicit the productivity of the research arena so that a better assessment of what should be enhanced or downsized and where future investments should be increased or decreased can be made.

No one can estimate *a priori* the impact of NCRA on each of these and many other outcomes; no one knows in advance how many additional research findings or related products may be generated with the help of the NCRA. We only know that each of these elements will be positively affected.

RAND NCRA Final Report

In 2004, the National Institutes of Health tasked The RAND Corporation to model and assess the feasibility of a clinical research enterprise that is vastly different from that of today, which is based on a biomedical model. This document is RAND's Task IV deliverable for the "Development of a Conceptual Model and Feasibility Assessment of a National Clinical Research Associates Program." It is the final report for the project and, as such, is something of an omnibus. It answers a variety of questions: on problems that led to the development of the NCRA concept, on incentives and disincentives for community provider participation, and on financial advantages and non-financial disadvantages of using an NCRA. It presents a description of the dimensions making up the program and a number of scenarios for development of the program that have different cost implications. It also poses different advantages and disadvantages of such a program. All the information taken together presents what the RAND team has come to view as a historic undertaking that has the potential to effect positive change for the nation in the 21st century in the way the transcontinental railroad did in the 19th century and the Internet did in the 20th century. This document should be of interest to the National Institutes of Health and to the lay public interested in clinical research.

Opportunities and Challenges in Clinical Research and the Need for a New Approach

The United States leads the world in investment in biomedical research and healthcare (Mathieu, 2005). The substantial return on these investments is seen in the remarkable scientific breakthroughs of the past few decades and the continually accelerating advances in biomedical knowledge that promise to revolutionize health care and significantly improve Americans' health. For example, extraordinary advances in basic science and genetics, and the application of molecular biology to animal and human systems, have yielded a new understanding of how disease might be prevented and treated. The recent completion of the sequencing of the entire human genome has further accelerated the pace of scientific advances and the opportunities they create (Sung et al., 2003).

Yet, the pace of translation of new knowledge into actual clinical care and improvements in human health may be lagging behind the pace of gains in new knowledge. For instance, despite advances in knowledge and treatments for many conditions, recent reports, such as two from the Institute of Medicine (Institute of Medicine, January 1, 2003; July 1, 2001), show that a relatively small proportion of that knowledge is consistently used in actual practice and that U.S. health outcomes, such as life expectancy at birth, continue to lag behind those of other countries. With more than $250 billion invested in NIH since 1950, some have questioned whether clinical research in the United States is organized and operates as effectively and efficiently as it might. If not, what enhancements could facilitate more-rapid translation of biomedical knowledge and clinical science into widespread practice?

These concerns have been heightened by rapid changes occurring in the healthcare system itself and recognition that even if the healthcare system (or the pace of new biomedical knowledge) remained unchanged, research infrastructure and capacity are inadequate to meet existing challenges (Heinig, Quon, Meyer, & Korn, 1999; Snyderman, 2000; Sung et al., 2003). For example, it is clear that rising costs of clinical research, inadequate funding of investigators and their research, escalating regulatory burdens, chaotic health-delivery infrastructures, competition between health plans and insurers, insufficient information systems, insufficient numbers of clinical investigators, and limited patient participation are hampering the effectiveness of national clinical research (Campbell, Weissman, Moy, & Blumenthal, 2001; Frist, 2002; Lenfant, 2003; Institute of Medicine, July 1, 2001; Oinonen, Crowley Jr., Moskowitz, & Vlasses, 2001).

Recognition of these concerns has prompted the realization that new kinds of "laboratories" that allow for clinical research in the actual settings in which patients typically get care are needed. These laboratories or series of laboratories are needed for translating basic science into human studies and for translating new clinical knowledge into clinical practice. While academic medical centers (AMCs) and clinical research organizations (CROs) have provided excellent settings for Phase I and II trials, care in those settings often differs from settings in which most Americans receive their health care, such as in community-based offices, clinics, and hospitals. Other common venues for care are neither well represented in clinical research, such as urgent care settings, emergency rooms, chronic-disease and rehabilitation hospitals, nursing homes, schools, and work-related settings, nor in the field (where cardiac arrests and traumatic injuries are first evaluated and treated).

If clinical research could be conducted in all the diverse settings representative of where patients receive care, then the value of advances in clinical sciences could be more systematically evaluated and effectively applied. The translation of new knowledge into clinical practice and health decisionmaking could be informed by patients representative of the community. Since patients receive care from providers in venues that are also representative of the community, the results are likely to provide scientific advances that will inform basic scientists, as well as those engaged in clinical practice and in health decisionmaking.

Reengineering the Clinical Research Enterprise to Involve Clinicians

In response to concerns such as those above, the NIH has launched an innovative initiative known as the NIH Roadmap for Medical Research (Zerhouni, 2003). The Roadmap encompasses virtually all steps of the research- and translation-process from basic biomedical research to developing and disseminating treatments based on clinical research to providers of clinical care. It anticipates complex scientific and healthcare challenges of the 21st century that will affect the types of multidisciplinary teams and flexible research infrastructure needed to meet these new opportunities and challenges. NIH envisages the Roadmap as a framework of priorities to be addressed at local and system levels.

One of the priorities identified in the NIH Roadmap is the reengineering of the current clinical research enterprise in ways that will accelerate and optimize the clinical-research process and infrastructure. NIH's definition of *clinical research* includes patient-oriented research, in which an investigator directly interacts with human subjects, epidemiological and behavioral studies, outcomes research, and health services research. This definition suggests that a broad array of clinical providers and patients within a wide spectrum of clinical settings and contexts should be available for clinical research studies. One critical ingredient for the successful conduct of clinical research is the availability of a cadre of clinicians who are willing and able, in a time-efficient and cost-effective manner, to enroll patients in clinical trials.

In response to the shortage and relative lack of diversity of providers participating in clinical research, the Roadmap proposes a National Clinical Research Associates (NCRA) Program that would attract a cadre of practicing providers to the field of clinical research (Zerhouni, 2003). "Associates" would participate in clinical research in the community. Enlisting providers who are actively delivering clinical care into the research arena would not only make available a large number of those providers' patients as research participants, but it would provide NIH with an opportunity to study research questions in the community on an unprecedented scale. Instead of limiting most clinical research to patients seen by providers affiliated with academic institutions, NCRA would enable many community practices and patients to participate in clinical research. Increased participation by and feedback from community providers and patients may help inform biomedical scientists how to more effectively design research studies and treatments and facilitate dissemination of evidence-based approaches to prevention, diagnosis, and treatment into widespread and routine use. In addition, at this dawn of a new era of genetics and biomedical technology, participation by and input from a more diverse and representative set of providers and patients may also accelerate biomedical scientists' understanding of how biological variability contributes to illness susceptibility and treatment success. In short, NCRA would offer a direct response to concerns about a lack of community-provider involvement in clinical research and help ensure the relevance of clinical research to everyday practice.

Emerging Context for NCRA. When first conceived, NCRA was intended as a mechanism for supporting the new clinical research environment. This environment was (and still is) characterized by the rapid development of new analytic tools, information and communication technologies, and the intent to simultaneously pursue multiple, large, translational studies. The concept of NCRA was developed to link the extraordinary biomedical advances with real-world clinical realities. While it is clear that new biomedical knowledge and breakthroughs are likely to accelerate over the next decades, the ways in which these advances will apply to clinical challenges are less certain. What is certain is that rapid changes in society and unexpected events can influence research priorities of both biomedical and clinical sciences. Shifting demographics is associated with changes in the burden of diseases away from acute and more toward chronic diseases. New diseases and threats of associated pandemics (e.g., avian flu) are major concerns. Finally, unanticipated events, such as "September 11" and the mailing of anthrax through the United States' postal system, the occurrence of a major natural disaster that affects the United States' economy (e.g., Hurricane Katrina), and the Iraq War can have a profound influence on priorities for research and the allocations of resources to address them. Optimal strategies for translating biomedical discoveries to clinical advances will require a flexible, interdisciplinary approach involving broad representation of patients and providers and a faster, more efficient execution of studies.

Goals of NCRA

The broad goals underlying the design and implementation of NCRA are to

1. Create networks and partnerships that are diverse and representative of all healthcare and clinical research stakeholders
2. Improve efficiency and productivity in conducting clinical research and in disseminating new knowledge to healthcare providers (i.e., "reengineer" clinical research)
3. Promote a wide array of studies that will be applicable to a large number of patients, with results that will be available for review and dissemination by community providers, as well as by scientists (i.e., providing a deeper understanding of biology and promoting interdisciplinary research teams).

To achieve these overall goals, what is needed is a stable infrastructure that will enable a large number of providers and patients to participate in clinical research. Providers will need to be recruited. They will need adequate training and support so that they can continue their involvement with clinical research across studies and time. A new kind of research infrastructure is required that will address the realities of clinical research and clinical practice: costs, liabilities, and opportunities. Although there are exceptions, existing research infrastructure (e.g., subject recruitment, protocol development, equipment of administration sites) tends to be based on a traditional biomedical model that focuses on questions generated in the laboratory by the basic scientist—an infrastructure that has worked very well for bench research and some types of clinical trials but that generally is not well suited for supporting unique challenges of community-based researchers conducting the kind of research envisioned.

Methods

To develop a conceptual model of NCRA and assess its feasibility, RAND used an iterative process that incorporated input and feedback from a variety of sources and stakeholders. At various points during the project, we incorporated all information obtained to that point into our assessments and model development. We then presented our assessments and developing models to key informants and elicited feedback from the informants. That feedback was used to identify unresolved issues or needed refinements to the model. We then repeated various parts of this cycle until all outstanding issues were satisfactorily addressed.

Data sources for our literature review included academic and trade journals, Web pages, and public- and private-sector reports. Interview data came from a diverse group of stakeholders, ranging from individual community providers not currently involved in research to leaders of large clinical-research networks and national professional associations (see below).

Key Stakeholder Interviews. We focused on interviews with five key stakeholder groups (Table 1).

Table 1: Number of Interviews, by Stakeholder Type

Stakeholder	# Interviews
1. Community providers (e.g., individual primary care physicians, dentists, nurse practitioners) and provider organizations (e.g., health plans, large community practices) not currently participating in research)	37
2. Individual providers and healthcare provider organizations already participating in clinical research	30
3. Leadership and coordinators of clinical research networks (e.g., CCOPs, AMC leaders, PBRNs) that can inform or serve as prototypes for NCRA	80
4. Representatives of private-sector organizations (e.g., CROs) and stakeholders (e.g., professional associations, pharmaceutical companies) with relevant experience and interest in potential NCRA activities	77
5. Representatives of public and government entities (e.g., leaders from NIH Institutes and other federal agencies) with relevant experience and interest in potential NCRA activities	19
Total	243

We sought to identify a reasonable number of informants in each key category (e.g., providers without research experience) and subcategories (e.g., primary care physicians or dentists) and also to ensure that the sample was diverse with respect to geography, informant demographics, knowledge, and experience base. We emphasized interviews with informants who could provide data on specific costs of conducting clinical research in community settings.

Stakeholder informants were identified through a "snowball" sampling, in which we asked each informant to identify additional individuals we should interview from selected categories. This snowballing was an iterative process in which new leads from interviews and feedback from the NIH project officer continually expanded the

number and types of informants identified. At the same time, our targeting of specific individuals to interview was informed by emerging themes and issues for which we believed additional interviews with representatives from a given stakeholder group would be helpful. We conducted a total of 243 interviews between September 2004 and October 2005. Table 1 shows how these interviews were distributed across the different types of stakeholder groups.

We conducted the interviews using semi-structured protocols designed for different types of stakeholders. The protocols served as a general guide and had sample probes rather than a set of specific questions that was asked of every respondent. Before the interview, all informants were sent descriptive materials about the NIH Roadmap Initiative and the proposed NCRA Program, the purpose of the interviews, and a consent protocol. These materials and procedures were reviewed by the RAND Institutional Review Board (IRB) prior to beginning interviews. At the beginning of each interview, key aspects of the project and an oral-consent process were discussed. Each interview was conducted by one or more of the project investigators. In all, nine team members led and/or participated in interviews. Most interviews were audiotaped and transcribed into text.

At the conclusion of each interview, the interviewer(s) identified any key themes and issues raised during the interview. These themes and issues were presented at a weekly debriefing meeting attended by all investigators participating in interviews. This approach served to facilitate rapid sharing of new information and themes identified, and also to identify issues that should be further developed in upcoming interviews. As a final step, two or more investigators systematically reviewed all transcripts within a couple of weeks of the interview to identify key themes. Table 2 shows examples of interview topics during different stages of the project interviews.

Table 2: Sample Interview Topics Emphasized in Early and Later Stages of the Project

Early Phases	Later Phases
Incentives and disincentives for provider participation; organizational barriers; motivators Strategies for provider participation and retention Ethical and professional issues Advantages and limitations of different types of research networks/organizations, by study and provider type Potential role of emerging information systems Specific recommendations to NIH on NCRA design	Reactions to proposed NCRA models Best practices in community research networks NCRA as complementary to or in competition with providers' organizations Issues related to partnering Optimal configuration for different types of NCRA studies Governance, oversight, and quality control for NCRA Liability and marketing concerns Addressing privacy, HIPAA, and institutional review board issues Costs associated with conducting various types of clinical research studies Specific recommendations for modifications of NCRA design (e.g., changes required for selected stakeholder participation in or support for NCRA)

We obtained cost estimates from a variety of different sources. We used detailed study costs from previously funded research that funders, researchers, and entrepreneurs generously shared with us. Additionally, we used informants who were familiar with current or past clinical research budgets, including site PIs of large, NIH-funded multi-site clinical trials, clinical research project managers, and budget monitors. As we designed the different components and personnel that make up NCRA and identified their major tasks, we contacted informants and asked them to provide cost estimates for completing the tasks. For tasks or activities, informants either provided us actual unit costs (e.g., lab costs) or provided other information, such as estimates of the time it took a staff member to complete the task, the education and training of that person, and the annual salary of a person in that role (including indirect costs), which we then used to back out the cost for the task. Whenever possible, we obtained multiple types of information related to costs to ensure that we could best fit the data to the various types of study complexity and numbers expected to characterize NCRA.

Key Findings from Interviews Regarding Incentives and Disincentives Associated with Community Provider Participation in Clinical Research

In this section, we describe responses to the issues raised in the early interviews.

Key Barriers to Provider Participation in Clinical Research. Financial considerations were consistently the strongest concerns of providers and stakeholders. Although informants varied somewhat on the specific disincentives they emphasized, they almost universally agreed that economic considerations were paramount,

particularly given the emergence of managed care. Some informants stressed the importance of salary or financial reimbursements associated with the conduct of clinical research; others emphasized concerns about time constraints and the trade-offs between time spent on clinical activities and time spent on research activities. Others focused on concerns regarding the cost of space, equipment, and personnel required for clinical research and the potential for research to disrupt patient flow and care.

Providers consistently expressed concern about the burdens associated with institutional review board (IRB) applications, report generation, and communications with the principal investigator, data-coordinating center, and regulatory agencies regarding protocol design, protocol changes, IRB changes, and data quality. Providers also professed a belief that funders underestimate the administrative burdens associated with the conduct of clinical research in the community. Providers lauded the potential contributions of information systems, but they also expressed dismay that advances in information technology did not necessarily decrease their work burden—and sometimes increased it.

Many community providers, particularly primary care providers, expressed concern that their participation was valued only for the recruitment of patients, rather than for the providers' clinical expertise or insights into important clinical challenges that could benefit from biomedical advances. In fact, some primary care providers indicated that they would not want to participate in NCRA unless a clear commitment was made to involve providers in some components of the research process beyond just recruitment (e.g., creating opportunities for provider input into choice of specific study topics or design).

Providers admitted that the prospect of clinical research in their practice prompted some fear about how their patients would react to being invited to participate in a study. Whereas typical studies might benefit society, direct benefits to their individual patients would generally be small, although the study might impart some risk to them. Providers also expressed the concern that enrollment of their patients into studies would expose the patients to providers in an academic medical center (AMC) who would "steal them away," resulting in a lost relationship and revenue. Some providers also stressed concern regarding liability insurance. While those associated with AMCs were confident that their participation in research would be covered by their malpractice insurance, others more removed from academic centers feared that they would be liable if a patient experienced a medical problem associated with the research.

Key Incentives for Provider Participation in Clinical Research. Despite the perceived barriers to clinical research participation, many providers were intrigued by the possibility of participating in research studies, especially if they thought that it could contribute to improving patient care. Although some providers acknowledged that the opportunity to earn extra income was a consideration, most providers emphasized nonfinancial reasons for their interest—for example, a chance for intellectual stimulation and collegial collaboration that often was lacking in their day-to-day practice. Participation in scientific pursuits was particularly appealing to primary care providers, who felt increasingly constrained by proliferating productivity standards and paperwork requirements. Providers also cited the potential prestige of being engaged in NIH-sponsored research and the professional recognition that accompanies such participation. Many also recognized that research participation was a means for attracting patients to their practice and for accessing state-of-the-art treatment and diagnostic tests otherwise unavailable to the patient.

Not All Providers Are Interested in Research. Despite the appeal research holds for many providers, not all practicing clinicians are interested in participating in research. Indeed, regardless of how little effort may be required of a provider to participate in a study or how extensive the incentives and benefits, some providers will not be interested in research participation.

Precise estimates of the proportion of providers with no interest in participating in research versus those with potential interest who are not participating in research are not available. Nevertheless, there is general consensus among the providers and other sources with whom we checked that only a small fraction of potentially interested community providers are currently involved or have ever been involved in clinical research.

What Strategies May Be Effective for Involving Providers in Research? With recognition of the many benefits of clinical-research participation, several strategies for building a network of providers for ongoing clinical-research participation have been used successfully. One set of strategies directly incentivizes provider participation. Principal investigators of large studies often publicly recognize providers who recruit patients for their studies, at national meetings or in journal articles, and may be invited to participate in meetings announcing cutting-edge work. Some providers highly value the receipt of a plaque or certificate for their wall. In some settings, provider payments have increased to more closely approximate clinical income. Several

networks affiliated with national professional societies are working together with their societies to provide continuing medical education (CME) credits to society members who participate in their clinical research network.

In other settings, strategies for building a network of providers have focused on improving infrastructure or incentives for the conduct of clinical research. Some have built an infrastructure and incentive system for the network in the context of existing departments or units. For example, some AMCs and academic research organizations (AROs) have invested extensively in the use of a network of clinical research coordinators and clinical research associates to support providers. This approach is similar to techniques used by commercial clinical research organizations (CROs). It is expected that this set of interventions will reduce the need for small practices to hire their own research administrators and other research staff. Yet, while effective in some settings, some informants observed that putting a study coordinator into practices or hospitals has the potential for creating unexpected problems. For example, animosity between the coordinator and the practice's nurses has occasionally occurred, because the goals of the research coordinators and those of the clinical nurses clash regarding the use of time, space, and other resources. Other informants noted that the costs of such research personnel placements can be very high and not necessarily efficient for recruiting patients. For instance, costs and time associated with the coordinator traveling between office settings are often high. Many providers also had concerns about the cost of space being used by the research coordinator, since that space could have been used for the delivery of clinical care. Efforts such as those described above have been made to align the incentives of provider-researchers with the successful conduct of clinical research. However, it is unclear whether such isolated interventions can successfully engage large numbers of community-based providers whose professional incentives are not primarily aligned with those of the conduct of research.

A third set of strategies has involved more narrowly defining the responsibilities of providers as they participate in clinical research. For example, with this type of strategy, a clinician may only need to see research patients on first and last research visits, with a study coordinator seeing patients in between.

We found some examples of organizations successfully addressing selected provider concerns, but these were the exceptions rather than the rule. Most cases involved the conduct of low-complexity observational studies, with providers involved in studies as time and interest allowed, as compared with a more-sustained, more-predictable approach to research participation. Most settings where community providers were at least moderately involved in research involved private, for-profit organizations (e.g., CROs) that were entirely focused on industry-sponsored research and were able to compensate providers at a high rate.

In general, the most successful examples of community providers participating in research involved clinicians who had fundamentally restructured their practices so that they were completely or mostly dedicated to performing research studies. In these cases, providers had the opportunity to earn well beyond what they could earn doing clinical care and likely well beyond what NIH could afford to do. Such providers tended to place less emphasis on the relevance of the research topics to their clinical practice than did other community providers.

While each of these strategies has been satisfying in some respects, they typically address one aspect of the providers' challenges but do not provide enough support to sustain the participation of providers across time and studies. Some other strategies for motivating provider participation in clinical research have been even less successful.

Which Strategies Have Not Worked? As the proportion of providers involved with managed-care networks has grown, so have expectations regarding provider clinical productivity. Such pressures have translated into more difficulties in provider recruitment for clinical research (Ross et al., 1999; Wilson et al., 2000)—difficulties that have posed a greater challenge for publicly funded than privately funded research, since provider reimbursements are typically higher with the latter. However, increased competition and tighter profit margins in the pharmaceutical industry have reduced the generosity of payments to CROs, in turn, reducing the financial incentives and infrastructure support previously successful CROs have been able to offer providers. Indeed, many providers mentioned having agreed to recruit for a CRO with the assurance that the burden for clinical-research participation would be minimal. In fact, what they experienced was an amount of work that was greater and support that was less than they had anticipated. In some instances, such an experience has permanently turned providers against clinical research. Many field recruiters have advised that simply advertising a study and offering some assistance to providers to participate in the study is not an effective strategy for recruiting or retaining providers. In most cases, providers will not participate, and the majority of

those who do quickly find that the amount of work involved is more than they were led to believe. The majority of research-naïve (and even many research-experienced) providers initially overestimate how many patients they can recruit to a study in a given time. This recruitment shortfall has downstream effects for the principal investigator and research enterprise, because the principal investigator will have to initiate additional recruitment strategies to recruit more patients, delaying study completion and increasing study costs.

Various types of research networks have been used to try to engage providers in research and are often initially met with enthusiasm. However, over time, many providers do not hear about studies and do not feel a sense of membership in the network. Providers indicated that research organizations have underestimated provider administrative burdens, the number and types of IRB revisions, the complexity of data-entry requirements, the burden to provider offices associated with audits, and the challenges of meeting study inclusion and exclusion criteria. Organizations have generally not been able to effectively build networks that sustain a high and ongoing level of camaraderie. Provider retention across studies and time has been low. Research-naïve providers often received minimal training or guidance. Once they realized that clinical research participation is more difficult than they had anticipated and requires substantial support not available to them, they disengaged from research after participation in one or two trials. Providers also expressed dismay regarding the complexities of using information technologies as a tool for research. Although they had hoped information technology would improve their efficiencies, many of these systems are not yet harmonized to fully interface with major data-management systems. They require more adjustments than most providers can manage in their office systems.

Review of many of the previously used strategies suggests that, in the current organization of clinical research, providers do not have the resources to successfully engage in clinical research without substantial support from an external organization. Any effort to successfully attract and retain a large cadre of providers will need to focus on strategies and systems collaboratively involving providers, organizations, and NIH to effectively recruit and retain providers.

PROPOSED MODEL OF NCRA

In view of findings such as those highlighted above and continuous feedback from key stakeholders and NIH staff, RAND recommends the model of the NCRA described below.

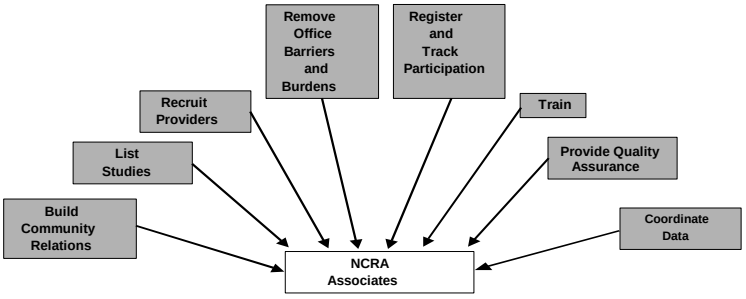
What Is NCRA?

The National Clinical Research Associates (NCRA) Program, as conceptualized, is a coordinated mechanism for bringing large numbers of community providers into the research enterprise. NCRA can be defined along three dimensions. First, NCRA is a network of providers who will participate in clinical research in the context of delivering clinical care. Second, NCRA is a well-integrated set of services designed to identify, recruit, retain, and support those providers who conduct research in the clinical-care setting in a manner consistent with the high standards that characterize NIH research. Third, NCRA is an administrative and coordinating capacity that oversees the functions of NCRA and its associated stakeholders. These three dimensions work together as a tool that will further the efficiency and productivity of research and the dissemination of new knowledge to healthcare providers, create networks that are diverse and representative of all healthcare and research stakeholders, and promote a wide variety of studies applicable to a large number of patients. In addition to the three dimensions that make up NCRA, NCRA represents a way to organize and finance clinical research and can be characterized as a flexible tool to be shared across all NIH Institutes.

NCRA Is a Network of Providers. As a network, NCRA is expected to scale up to 40–60,000 providers capable of participating in clinical research. The network will be stable, with provider retention across time and studies far exceeding the norm of today's research provider. The NCRA network has the flexibility to involve any configuration of specialty type preferred by NIH. Although initially developed for community primary care providers (e.g., family medicine, pediatric, internal medicine, and obstetric/gynecologist physicians; dentists; and nurse practitioners), NCRA is flexible enough that other community providers (e.g., medical subspecialists), other specialty providers, specialty networks, and academic providers can also make use of the NCRA mechanism.

NCRA is a Set of Services for Supporting Participating Providers. To motivate a stable cadre of providers to include research as a component of their professional lives, a system of support services for these busy practitioners of clinical care needs to be implemented (Figure 1). To meet these needs, NCRA will fund a set of service entities (mainly through subcontracts). These entities and the services they will provide are displayed in Figure B of Appendix B.

Figure 1: Services Can Tip the Balance to Motivate Provider Participation



Community Relations Subcontract: To ensure that providers are aware of NCRA and the research opportunities available to them and their patients, NCRA will subcontract to a community-relations organization, which will help NCRA promote the importance of clinical research to providers and their professional organizations and emphasize the value patients derive from research, particularly that conducted in community settings. Providers need to be informed of how NIH and their specialty societies support NCRA.

Registry of Providers and Studies (ROPS) Subcontract: Once providers are aware of NCRA, they need a uniform platform for registering their interests and learning about salient study opportunities. The NCRA Registry of Providers and Studies (ROPS) provides this service for providers as a dynamic Web-based registry that will list the identity of providers and their productivity in terms of completed training, studies initiated, and patients enrolled. The Web-based system also serves providers by logging in provider questions and responses, listing study protocols, offering chat sessions for providers, having a confidential venue in which providers can register complaints or concerns, listing key events, and sharing information about consenting providers with research-associates' organizations. ROPS is envisioned as a subcontract overseen by NCRA administrative staff.

Research-Associates' Organization (RAO) Subcontracts: To recruit, support, and retain providers and to overcome the innumerable barriers and disincentives that providers face in participating in clinical research, NCRA will engage approximately 30 to 40 research-associates' organizations (RAOs). RAOs may be any of the following: AMCs, AROs, practice-based research networks (PBRNs), CROs, community hospitals, multispecialty groups, health maintenance organizations (HMOs), and clinical trial networks (CTNs). Each type of organization brings distinct strengths and notable weaknesses to the table, and it is unlikely that any one type of entity will be able to support all of NCRA's needs. Accordingly, collaborations across organizations are strongly encouraged.

RAOs will be incentivized to remove the barriers keeping clinical providers from participating in clinical research and to provide support to them by identifying providers who are likely to engage diverse patient populations that will be eligible for specific study protocols. RAOs will recruit providers to participate, and they will address questions and concerns providers may have. RAOs may also assist providers with NCRA registration, with refitting of their office infrastructure to facilitate research, and with patient recruitment efforts.

As a supplement to services available through ROPS, RAOs will help providers review study protocols and evaluate which protocols are most likely to be successful in the providers' office setting. RAOs also will help providers understand study-specific reimbursement strategies so that providers can identify a subset of studies in which they are likely to be able to successfully recruit patients for study participation within the allocated budget in their office settings. Table 3 summarizes ways RAOs can help providers participate in NCRA.

Table 3: Ways RAOs Help Providers Participate in NCRA

RAOs Recruit Providers into NCRA
Identify potential Associate recruits (outreach)
Educate about NCRA benefits, responsibilities, and processes
Provide access to materials describing NCRA for independent provider review
List all studies, eligibility, and inclusion/exclusion criteria
RAOs Help Providers Think About How to Conduct Research in their Own Office Settings
Assist providers in thinking through the business implications of participation
Prepare providers to submit key documents and register themselves with ROPS
Help providers register by mail if they have no Web-based access
Contact and encourage providers who have partially completed registration on ROPS to complete the process
RAOs Help Providers Considering Their First Study
Explain study protocol and training requirements to provider
Ensure that all administrative requirements are met
o Identify and guide interactions with IRB
o Evaluate liability insurance
o Identify certified laboratories and pharmacies
o Coordinate referrals for multiprovider studies
RAOs Help Providers See How Research Works in the Office Setting
Review all procedures/tasks
Consider and demonstrate how protocol will affect workflow
Identify staff person responsible for specific tasks (e.g., scheduling)
Set enrollment goals
Establish study timeline
Define how data quality will be assured
RAOs Help Providers with Finances When Considering Their First Study
Explain how reimbursement is set
Explain study reimbursement schedule, including reimbursements and insurance coverage
Calculate staff time that would be covered and help determine whether such coverage is sufficient
Review checklist for costs
RAOs Help Providers Prior to Initiating Their First Study Implementation
Work with providers to complete IRB requirements
Check appropriateness of liability insurance
Advise provider on how to recruit for a research coordinator
Help establish study-specific processes (e.g., scheduling, record keeping, storage)
Facilitate (and perhaps help compensate) cost of starting up high-speed Internet connection for providers
RAOs Provide Support Across All Studies
Provide consultation to providers throughout the study
Ensure that affiliated providers do not enroll so many patients that research activities swamp the providers' clinical responsibilities
Provide some enrollment and quality-assurance checks with respect to whether the study protocol is being followed (e.g., audits)
Track patients who switch providers and try to retain them in the study by linking them to another study provider

Additionally, RAOs allow providers a sense of community by offering communications and updates, by sponsoring principal investigator talks in which providers can participate, and by sponsoring other regular gatherings of providers. RAOs inform providers about procedures and policies to address primary provider concerns about losing patients to subspecialists involved in the research protocol.

In summary, RAOs directly serve providers by removing barriers and disincentives for provider participation in clinical research. There is no single way for RAOs to support providers. Their services are broad but responsive to the unique needs of providers and their office settings. For example, for one provider, the RAO may fulfill a need by providing access to shared study coordinators and nurses, whereas, for another provider, the RAO most effectively helps providers by assisting them to modify their practices and patient flows. In one setting, the RAO directly assists with patient recruitment. In another, the RAO supports research-staff identification, training, and information technology support.

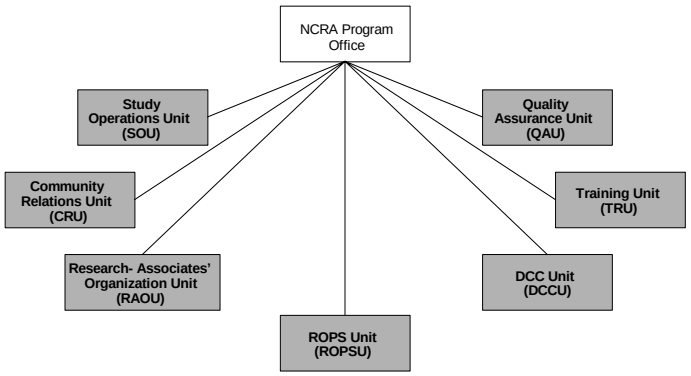
NCRA is constructed to facilitate RAO success, and RAOs are tied conceptually and contractually to NCRA administrative functions via the RAO Unit. RAOs are supported via free-market principles to use their unique strengths to best support provider recruitment and retention, rather than being mandated to use a predetermined set of strategies. In this way, RAOs can work locally with providers to best achieve NCRA goals. As a checks-and-balances mechanism, the future of RAOs depends upon the successful support of providers and of providers' successful engagement of patients in high-quality research.

Web-Based Training Services: To ensure that providers have the appropriate generic research skills, NCRA will offer Web-based training. Providers can partake of the training at their convenience, without having to travel away from their clinical practices. For instance, Web-based training will be offered that allows consistent

training, even when providers and staff members receive training at different points in time and place. NCRA provides basic introductory research training for providers and facilitates the dissemination of study-specific training as specified by principal investigators. Upon completion of training modules, ROPS provides the service of tracking completed training and linking those data with provider-productivity data, thereby generating an Associate status for each provider. This status reflects provider research productivity and is associated with incentives and rewards for providers.

Quality Audits: As a supplement to training services and other forms of support through ROPS and RAOs, NCRA incorporates quality-assurance efforts that directly interact with providers via audits that will occur within the providers' offices. These efforts assure providers, as well as the larger research enterprise, that research conducted in providers' offices will function at the high standards characteristic of NIH research. When providers have concerns about protocols, enrollment, data, and/or reimbursement, they can communicate their concerns through ROPS and/or with their study-specific RAOs. In this way, NCRA assures providers that their voices are heard, particularly with respect to quality and safety concerns throughout the research process.

Figure 2: NCRA Administrative NIH-Led and -Staffed Units



Data-Coordinating Subcontracts: Providers participating in research are responsible for submitting data, as specified by protocols, to data-coordinating centers. RAOs support providers in this task by guiding them toward efficient strategies for data transfer. Data-coordinating centers then provide reimbursements to providers in exchange for their services, according to a predetermined, market-based reimbursement strategy.

In aggregate, these services will make feasible sustained clinical-provider participation in clinical research. However, the delivery of these services requires coordination, which will be the administrative responsibility of NCRA.

NCRA Acts as an Administrative and Coordinating Center. Administrative structure and coordinating capacity are required to support the integrity of NCRA as it delivers services to Associate providers. The NCRA administration is envisaged as the aggregation of an NCRA Program Office and seven units within the greater NIH, which are independent of individual Institutes (Figure 2). These will be the main vehicles leading the effort to make NCRA, and its potential to influence the clinical-research enterprise, a reality. Although the actual delivery of services described above will be done through subcontracts, a small administrative staff will be assembled to manage and oversee the integration of services.

The *NCRA Program Office* will recruit, hire, and monitor the performance of unit directors; set NCRA-wide policies and procedures; approve major unit elements; make study-specific decisions when necessary; oversee resource allocation; and maintain high visibility for the NCRA system.

The *Research-Associates' Organization Unit* (RAOU) will determine and periodically revise the number and kinds of RAOs needed to complete the mission of NCRA; establish and maintain expectations and standards for how RAOs operate; recruit, select, and renew qualified RAOs to participate in NCRA; provide initial and ongoing support services to RAOs, to assist them in the recruitment and support of providers; and monitor and evaluate RAOs on a regular basis.

The *Registry of Providers and Studies Unit* (ROPSU) will oversee the design and implementation of the ROPS in the early years of implementation and operation. In subsequent years, the unit will transition to maintenance and improvement tasks, such as regularly updating and monitoring the data and developing new features.

The *Study Operations Unit* (SOU) will contribute to and participate in refinement of study portfolios; develop a mechanism for assigning reimbursement amounts to research tasks; encourage insurers to reimburse research-related clinical activities; and establish fixed per-patient and per-provider reimbursement schedules for providers and RAOs, based on the completion of specific research tasks. One mission of the Study Operations Unit is to operationalize the existing proposal-evaluation and protocol-development processes to

ensure that they are aligned with NCRA goals and infrastructure. Initially, SOU's involvement in developing the proposal design and study protocol will be indirect: SOU will suggest adaptations through appropriate platforms to prepare studies for the NCRA system and provide technical assistance in listing and costing research-associated tasks. Over time, SOU may play a larger role in this process, taking part in decisionmaking with the greater NIH community. It is expected that a partnership will develop over time, wherein the larger NIH community and NCRA work together in defining and selecting study portfolios that best fit NCRA's goals and structure. SOU can gather evidence about which studies work well under NCRA and which do not, and provide feedback to NIH for further refinements of the study-selection process.

The NCRA design calls for utilization of incentives, many of them financial. To accurately estimate the costs and required incentives for research-associated tasks, the SOU will develop a scheme, or taxonomy, for assigning payments to these tasks. For clinical tasks that can be reimbursed via third-party payers, SOU will refer to insurance rates as guidance on payment amounts. The SOU will ensure that, in advance of a protocol being finalized, the PI, the RAOs, and the providers are well versed and clear about exactly which study-specific-protocol services are covered. This clarity is particularly important, since one of the main reasons providers cite for not participating in clinical trials is their fear that they or their patients will be liable for protocol-induced costs. Similarly, one of the main fears expressed by research-associated organizations is that they will be liable for protocol-associated costs. When RAOs and providers are confident about which costs are covered and by how much, their costs are predictable and they can establish their own strategies for managing resources.

The *Training Unit* (TRU) is responsible for ensuring that NCRA Associates are well trained and prepared to conduct high-quality research. TRU will establish initial training courses for new NCRA Associates (research basics, HIPAA/IRB, and refresher courses), maintain and update the training courses, and facilitate study-specific training requests on a case-by-case basis.

The *Data Collection and Coordinating Unit* (DCCU) will be responsible for coordinating and supporting the data flow for specific studies, as well as that for the NCRA system overall. At the outset of NCRA, each study will plan and budget for its own data center(s). Over time, to achieve efficiency and consistency gains, NIH and NCRA may consider establishing a centralized data center, geographically distributed data centers, or study-content data centers. In its fullest capacity, the DCCU will track and monitor enrollment and patient burden; administer training-initiation payments; promote standardized forms, variables, and other templates to enable easy and reliable data collection, transfer, storage, and sharing; and act as a study-specific data center for PIs who choose DCCU as their study data center. In the interim, the DCCU will facilitate coordination between RAOs and study-specific data centers, monitor enrollment and patient burden, and administer payment to providers for training in research basics.

The *Quality Assurance Unit* (QAU) will coordinate the development and adoption of quality standards for all aspects of clinical research adopted in NCRA units; establish and perform systemic checks or audits on the quality of process and outcomes and, thereby, assess the effectiveness of quality-control mechanisms; collect and document the progress on quality-control activities from the Study-Specific Executive Committees and NCRA units; and implement procedures for case documentation and quality improvement.

The *Community Relations Unit* (CRU) will help increase awareness and communicate key features of NCRA to the public and key NCRA stakeholders; assist RAOs and PIs in their community, media, and other publicity efforts; and disseminate information about new knowledge produced and other accomplishments of NCRA.

Units are designed to start in Year 1 to ensure sufficient time and resources to carry out their tasks. The units will work individually and in collaboration to complete their tasks, both during the implementation phase (Years 1-3) and operational phase (Year 4 and on). As is characteristic of many important large new projects, much of the success or failure of NCRA wii depend on the countless decisions that will need to be made during the implementation phase of NCRA.

Highly capable individuals will be required to transform the complex NCRA from a theoretical model into an efficient, cost-saving, successful reality. For it to work optimally and provide all the suggested benefits will require that the unique issues be addressed and that there be interrelationships among three dimensions—NCRA Associates, NCRA services, and NCRA’s administrative functions—described in the next section.

Characteristics of the Ideal NCRA and How NCRA Will Achieve Its Goals

Functioning together, NCRA Associates, NCRA services, and NCRA's administration are a tool that will further the efficiency and productivity of research and the dissemination of new knowledge to healthcare providers, create networks that are diverse and representative of all healthcare and research stakeholders, and promote a wide variety of studies applicable to large numbers of patients. With its three dimensions properly engaged, *NCRA is a powerful tool to be shared across NIH Institutes.* Its goal is to establish and maintain a large diverse network of NCRA Associates and the means to support the Associates. Once established, Institutes can use and reuse these network and support mechanisms to run multiple, large, national studies of their choosing. The following are 11 characteristics that NCRA must demonstrate to achieve its goals.

1. NCRA should be both robust and flexible. Thanks to the three different dimensions, NCRA is expected to be both robust and flexible. NCRA's flexibility comes into effect in the various types of studies, number of providers, and provider specialty types it can accommodate, and in its ability to adopt a wide range of solutions for confronting emerging barriers. Its robustness resides in its ability to support providers and clinical research in general under potentially changing circumstances. NCRA is specifically designed to give providers a secure foundation with its NIH-associated units while devolving decisions about how to best recruit and support providers down to the local level of the RAO. RAOs are in the best position to know the specific characteristics and needs of their providers and will be best able to adapt their support services and recruitment strategies to specific types of providers. The role of NCRA administration is to help coordinate the overall development of NCRA and to address issues that are primarily at a national level, such as centralized IRBs, insurance, provider liability, and transgovernmental collaborations.

2. NCRA needs strategies to support busy practitioners so that neither the quality of research nor the quality of care delivered is compromised. Any attempt to give decisionmaking authority to participants throughout the system will need to be accompanied by a well-designed accountability system. Quality assurance will need to be emphasized for ensuring the safety of patients and the scientific endeavor as community providers with little or no research experience become central to the research enterprise. NCRA will build confidence in the clinical research enterprise by articulating standards for conducting research in a clinical-care setting and providing training, credentialing, and quality oversight. The NCRA Training Unit introduces providers to fundamental research training, the ROPS Unit tracks the training achievements of providers, and the Quality Assurance Unit (QAU) ensures that research conducted through NCRA is subjected to a high and effective level of quality control at all stages of research. Study-Specific Executive Committees will be responsible for careful oversight from beginning to end of all NCRA studies. Proper human protection and safety are a priority for NCRA, because all the promised benefits of clinical research through NCRA do not mean very much if human subjects are not properly protected.

3. NCRA must offer concrete strategies for addressing provider concerns about the cost of participation in clinical research. Building upon the three dimensions of NCRA, NCRA offers a unique set of financial incentives for promoting clinical research in community settings. NCRA's primary goal is to remove disincentives and increase incentives for providers wishing to participate in clinical research. To this end, NCRA will use market-driven models to reengineer the clinical research enterprise and, more specifically, to alter incentives of providers and the RAOs, thereby maximizing the combination that would be most suitable in achieving costs and goals. The core of this strategy focuses on (a) fairly compensating providers for their time and efforts and (b) compensating RAOs to recruit and retain providers by removing burdens and supporting them as needed.

Although nonfinancial incentives, such as prestige, personal satisfaction, and benefits for patients play a key role in motivating providers to participate in research, they cannot substitute for fair financial compensation for services. When providers are minimally involved with research, removal of the most pertinent disincentives (e.g., burdensome inclusion/exclusion criteria and inefficient data-collection strategies) is most appreciated. However, as the level of effort and participation increases, monetary compensation becomes of greater value—until it is a necessity. To recruit and retain a large number of providers, NCRA will need to adhere to a replacement-value principle: The provider's effort and time will need to be compensated at the same level as they would have been if the provider were engaged in clinical care instead (for the equivalent effort and time).

Toward this goal, the Study Operations Unit (SOU) will establish an overall reimbursements schedule for the most common research tasks. The schedule will take into account cost variation across geographic regions, stratified by specialty type and clinical and research experience. All studies fielded within the network will have

as a requirement the explicit budgeting of expected provider costs. Task-specific reimbursement amounts will be set before protocols are finalized. Providers will have the opportunity to review expected reimbursement rates before agreeing to participate in a study. RAOs will be available to help providers evaluate whether NIH payments will cover their costs. If they will, the provider is likely to be a successful research provider. If they will not, the provider, when reviewing the protocol, can register concerns with NCRA via the ROPS. NIH may elect to change reimbursements or the provider can decide not to participate in that study.

In addition to the per-patient reimbursement, which will be defined by the protocol with rates set by SOU, providers will receive a one-time reimbursement for completing the initial basic training and a one-time training reimbursement for their participation in each study (commensurate with study-specific training requirements).

RAOs will also be compensated for recruiting, supporting, and retaining providers through two main mechanisms. The first mechanism, annual infrastructural support provided by NIH, provides funds that RAOs can use to offset support for trainers and study coordinators, maintain databases, and support outreach efforts—expenditures that have been estimated at approximately $500,000 annually. The second mechanism, varying how per-provider and per-patient reimbursements are distributed on a study-by-study basis, has a default, which means that distributing study costs to providers and RAOs will occur through a Pass-Through financial model and, in exceptional cases (exceptionally large or exceptionally expensive studies), through a Master-Contract financial model. In the Pass-Through model, the SOU will set three rates for each study: (a) a per-provider reimbursement to be given to the provider for participation in the study, (b) a per-patient reimbursement for each patient that the provider enrolls and collects data from, and (c) an RAO-compensation rate that is a fixed percentage of the per-provider and per-patient reimbursement rates (estimated at 5%). The latter reimbursement will be paid to the RAOs for their efforts to recruit and support their affiliated providers.

4. NCRA must ensure that the voice of the provider is heard. Providers must feel that their voice is being heard so that they can take their rightful role as the key constituents in the NCRA. Otherwise, providers will have little stake in clinical research or NCRA, and they will not contribute in a sustained manner. Providers with NCRA Associate status will be acknowledged as members of a prestigious set of providers distinguished by research training beyond that of most practicing providers and by participation in the conduct of NIH clinical research designed to improve the health of the American people. As a group, NCRA Associates should have considerable power to influence change in the way research is conducted and used.

NCRA incorporates several features to facilitate discussion and feedback between providers and investigators. For example, ROPS provides a chat-room environment, in which providers can list questions and concerns, as well as share experiences regarding research participation. ROPS also provides a specific venue for providers to indicate study questions they find of interest to their clinical practice, and to indicate providers' views regarding how to improve the efficiency and rigor of studies performed in clinical practice. In fact, ROPS will periodically survey providers on their satisfaction with NCRA and solicit their recommendations for how to improve NCRA's functions in supporting providers. ROPS systematically communicates information it learns to the SOU, which uses this information to identify studies most likely to succeed in NCRA, as well as study-design strategies most likely to improve the efficiency and rigor of studies in clinical practice. NCRA has been designed so that RAOs and ROPS can communicate provider concerns to NCRA.

NCRA also understands the value that community providers assign to belonging to a professional group. ROPS will be the main facilitator of this sense of belonging for the national NCRA; RAOs will facilitate providers' sense of belonging to a smaller supportive structure.

5. NCRA is designed to include numerous checks and balances to ensure efficient and effective operation. The NCRA Program Office will be the decisionmaking body, creating a flow of information to enable providers, RAOs, and others to make informed decisions and overseeing NCRA implementation and operation. It will coordinate the efforts of each Unit, which, in turn, will be responsible for the overseeing of or coordinating with other Units or entities. RAOU is responsible for the selection, oversight, and support of RAOs as they recruit and support providers. RAOU will consult with ROPSU and QAU in deciding what are the appropriate and measurable indicators to use in assessing RAOs' study-specific and across-study performances. Such measures will be approved by the NCRA Program Office.

Every unit in NCRA will implement procedures or controls to ensure that NIH standards are met. Thus, for example, human-subjects-protection quality checks will be the responsibility of everyone in NCRA, from the

providers and PIs to the RAOs and the QAU. Finally, to build confidence and trust in the clinical research enterprise, many more stakeholders will be looking over the research processes and outcomes than ever before. Thus, NCRA will have multiple levels for assuring the safe, efficient, and effective conduct of research across community providers.

The QAU will ensure the effective adoption, use, and monitoring of quality-control mechanisms by all NCRA stakeholders, which will contribute to the greater NCRA goal of improving efficiency, integrity, and productivity of the clinical research enterprise. The QAU will achieve this mission by (a) leading the effort to articulate NCRA standards of quality that should be observed in all aspects of NCRA research, (b) assisting all NCRA units in designing and implementing quality-control mechanisms that aim to meet the NCRA standards, and (c) taking on a monitoring role in the long run to ensure that NCRA quality-control mechanisms are effective in promoting the standards. The QAU will also perform the traditional quality assurance function of checks, or audits. Examples of audits include random protocol reviews, trial-site audits, database audits, compliance checks with regulations, and Registry of Providers and Studies (ROPS) functionality checks. QAU will actively monitor whether quality is effectively being controlled for clinical research conducted through NCRA, not only for the successful conduct of each study but for the viability of NCRA as an enabling infrastructure for clinical research.

When the information collected by the QAU suggests that corrective action is needed at the study level, the QAU will present the issue within a particular NCRA Unit or across several Units and will make recommendations to the respective decisionmakers, whether that is the NCRA Program Office, an NCRA Unit director, or the chairs of the appropriate Study-Specific Executive Committee (SSEC). The Unit will play a role in categorizing problems across the avenues mentioned above: articulating quality standards, implementing quality-control mechanisms, and monitoring quality. As appropriate, the QAU will notify other federal agencies, including the Office for Human Research Protections, the Office of Research Integrity, and the Food and Drug Administration, of any abnormalities or misconduct.

Each study will have a Study-Specific Executive Committee with representatives of each Unit who will meet regularly to evaluate study progress and challenges. The SSECs, Unit-specific annual reports, and audits on quality control may reveal many types of problems that can be conceptualized at the study level (specific to a study), Unit level (unique to a Unit), or at the system level (multiple Units). The QAU will develop measures to categorize the problem; once the problem is categorized, the QAU will collaborate with the respective parties (e.g., the PI's institution, NCRA Unit director) to initiate quality improvement. The QAU will serve as a resource, offering recommendations and/or best practices gathered within and outside of NCRA.

DCCU will receive updates on patient enrollment and burden from study-specific data centers on a regular basis. It will use the updates to monitor NCRA-wide capacity for studies. This capacity-monitoring will inform NCRA and NIH in planning the study portfolio, so that there are a sufficient number of providers and patients who can be recruited for future studies, and to monitor patient burden.

An additional check on the system is the SOU documentation of average earnings of provider types across specific geographic regions, stratified by specialty type and clinical and research experience. This will be compared to the respective provider earnings associated with the research task payments specified by the SOU. If any discrepancies in this comparison are found, the SOU can periodically adjust the study-specific per-patient reimbursements.

Providers indicate their satisfaction with NCRA with their actual rate of participation with clinical research. When providers "vote with their feet" by not enrolling patients, the problem is promptly noted by both RAOs and data centers. The information is fed back to ROPS and NCRA's Data Collection and Coordinating Unit, which will present the data in a systematic manner to the NCRA's Study-Specific Executive Committee (which will include provider representation).

6. NCRA must be stable and predictable for both researchers and providers. If NCRA is to succeed, it must offer a stable and predictable environment for both researchers and providers. On the one hand, researchers will require a large, diverse, and predictable pool of experienced providers upon whom they can rely to conduct research. Providers, on the other hand, will require a large, diverse, and predictable pool of studies from which they can choose. Here, we include not only individual community providers but also larger provider organizations, such as the health plans of which an increasing number of providers are part. Because both

providers and managed care organizations employing providers have emphasized the importance of predictability if clinical research is to successfully fit into clinical practice, the NCRA infrastructure is designed to give providers key information to help them decide whether their participation is feasible and likely to be successful. When activities are predictable, they can be accurately budgeted for, managed in time and space, properly staffed, and monitored. Predictability is one mechanism NCRA can use to reduce the time commitment of NCRA Associates and, thus, the costs of NCRA. It can also increase the appeal of provider organizations supporting clinical research indirectly or through an RAO. If these organizations see NCRA as predictable and consistent with their business models, they are more likely to develop policies necessary to involve their providers.

Reimbursement schedules are established in advance of providers' and RAOs' agreeing to participate in studies. NCRA's Study Operations Unit works with NIH Institutes and insurers, as well as with independent sources, to establish fair-market reimbursements for research-associated tasks fulfilled by providers. NCRA's ROPS and DCCU periodically review study-specific patient enrollment data. Problems are brought to the attention of NCRA's Study-Specific Executive Committees, which consider strategies for improving enrollment.

7. NCRA must engender provider trust. NCRA is structured to engender provider trust across multiple dimensions. Providers are concerned about clinical research on behalf of their patients. Randomized trials evaluating new drugs or devices are particularly suspect in the minds of minority and low-income individuals and their communities because of prior abuses by investigators, such as in the Public Health Service (PHS) Syphilis Study in Tuskegee, Alabama, or because of general mistrust of how government officials or scientists will use health information (Hoyo et al., 2003; Osei, 2003; Wright et al., 2004). Similar issues of distrust about use of a patient's personal health information also arise with observational and epidemiological studies. Most practicing clinicians are aware that their patients have such concerns and, consequently, may be reluctant to discuss potential research opportunities with their patients. NCRA has the potential to proactively build provider and patient trust by building the infrastructure and activities to facilitate equitable and diverse involvement of providers and patients in clinical research. To achieve these goals, NCRA can build upon a recent report, *Public Trust in Clinical Research,* prepared by the Director's Council of Public Representatives (COPR, 2005). The issues addressed in the report and the recommendations it offers focus on clinical research overall, with some suggestions particularly pertinent to NCRA and provider and patient trust. For example, COPR Recommendation #2 suggests interventions to "encourage change in the culture of the scientific community to ensure that medical research is viewed in the context of a long-term commitment to the community, not a one-time research study." The action item associated with this recommendation is to build on the efforts of the NCRA Program for involving a broad and diverse set of community providers in research. COPR Recommendation #6 suggests "action to interest community providers in clinical research and maintain their involvement." Again, this is the central mission of NCRA.

Clinicians, particularly those working in community settings, may also be reluctant to engage in research because of first- or second-hand experiences in which the amount of time and effort required went well beyond what investigators led them to believe they would be expending, and/or the compensation they received fell far short of covering the financial costs their practice incurred. Even if financial compensation is perceived to be fair, many community providers may distrust academically based clinical investigators because they believe that such researchers have little understanding of the realities of community-based practice and the patients it serves (Asch, Connor, Hamilton, & Fox, 2000). Community providers may also fear that academic investigators will dismiss any input from community clinicians. NCRA's three-dimensional approach involving providers, support organizations, and administrative units specifically address the financial and nonfinancial concerns of providers and afford mechanisms for providers to share their concerns if they believe their concerns are not being addressed. Because providers are so central to the clinical research enterprise, RAOs are designed for the sole function of supporting providers throughout the research process, from registration to patient enrollment to study completion. This assistance extends to the RAO representative visit to the provider's office to help determine the best way to incorporate clinical research into the provider's workflow. To ensure that RAOs are doing their job and are responsive to providers, a mechanism has been set up through the ROPS by which providers can express directly to NCRA leadership any concerns they have about RAOs. Providers are not limited to a particular RAO, but instead are free to affiliate with any RAO. This allows providers to work directly with RAOs that best serve their purposes. The RAOs are evaluated according to how well they are able to help providers register successfully in NCRA, enroll patients, and follow patients through the full study.

Another vehicle for engendering provider trust depends upon NCRA addressing the ethical concerns about being involved in research**.** Concerns about provider payment for patient enrollment in clinical research emerge occasionally, since payment can introduce a conflict of interest for providers. Payment encourages providers to enroll patients in research studies, although it might not be in the patients' best interests. Patients may feel obligated to enroll in studies recommended by their provider, even though they are not inclined to do so. NCRA will build confidence in the clinical research enterprise by articulating the ethical standards for conducting research in a clinical-care setting and providing quality oversight. NCRA should adapt a code of ethics to address a host of issues that define the conduct of all members of the operation.

8. NCRA considers provider interest in clinical research topics as a means to facilitate provider recruitment and retention. Even when the fiscal and administrative burdens of research participation are lessened for clinical providers, their participation depends upon providers believing that the conduct of clinical research will be of value to them and their patients. NCRA will convene a series of discussions to learn from community-based providers, patients, patient advocates, and public health and policy decisionmakers which types of research questions are interesting to practicing physicians, dentists, and nurse practitioners. The earliest studies to be conducted within NCRA will include studies that practicing providers find interesting. The NCRA's Study Operations Unit (SOU) will solicit from its constituents research ideas they consider interesting. ROPS will have both a Web-based system and paper-based system for providers to indicate study topics they find of interest, as well as study-design strategies that will facilitate the conduct of research in providers' offices. The SOU also will enlist the help of specialty societies and PBRNs that have identified research topics of interest to community-based providers.

9. Patient recruitment will be facilitated by NCRA. It is expected that many of the strategies NCRA will use to motivate provider involvement will also encourage patient enrollment in clinical research. In addition to provider encouragement of patients, NCRA will help to make research more relevant and to decrease the burden of participation. One consistent incentive for patients across all clinical research studies is the knowledge that their provider is affiliated with the nation's and, perhaps, the world's, premier health agency, NIH. Such an incentive may be especially powerful for patients in remote areas, whose providers are not affiliated with medical universities or major medical centers. Providers may explain to their patients that their participation is advancing medical-care knowledge and that the provider will be updated on all findings from this and other research studies so that the provider's medical care remains state-of-the-art. Providers who contribute to research on clinical decisionmaking are likely to gain additional trust from their patients. This type of trust will be effective in counterbalancing the concern that patients sometimes have of being "guinea pigs" in a laboratory. Instead, when the provider, the patient, and the provider-patient dyad understand the nature of the clinical question being addressed, and understand how their participation in the research trial will address that question and represent their own interests, patient trust in their provider, and in clinical research, is likely to increase. There are additional study-specific patient incentives to participating in research, including the availability of free or new drugs, access to state-of-the-art care for the course of the study, and monetary incentives for studies that are especially taxing for the patient. Clinical research with direct relevance to patients will improve patient options for disease prevention, diagnosis, and treatment in the community setting. Particularly with the introduction of genomics and proteonomics, disease prevention is evolving to potentially benefit individuals and families, even prior to the onset of disease. Having a stable cohort of providers participating in clinical research may encourage patients to become more interested in participating in clinical research. In turn, this increased interest may translate into a more reliable system for recruiting patients, may increase the number of patients recruited per time period, and may lower the expected cost of recruitment per patient. Additionally, the relationship patients have with clinical providers can motivate more patient recruitment and provider input into study designs most appropriate in community settings. Diversity-focused recruiting would enable studies to address racial and other social disparities in healthcare provision. Involvement of a wide variety of providers is expected to provide increased accessibility of clinical research to a wider group of patients.

10. NCRA must address provider and patient fears regarding adverse patient outcomes. In association with the NCRA Quality Assurance Unit (QAU), a Study-Specific Executive Committee will provide oversight to each NCRA study to ensure that research conducted through NCRA will be subjected to a high and effective level of quality control at all stages of research. High-risk NCRA studies will be associated with a Data Safety Monitoring Board, just as non-NCRA studies are. Proper human protection and safety are definitely a priority for NCRA. With the QAU as a key NCRA structural unit, providers, PIs, and RAOs are all involved in improving accountability in clinical research. The QAU also will conduct audits to make sure that the protocol is being

observed and that safeguards are in place. Additionally, many more stakeholders will be looking over the research process and outcomes than ever before, to build confidence and trust in the clinical research enterprise.

As a component of training, providers will learn conceptually how a member of the research team is expected to define and approach adverse outcomes, and how their particular study defines them. They, and their research support staff, will be trained in how to complete appropriate reporting forms for data centers and, where appropriate, for research sponsors or FDA. Institutional review boards will review all NCRA projects, and informed-consent documents will be approved prior to use. Study-specific training will teach providers and staff how to obtain informed consent.

11. NCRA must simplify provider approach to IRB and HIPAA certification. NCRA's Training Unit will establish a centralized, online process for providers to become trained and certified in IRB/HIPAA regulations. Providers may use this centralized mechanism, or they may submit the current IRB/HIPAA certifications they obtained through their RAOs. Part of an RAO's responsibility will be to ensure that providers obtain IRB/HIPAA certification. Additionally, RAOs will facilitate providers' contact with IRBs. For providers who have no affiliation with an institution having an IRB, the RAO will attempt to bring the provider into the purview of the RAO's associated IRB. Ideally, with time, NIH will develop a centralized IRB that can be used readily by providers across settings. In the interim, the RAOs will direct providers to IRB review committees as needed.

12. NCRA must have the ability to respond to (and promote) larger, systemic changes to research. NCRA must be able to anticipate, promote, and respond to large, systemic problems related to the conduct of clinical research. For example, NCRA will need to adapt some of its procedures if NIH centralizes parts of the IRB approval processes. NCRA is also likely to promote ways in which insurers can contribute to reimbursement for research-associated clinical services and develop a national plan to deal with provider liability issues.

Cost Assumptions and Analyses Under Varying Scenarios

Many of the above-described characteristics of the Ideal NCRA revolve around flexibility and cost-effectiveness. In this section, we discuss how NCRA will achieve these outcomes.

NCRA Capacity, Cost, and Efficiency Estimates. In creating a stable and robust, yet flexible, and cost-effective network of 40–60,000 providers from a wide variety of practice settings who would participate in high-quality clinical research across a broad set of study types, we have had to design NCRA to rely on free-market principles tempered by layers of checks and balances, optimized economies of scale, and a strong but lean central administration.

The implementation of NCRA is envisioned to occur in two phases. During Phase 1 (Years 1-3), the administrative and service infrastructure needed to run NCRA will be established. (Key tasks to be completed during Phase 1 are outlined in Table 4.) During Phase 2 (Years 4-8), NCRA will begin to recruit providers and run studies and will expand to its full capacity over a 5-year period.

Table 4: Key Infrastructural Tasks to Be Accomplished During Phase 1 (Years 1-3)

Year	Key Tasks
Pre-NCRA	NIH allocates budget for NCRA, endorses the basic NCRA administrative plan, and hires key personnel to staff each of the NCRA units
1	(a) Solicitations for ROPS and Web-based training are distributed, proposals are reviewed, and contracts are awarded; and (b) work begins on ROPS
2	(a) Work begins on Web-based training; (b) solicitation for 3 model RAOs and a community-relations subcontract are distributed, proposals are reviewed, and contracts are awarded; (c) SOU begins to develop cost schedules for clinical research tasks; (d) pilot feasibility studies are designed; and (e) ten studies are selected to begin in Year 4
3	(a) ROPS and Web-based training are completed; (b) model RAOs begin work and report on feasibility issues; (c) the community-relations subcontract begins; (d) a solicitation for 27 additional RAOs is distributed, study proposals are reviewed, and contracts are awarded; (e) SOU works with study PIs to make protocols appropriate for NCRA; (f) QAU develops protocols and strategy for conducting provider site visits starting in Year 4; and (g) DCCU considers optimal strategies for fielding all ten studies according to their timelines and expected RAO/provider/patient supply

Table 5 presents NCRA capacity, cost, and efficiency estimates for an optimal NCRA. At its peak, it is estimated that NCRA has the potential capacity to (a) initiate up to 40 large multi-site studies per year; (b) support up to 100 ongoing multi-site studies per year; (c) enroll up to 25,000 new providers per year; (d)

involve a cadre of approximately 60,000 providers per year; and (e) recruit over 1 million patients per year. To accomplish these upper limits, it is estimated that NCRA would need the assistance of at least 40 RAOs.

The costs of NCRA can be divided into infrastructural costs (e.g., administration, subcontracts, and other required services) and the costs associated with the portfolio of studies that is run through NCRA. Indirect costs are embedded in the budget projections. All of the proposed NCRA Units are budgeted to have 25% indirect cost for full-time equivalents (FTEs) and 50% indirect cost for subcontracts. Study-specific costs also include indirect costs based on sample studies. The costs of developing NCRA's infrastructure during Phase 1 are estimated to be approximately $20 million over Years 1-3. The estimated infrastructural costs for running and maintaining NCRA in subsequent years ranges from $30 million in Year 4 to $48 million in Year 8.

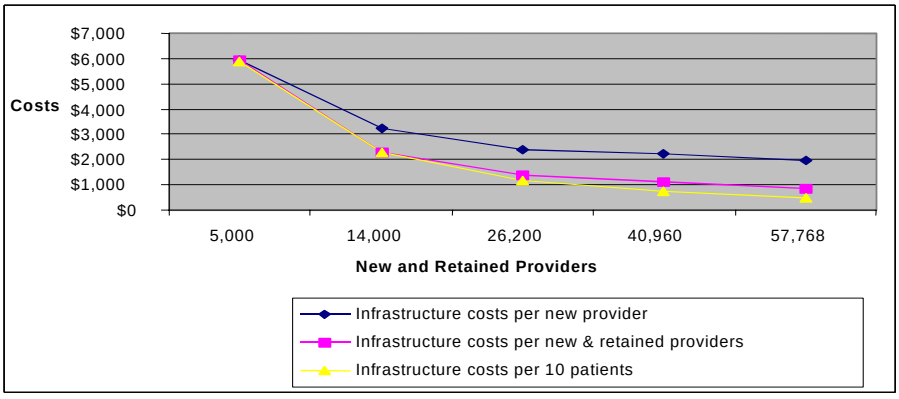
Although it is inherently difficult to project study-related costs, we have conservatively calculated costs based on a portfolio of relatively expensive studies. Therefore, the study-related cost estimates in Table 5 represent the upper bound that NIH should expect to spend per year and range from $85 million in Year 4 upwards to close to $2 billion in Year 8.

Table 5: Estimates of NCRA Capacity, Costs, and Efficiency (Full-Scale NCRA Will Support $1.9 Billion of Clinical Research Studies)*

	Year							
Capacity Estimates	1	2	3	4	5	6	7	8
New providers				5,000	10,000	15,000	20,000	25,000
New & retained providers				5,000	14,000	26,200	40,960	57,768
Total patients**				50,000	140,000	310,000	608,000	1,008,400
New studies				2	10	20	30	40
Ongoing studies***				2	12	32	62	100
RAOs			3	30	30	30	40	40
Cost Estimates ($millions)								
Total study-related costs	$0	$0	$0	$85	$273	$628	$1,212	$1,981
Infrastructure costs	$6	$8	$10	$30	$32	$36	$45	$48
Total Cost	$6	$8	$10	$114	$305	$663	$1,257	$2,029
Per-Unit Estimates								
Infrastructure costs per total costs	100%	100%	100%	25.9%	10.6%	5.4%	3.6%	2.4%
Infra. costs per new providers				$5,915	$3,224	$2,367	$2,250	$1,939
Intra. costs per new and retained providers				$5,915	$2,303	$1,355	$1,099	$839
Infra. costs per total patients				$591	$230	$115	$74	$48
Total costs per patient				$2,283	$2,178	$2,139	$2,068	$2,013
Total costs per provider****				$22,834	$21,781	$25,311	$30,698	$35,131
Providers per RAO				167	467	873	1,024	1,444
Patients per provider				10.0	10.0	11.8	14.8	17.5
Patients per study				25,000	11,667	9,688	9,806	10,084

*No inflation was assumed across all cost analyses.
** Assumes that new providers and one-year veterans enroll 1% of their patients, two-year veterans enroll 2.5% of their patients, and providers with three or more years of experience enroll 5% of their patients. We assumed that, on average, each provider serves approximately 1,000 patients.
*** Studies are assumed to last 4 years.
**** Total costs per provider increase over time because providers with more experience are assumed to recruit more patients each year.

Figure 3: Unit Infrastructural Costs for Providers and Patients



The cost estimates presented in Table 5 should be reviewed with the following caveats in mind. First, NCRA becomes more efficient as it grows in providers and studies. As Figure 3 shows, infrastructural costs per new provider, per new and retained providers, and per patient drop sharply as NCRA expands. A decrease in unit-infrastructural costs associated with increasing the number of providers involved with research is noted. Involvement of fewer than 25,000

providers is not taking advantage of additional potential savings associated with infrastructure. Other economic indicators also point to 25–30,000 providers as the optimal threshold for achieving the best savings possible. The proportion of infrastructural costs to total costs falls sharply as the number of studies run through NCRA increases, to the point where infrastructural costs represent less than 3% of the total costs for conducting research (see Table 5). Further, the number of studies (and the fit between the studies and the type of providers sought) also plays an important role in increasing efficiency. Although NCRA can be used for any type of study, it will run most efficiently if used to field studies involving a minimum of 500 patients. Very small studies (with fewer than 500 patients) tend not to require the extensive support that NCRA will provide, but they will still generate study-establishment and -maintenance costs. Although substantial value will be gained by fielding large studies through NCRA, smaller ones will have comparable costs but will not reap the same benefits as large studies. Similarly, the more complex the portfolio of studies to be fielded with NCRA, the more effectively its capacity will be utilized, and the more cost-effective it becomes. The size and complexity of the studies in the study portfolio will determine the number and kinds of RAOs needed, which, in turn, will determine cost-effectiveness.

Second, NCRA has been designed to be extremely flexible about the number and size of studies it can accommodate. Study-specific costs in Table 5 represent the upper bound of potential research dollars that Institutes could conduct through NCRA. NIH, for example, might decide to conduct fewer or less-expensive studies per year, therefore significantly reducing the overall study-related costs.

Third, NCRA has always been envisioned as a tool shared across all of the Institutes. Its goal is to establish and maintain a large, diverse network of NCRA Associates, and the means to support the Associates. Once established, Institutes can use and reuse these network and support mechanisms to run multiple, large, national studies of their choosing. As a result, it seems reasonable to assume that the bulk of the infrastructural costs of NCRA will be shared across the Institutes and that the study-specific costs will be borne by those Institutes that choose to utilize NCRA. The advantage for each of the Institutes is that they no longer have to invest in developing their own unique networks for studies recruiting community providers.

Finally, RAND anticipates that it will be virtually impossible to efficiently and cost-effectively recruit and retain a large number of providers without an NCRA-like mechanism. RAND expects the cost of recruiting the same number of providers for clinical research to rise with or without NCRA. The tightening of third-party reimbursements for clinical activities has increased the pressures on community clinicians so that they are less willing to (a) engage in activities for which they are not adequately compensated for their time; (b) take on new and unpredictable risks; and (c) engage in activities that are not directly relevant to their practices and patients. Success will come only with a serious, well-organized effort that assures providers that there will be a predictable stream of adequately reimbursed and relevant research opportunities, paired with limited risks to them and their practices.

Emerging Context for NCRA in 2006. Since NCRA and its initial scope were proposed in 2003, there have been significant changes to the NIH and the healthcare-delivery environment in which NCRA was to exist. As with many other government agencies, NIH is being asked to reevaluate and downsize many of its long-term initiatives in the face of a weakened economy. The NIH budget, which had been steadily increasing for years, has started to decline, thereby shrinking the funds available for clinical research (Mamula, http://pittsburgh.bizjournals.com/pittsburgh/stories/2006/01/09/story2.html; last accessed January 30, 2006). In this changing context, it will be more challenging for NIH Institutes to part from the status quo and accommodate the implementation of NCRA. A careful examination of capacity, cost estimates, and unit costs associated with differing NCRA scenarios can provide a mechanism for the Institutes and others to understand the implications of various options. Given NIH's current budget situation, it is important to determine whether the size of NCRA can be reduced.

Individual Cost-Reduction Strategies Considered. We considered five strategies for reducing the costs of NCRA. Below we describe each of these strategies individually, and then compare the strategies in Table 6, beginning with the originally proposed NCRA in Column 1 (bold) (designed to optimally support the recruitment and retention of a diverse set of approximately 60,000 providers).

1. Although we considered downsizing NCRA's infrastructure, there is little room to make major reductions during Phase 1, and doing so would likely threaten the foundation of the system. If the goal of NCRA is to recruit and support approximately 60,000 providers to participate in large studies, capital investment is needed

to develop an adequate infrastructure. It will take a minimum of three years to launch an infrastructure of this magnitude, before recruiting providers and patients. (In fact, ideally, an additional implementation year would be optimal.) The RAO, ROPS, and Study Operations Units are all essential for NCRA to function. Eliminating either the Training or Quality Assurance Unit threatens the overall data quality and the faith that researchers and providers would have in using the NCRA. Eliminating the Data Coordinating Center Unit would threaten the efficiencies gained through standardization of protocols and consolidation of efforts. (Strategy 1 is not shown in a column.)

2. Reducing the number of RAOs offers some savings, but at a substantial price to the productivity of NCRA, particularly in the early years. Simulations suggest that limiting the number of RAOs to less than 30 severely limits the number and size of studies that can be run through NCRA. Savings associated with reductions in RAOs are likely to be negated by (a) increases in study-related costs due to increases in uncertainty in staffing and space requirements (retooling and downtime for providers are expensive) and reductions in the number of studies available from which providers can choose (less satisfaction is likely to predict lower patient enrollment), and (b) decreases in economies of scale (at both the RAO and provider levels) because of increases in time to break even in infrastructural cost and increases in provider labor costs. (See Table 6, Column 4). To keep the maximum number of providers that RAOs need to recruit under 1,500, which we think is an upper bound for any RAO, we had to reduce the number of new providers to be recruited to 10,000 and reduce the number of new studies to 30.

The next three strategies propose downsizing either later in NCRA implementation, in number of providers and studies, or in the implementation plan itself.

3. We considered the strategy of NCRA continuing with the original implementation plan but ceasing expansion in either Year 6 or 7, rather than continuing expansion through Year 8 (see Table 5), which would reduce the number of ongoing studies to between 40 to 60 per year, rather than the 100 per year originally projected, and would reduce the number of providers from approximately 60,000 to between 26,000 and 41,000. It would also reduce the number of projected patients from over 1 million per year to between 310,000 and 610,000. The costs savings, however, are significant in that, instead of spending over $2 billion in Year 8, the total costs of NCRA would range between $690 million and $1.2 billion. The trade-off for the cost savings is the reduction of efficiencies in infrastructural costs per provider and per patient. The advantage of this strategy over others is that it reduces the time it takes to reach optimal efficiency and ensures that NCRA is promptly filled with as many studies and providers as possible. (See Table 6, Columns 2 and 3. In Column 2, the plans are the same as presented in Column 1, but the expansion of NCRA is halted at Year 7, with the understanding that NIH now is under some budget constraints it did not anticipate when it initially considered NCRA. Column 3 is similar to Column 2, but it assumes the expansion of NCRA halts at Year 6 instead of Year 7.)

4. Another downsizing strategy is to significantly slow the rate of growth of the number of providers and studies that NCRA handles. For reasons already described, there is little savings in Phase 1 and most of the savings are seen in Years 4 through 8. We considered costs at Year 4 and Year 8 to illustrate what is gained and lost in NCRA capacity, costs, and efficiency as the scale of NCRA is reduced from the initial goal of recruiting approximately 60,000 providers (full NCRA) to a more modest goal of recruiting 32,000 (medium NCRA) and then 20,000 providers (small NCRA). The number of projected patients is reduced from over 1 million to 345,000 and 125,000, respectively. Compared to the original estimated total cost of approximately $2 billion per year in Year 8, the medium-sized NCRA costs approximately $1 billion per year and the small-sized NCRA costs approximately $700 million per year—but at a heavy cost in efficiency. The per-unit costs for new providers nearly doubles, from roughly $2,000 in the original plan to $3,400 and $3,800 in the respective downsized versions. The infrastructure costs per total patients multiplies more than fivefold from approximately $50 per total patients to over $260 per total patients. More important, downsizing significantly limits the capacity of NCRA to run multiple and large-sample studies. By Year 8, the original NCRA had the capacity to begin over 40 new studies per year and could average over 10,000 patients per study. In contrast, the medium NCRA is capable of only 10 new studies per year, with an average size of 8,500 patients per study, and the small NCRA is capable of adding only 5 new studies per year with an average size of 6,300 patients per study. The prior strategy (#3) of ramping up as originally proposed, but leveling off after Years 6 or 7 (not Year 8) provides much better results. (See Table 6, Columns 5 and 6. Column 5 launches NCRA from its beginning with a plan for a moderate [as compared to a full] effort. Column 6 launches NCRA from its beginning with a plan for a small [as compared to a full] effort.)

5. Rather than trying to downsize NCRA and eliminating all the efficiencies that come with economies of scale, another strategy is to plan a two-stage NCRA implementation: the first stage would be a demonstration project, and the second stage would be the full, but delayed, implementation of NCRA informed by lessons learned from the demonstration. This alternative would allow cost savings in the immediate years while preserving the substantial cost savings expected with full NCRA implementation. Additionally, it would provide the benefit of being able to evaluate early on important lessons that might be learned from the proposed demonstration.

The demonstration project would be designed to establish a *mini*-NCRA capable of recruiting providers for all large, NCRA-appropriate NIH studies over three years. Although the demonstration NCRA would only be one-eighth the size of the full NCRA and would recruit providers for only three years, we would still expect it to enroll approximately 4,400 active providers and have the capacity to recruit approximately 52,000 patients by Year 3. The demonstration NCRA would therefore be responsible for recruiting all patients for some studies or a portion of all the patients needed in any one study.

The aims of the demonstration would be to (a) establish a small network of community providers; (b) select five diverse RAOs as service-delivery entities to recruit, train, and support providers; (c) establish an administrative entity to oversee and coordinate efforts; (d) build an ongoing monitoring and evaluation process to assess the productivity of the network and its associated costs; (e) perform continual monitoring and generate lessons learned for service delivery; and (f) assess how the administration of the services and network could be transferred or scaled up to a larger national NCRA (with particular emphasis on what could be individualized and which lessons could be generalized across settings, providers, and studies).

The RAOs would be responsible for recruiting a heterogeneous population of providers to meet the needs of the ongoing studies. Instead of establishing subcontracts, as would be done in the larger NCRA, the administrative entity would work with the RAOs and PIs of the studies to establish simplified versions of ROPS, basic training modules, and quality assurance. The demonstration would illustrate how well RAOs could recruit providers for different kinds of studies over a 3-year period. The kinds of problems the RAOs encountered and creative solutions they developed in response to these problems would provide important lessons learned that could be used to reduce the time needed to develop a full-blown version of NCRA.

The demonstration is not designed to actually test the cost efficiencies of NCRA. First, providers engaged in this type of demonstration effort are only likely to engage in studies of low to medium burden. Second, although providers are likely to participate more than they traditionally might, due to the extra support provided by the RAOs, they are not likely to hire full-time staff or make real structural adjustments to their practices that would translate into real cost savings. Without enough studies and long-term predictability, providers would not be able to justify substantial changes to their practices. Third, a mini system, as such, cannot build on long-term checks and balances. Fourth, it will be difficult to make significant changes to the per-patient reimbursement schedules and, therefore, adjust reimbursement rates to real market values if most of the finances are controlled by the principal investigator, as compared with a more centralized unit such as the proposed SOU of NCRA. Finally, it will be impossible to calculate cost-effectiveness, since there are no economies of scale expected with this demonstration effort.

To be consistent with evidence-based science, it is recommended that funds be set aside to undertake an evaluation of a proposed NCRA demonstration. An evaluation by an objective outside organization is essential to ensure that an intervention or program is effective. There are two types of evaluations: process evaluations and outcome evaluations. In the initial years, we recommend that an outside contractor be hired to undertake an ongoing *process* evaluation of the implementation of NCRA so that NCRA can be continuously improved and lessons about what works and does not work can be documented and understood well. The process evaluation will be essential for ensuring that when NCRA scales up, the scale-up will move forward efficiently. Additionally, NIH will want to evaluate the *outcomes* of NCRA according to valued metrics. One such metric could be the number of community-based providers who participated in NIH-funded (or any) clinical research in the past year and the number of patients such providers were able to recruit. Currently, there is no solid measure of this important yardstick. During the pilot phase, NIH should fund efforts to identify and collect metrics on valuable outcomes against which the effectiveness of NCRA can be judged (not shown in Table 6).

Table 6 projects NCRA capacity, costs and per-unit costs across the originally proposed NCRA and five alternative cost-reduction scenarios.

Table 6: Estimates of NCRA Capacity, Costs, and Efficiency Across Cost-Reduction Strategies

	Full NCRA Designed for Optimal Efficiency	Moderate NCRA		Small NCRA	
	Full expansion to Year 8	Halt expansion at Year 7	Halt expansion at Year 6	Limited expansion in Year 8^#	Moderate expansion	Small expansion
Capacity Estimates						
New providers	**25,000**	20,000	15,000	10,000	12,500	8,500
New & retained providers	**57,768**	40,960	26,200	42,768	32,282	20,231
Total patients*	**1,008,400**	608,000	310,000	635,508	345,423	125,923
New studies	**40**	30	20	30	10	5
Ongoing studies**	**100**	62	32	90	40	20
RAOs	**40**	40	30	30	30	15
Cost Estimates ($millions)						
Total study-related costs	**$1,981**	$1,212	$628	$1,408	$972	$657
Infrastructure costs	**$48**	$45	$36	$42	$42	$33
Total costs	**$2,029**	$1,257	$663	$1,450	$1,015	$690
Per-Unit Estimates						
Infrastructure costs per total costs (%)	**2.4%**	3.6%	5.4%	2.9%	4.2%	4.8%
Infra. costs per new providers ($)	**$1,939**	$2,250	$2,367	$4,223	$3,379	$3,882
Infra. costs per new & retained providers ($)	**$839**	$1,099	$1,355	$987	$1,308	$1,631
Infra. costs per total patients ($)	**$48**	$74	$115	$66	$122	$262
Total costs per patient ($)	**$2,013**	$2,068	$2,139	$2,282	$2,938	$5,480
Total costs per provider ($)***	**$35,131**	$30,698	$25,311	$33,916	$31,433	$34,106
Providers per RAOs (n)	**1,444**	1,024	873	1,426	1,076	1,349
Patients per provider (n)	**17.5**	14.8	11.8	14.9	10.7	6.2
Patients per study (n)	**10,084**	9,806	9,688	7,061	8,636	6,296

^ *Reducing the number of RAOs offers some savings, but at a substantial price to the productivity of NCRA, particularly in the early years. Simulations suggest that limiting the number of RAOs to less than 30 severely limits the number and size of studies that can be conducted through NCRA. Savings associated with reductions in RAOs are likely to be offset by (a) increases in study-related costs due to increases in uncertainty in staffing and space requirements (retooling and downtime for providers is expensive) and reductions in the number of studies available from which providers can choose (less satisfaction is likely to predict lower patient enrollment), and (b) decrease in economies of scale (at both the RAO and provider levels) because of increases in time to break even in infrastructural cost and increases in provider labor costs.*

Constraining the number of RAOs to 30 requires a reduction in number of providers and number of studies so that the 30 RAOs are not overburdened.

* Assumes that new providers and 1-year veterans enroll 1% of their patients, 2-year veterans enroll 2.5% of their patients, and providers with three or more years of experience enroll 5% of their patients. We assumed that, on average, each provider serves approximately 1,000 patients.

** Studies are assumed to last 4 years.

*** Total costs per provider vary according to provider experience level. Providers with more experience are assumed to recruit more patients each year.

Table 6 shows that the original plan for NCRA (Column 1) yields a system with the most capacity and the most efficiency. The original plan has the capacity to (a) recruit upwards of 25,000 new providers per year; (b) maintain a stable network of almost 60,000 providers; (c) recruit over 1 million patients per year; (d) start up to 40 new studies annually; (e) run over 100 studies simultaneously; and (f) support studies that, on average, have more than 10,000 patients. The original plan is also the most efficient: infrastructural costs represent only 2.4% of the total costs. On average, the infrastructural costs for recruiting a new provider are under $2,000 and when new recruits are combined with veteran providers, the average cost per provider drops to $839. The average infrastructural costs per patient are less than $50. The infrastructural costs for running such a system are approximately $48 million annually. When the system is being used to its fullest capacity, it has the ability to run close to $2 billion worth of study protocols annually. It is important to note, however, that NIH is not obligated to use NCRA to its full capacity and could significantly reduce the total costs by decreasing the number of studies.

Among the alternatives for scaling down NCRA, RAND sees the first two options in Table 6 (Columns 2 and 3) as being the most efficient. Although the total costs and capacity of the system are reduced substantially if the expansion of NCRA is truncated in Years 6 or 7, the system efficiencies are only moderately reduced. Unlike

the limited-expansion option (Column 4), both of these alternatives also ensure that the average size of a study (n) can remain at close to 10,000 patients. The last two options in Table 6 are the least attractive. Although they reduce the total costs to roughly $1 billion and $700 million annually, they significantly reduce capacity (including the average study size) and are generally more inefficient than the options of truncating the expansion of NCRA in Years 6 or 7.

After consideration of all of these strategies, RAND still believes Column 1 is the optimal strategy for achieving the best capacity and efficiency. If there are adequate funds for NCRA for the next several (i.e., five years), but there are uncertainties about the available funds for the period around Year 7 and beyond, then Columns 2 and 3 will be the best options. If it were clear that there would not be adequate funds to launch a full NCRA during the next decade, then beginning with a demonstration project as described in Strategy 5 above would be optimal.

Regardless of which NCRA strategy NIH selects, a series of pilot evaluations should be considered to further understand how to best develop NCRA. Appendix A presents brief synopses of several potential pilot studies.

What Are the Financial Advantages of Using NCRA?

NCRA, in its full capacity, makes it feasible to efficiently recruit a larger number of providers at a reasonable cost than would be required for recruiting the same number of providers without an NCRA. RAND's analysis indicates that it would be extremely inefficient and probably not feasible to recruit more than 20,000 new community providers without an NCRA-like structure. As recruitment moves toward community providers, and toward larger numbers of providers participating in clinical research, it is unlikely that a sufficient pool of providers will effectively participate in research across time, based mainly on volunteerism. For all provider types, our interviews revealed that the number of providers that can be recruited is a function of two factors: the level of monetary compensation providers expect to receive upon participation, and the burden of disincentives and obstacles that can be removed to make it easier to conduct clinical research. These two factors can offset one another up to a point. RAND interviews revealed that, initially, when providers are minimally involved with research (e.g., <2.5% level of effort), removal of the most pertinent disincentives would be better appreciated. However, as the level of interest, comfort, and ease with which a provider can engage in clinical research increases, monetary compensation becomes of greater value for the provider. NCRA is set to reduce the main disincentives and allow flexible adjustment of the level of compensation according to the desired number of providers.

NCRA is designed to engage providers in clinical research for the long term. It does so by reimbursing providers at a dollar amount commensurate with what providers would be reimbursed at if that time were allocated to clinical care (*fair replacement value compensation*) and by providing support to providers and their staffs for clinical research. NCRA is flexibly designed so that both the reimbursement levels are continuously adjusted (to reflect factors external and internal to NCRA) and the level of support given to providers is adjusted (to reflect the individual experiences and emerging needs of providers).

Our models indicate that if a large enough number of providers is needed for clinical research, then labor costs associated with recruitment of providers will be cheaper with NCRA than without it. Empirically estimating the exact point after which labor costs are lower with NCRA is difficult, because no convincing counterfactual for the possibility of recruiting a large number of providers was available at the time of RAND's analysis. Lower labor costs would be the result of many factors embedded within NCRA. Mainly, providers outside of NCRA typically begin with either inadequate or no reimbursement. After their first encounter, they often feel "burned" by the system. They find that the cost of clinical research was either higher than they were told or higher than they expected, and many experience financial losses. Also, health insurance reimbursements are being reduced, placing greater time and financial constraints on already-busy, stressed providers. Other providers, who might have been considering participating in clinical research, notice the burden and losses of their colleagues and become unwilling to participate as well. Patients are holding providers more accountable (via lawsuits) and have higher expectations of providers, including reduced waiting time. They do not trust clinical research and do not want to volunteer anymore. To attract substitutes for those who dropped out, as well as additional recruits, the rate of compensation for research participation now must be higher than it would have been otherwise. On the other hand, NCRA provides both non-financial and financial compensation. This dual approach provides a more supportive environment from the start. As such, the entire experience is a positive one that allows the initial compensation level to be maintained. Additionally, since NCRA has a system for providers to be heard, we expect providers' concerns to be addressed adequately and research questions to

be more applicable to the interests of the providers, thus contributing to their overall satisfaction. All these factors translate to lower required compensation. Thus, as the research enterprise seeks to fulfill its labor needs, NCRA providers will present as a fairly satisfied group willing to continue research participation over a long period of time. They will be willing to endorse the concept of research participation for colleagues. In contrast, with the counterfactual of no NCRA-like system, providers will typically be characterized as individuals with prior negative clinical research experiences resulting from fiscal losses or management crises. The relatively lower long-term provider-compensation requirements through NCRA are also a by-product of increased effectiveness of providers, who become better informed about clinical research, better trained, and who, with time, are able to perform more tasks per provider hour. With these assumptions, RAND expects NCRA providers to continue to participate in clinical research, in the long term, with lower reimbursement rates than non-NCRA providers.

NCRA's Infrastructure Is Cost-Effective. NCRA's suggested infrastructure takes advantage of scale economies—thanks to the number and size of studies that populate NCRA—as well as of the internal preservation of know-how. Like other complex mechanisms, it is expected that NCRA will have a steep learning curve and will rely heavily on learning-by-doing through its implementation and consequent use. In contrast with other clinical research studies for which the infrastructure is rebuilt every time a new study is begun and any acquired know-how is largely lost, NCRA will build upon its experience. In particular, NCRA's infrastructure adjusts over time to incorporate and use the acquired knowledge while constantly moving up on the learning curve. This adjustment, together with scale economies, will result in a more cost-effective infrastructure when compared to a system of individual clinical-research-study implementations.

Cost-Sharing with Third-Party Payors. Third parties will contribute to the costs of conducting research through NCRA via the per-patient reimbursements, as they currently do for clinically based, NIH-funded research. We identified four studies as prototypes for clinical research that NCRA might conduct. They include three clinical trials (one each related to diabetes mellitus, overactive bladder, and cancer, plus an observational study). Study budgets for three of the studies were estimated by a third-party consultant who specializes in assisting providers and the pharmaceutical industry in project costs. To assess who was responsible for each reimbursable, we carefully examined each of our sample budgets to determine which costs represented services consistent with routine clinical care. We assumed that these routine-care clinical costs could be borne by third-party payors, whereas remaining costs would be borne by the research sponsor (i.e., NIH). We also assumed that a component of NCRA and even the Roadmap initiative would involve a set of agreements such that research activities consistent with routine clinical costs would be reimbursed as described in the current CMS protocol. Some items clearly fell into one group (third-party payors) or the other (NIH). We found, however, that many reimbursable items were ambiguous. We based our decisions on what we know and have heard from individuals who conduct clinical research. When in doubt, we were conservative by assuming that NIH would bear the cost.

As shown in Table 7, per-patient reimbursements across the studies range from $1,639 for the observational study to $12,852 for the cancer trial. The total rates at which third-party payors contribute to the enterprise also vary. In the observational study, NIH bears 86% of the costs; in the cancer trial, NIH pays only 44% of the costs.

Table 7: Examples of Cost-Sharing with Third Party Payors

	Study				
	Diabetes	**Bladder**	**Observational**	**Cancer**	**Average**
Per-patient reimbursement^					
Paid by NIH	$2,295	$1,103	$1,414	$5,612	$2,606
% total	68%	62%	86%	44%	65%
Paid by Third-Party	$1,090	$663	$225	$7,240	$2,305
% total	32%	38%	14%	56%	35%
Total	$3,385	$1,765	$1,639	$12,852	$4,910

^ Per-patient reimbursement is calculated to represent all patient-related costs incurred by the provider in the process of conducting research.

Cost-Sharing with the Pharmaceutical Industry. Although some large pharmaceutical companies may express reluctance to participate in NCRA because of their desire to control the research infrastructures they use, there

are a few conditions under which the industry is likely to find NCRA participation attractive. First, smaller companies developing new products want to establish credibility by their NCRA-affiliation. Unlike larger companies, they may be willing to give up control in exchange for establishing credibility via a relationship with NCRA/NIH. Second, regardless of size, the pharmaceutical industry may be interested in opportunities that allow the establishment of effective dosages for patients using drugs known to be efficacious. For example, Pfizer provided financial support and drugs in the ALLHAT study to examine, in part, effective dosages for patients using drugs already established as efficacious (David, Cutler, & Gordon, 1996). Finally, the industry is likely to be interested in opportunities that quantify the incidence of rare events. FDA may also be interested in working with NCRA to obtain population estimates of rare adverse events, which traditional pharmaceutical studies and FDA databases cannot readily obtain.

What Are Some of the Non-Financial Advantages of Using NCRA?
Cost savings and cost-sharing are the main financial advantages of NCRA, but there are a number of non-financial advantages to using NCRA that merit outlining, quality being the foremost one.

- Overall quality of clinical research will improve with NCRA. Time for each specific task, time for completion of enrollment, and time for study completion will be better estimated than with the current system. High-quality providers and RAOs will be easier to identify and retain. Providers and RAOs will be incentivized to maintain high quality. Likewise, improved quality and effectiveness of care and better health outcomes should result from an expansion of the conduct of clinical research from a relatively small number of high-volume, high-intensity research settings and providers to a more decentralized set of providers and settings.
- It will be easier to track completed, needed, and successful research. Standardization of training and of materials conveyed to providers will allow more predictability and accountability.
- Fundamentally, NCRA can handle different and unique sets of problems associated with major public health risks, different healthcare-delivery organizations, and different types of providers. NCRA is designed to be flexible enough to accommodate the study of acute conditions (as is the current system), as well as the study of chronic conditions (unlike the current system), an accommodation enabled by the ability to handle the long-term longitudinal studies required to study the progression of chronic disease and to handle providers from multiple specialties. At the same time, NCRA is designed so that it can address diversity issues, handle studies associated with emerging health threats (such as avian flu), accommodate large patient samples, and allow for reuse of trained and engaged providers across multiple studies.
- Participation in NCRA clinical research might be used as a means to contribute to a provider's certification or as a means to supplement continuing medical education credits. Many providers are intellectually curious but frustrated by the lack of intellectual challenge in their daily practice. By engaging in NIH-sponsored clinical research, providers will know that they are contributing to the advancement of medicine. Moreover, to the extent that research questions align with a provider's particular interest in clinical issues, the more stimulated intellectually the provider will be and, if providers have input into research questions and protocols, they will have a sense that they are engaged in relevant and important research.
- High levels of provider participation in NCRA will accelerate adoption of evidence-based medicine and incorporation of findings into daily practice. Providers will see more of a connection between clinical research findings and the patients whom they serve.
- NCRA offers greater connectivity to the professional community that will be particularly valuable to providers in solo practices (such as dentists) and remote rural areas.
- Smaller independent hospitals and other healthcare facilities not affiliated with an AMC or other organization engaged in research view participation in clinical research as a way to potentially distinguish themselves from local competitors. Currently, many such organizations have little opportunity or access to resources to engage in clinical research.
- Health organizations with an established infrastructure for clinical research will gain additional infrastructure support to improve their systems. In association with the steady and sustained allocation of public or private money to optimizing the clinical research enterprise, commercial and non-profit organizations could become involved across multiple levels of production. The private sector will gradually shift how it allocates its resources and energies in ways that significantly increase the capacity (and generally the efficiency) of producing the desired product. For example, RAND reports consistently show that costs and time necessary to build and maintain a submarine fleet or aircraft carriers significantly increase when the Pentagon orders and funds a cluster of ships and then none for an extended period, since industry and all the contractors and subcontractors involved retool or reorganize to address other priorities (Birkler et al.,

1994). By the same token, it seems likely that key stakeholders (at all levels of the system) that will be essential to the operation and effectiveness of NCRA in recruiting providers and conducting research studies will gradually shift resources and alter policies to meet the demand for research support. For instance, large healthcare providers potentially will alter their infrastructure over time in ways that support research by the providers with whom they contract. Similarly, academic medical centers and professional societies also could be expected to change in ways that facilitate the type of research envisioned for the NCRA. Accordingly, we expect a contribution from the private sector to supplement the improvements in quality and efficiency expected with NCRA.

- Research results will have greater generalizability because the growing population of providers capable of engaging in research and the greater diversity of RAOs mean that the medical community will be more trusting of NIH-sponsored research. If providers feel that they and patients are benefiting from participation in NCRA, providers are likely to increase their participation in NCRA, which will translate into greater general support of NIH by the American public.
- To the extent that U.S. society values being a leader in healthcare research, NCRA will provide a competitive edge over other countries. It will provide more opportunities to recent medical school graduates. It may encourage many of the providers who do not value or track developments in evidence-based medicine to do so. It is likely to be especially important for providers who completed their training before the paradigm of evidence-based medicine dominated medical schools.

Disadvantages of NCRA

Just as there are many advantages, both financial and non-financial, to the implementation of an NCRA, there are some potential downsides to NCRA that need to be carefully weighed in deciding whether to move forward. First, NCRA will not be cheap. RAND estimates that the cost to establish the infrastructure for NCRA during the first three years ranges from approximately $6 million in Year 1 to $10 million in Year 3. Once NCRA becomes operational, the maintenance costs are projected to be approximately $30 million annually in Year 4 and stabilize at approximately $48 million annually in Year 8. Beyond these costs, study-related costs must be factored in.[1]

The cost-effectiveness of NCRA depends upon the number of studies conducted through the program. Ultimately, the more studies, the more long-term cost savings. How fast NCRA grows will depend on decisions made by NIH and Institute leaders. The more studies that leaders are able to funnel into NCRA, the more efficient the network will become and the faster NIH will realize cost savings. Related to cost-effectiveness is efficiency, and if NIH decides to go forward with the NCRA concept, the leadership should promote its use as much as possible so that that efficiency is maximized. Without a steady flow of studies in which providers can participate, there is a risk of violating the functionality of NCRA. Below is a discussion of potential disadvantages from the perspectives of three stakeholders.

Practitioners' Perspectives. Not every provider will be interested in joining NCRA, nor should they be. The engagement of 60,000 providers is likely to require participation of approximately 7% of community primary care providers. With NCRA studies, as with all studies, study protocols will define eligibility requirements. Even with the services and supports provided by NCRA, not every provider will be eligible or want to participate in each study. However, with NCRA, the likelihood that providers will sign up for study participation and then renege on their commitment is much smaller than at present, since NCRA Associates will have access to study protocols and reimbursement rates prior to their agreeing to participate in any particular study.

Providers may not fulfill the study-specific enrollment quota set *a priori*. However, ROPS will maintain a mechanism for providers and RAOs to report any difficulties they have in patient recruitment, to catch the attention and assistance of the study principal investigator. Also, the principal investigator and RAO might allow the provider group to re-estimate downward their targeted patient enrollment, preventing any negative comments from being registered in the ROPS. Additionally, RAOs are responsible for monitoring and assisting providers in their recruitment efforts. When study enrollment is low across providers, the Study-Specific Executive Committee evaluates reasons for low enrollment and considers how inclusion/exclusion criteria, enrollment goals, timelines, or reimbursement strategies might be altered to be more compatible with realities empirically noted in the field.

[1] The above-mentioned values correspond to the suggested full-capacity NCRA.

Legal liability for research participation for practicing providers unaffiliated with an academic institution remains unresolved. Providers need to understand the importance of verifying their liability coverage prior to participation in clinical research. Explicit wording to this effect should be included in any clinical research agreement. To help providers understand liability issues, NCRA will have to lay out the principles of provider liability in an informational document to outline the expected role of the research sponsor and its relationship to the provider's malpractice insurer for research-associated activities for clinical providers.

Providers may feel limited to partnering with the RAO(s) in their geographic vicinity. It is natural to partner with an organization that is proximate, because it is easier to form relationships and meet regularly. However, when a provider is not satisfied with his/her RAO partner's performance in NCRA, that provider may hesitate to solicit the help of a less proximate RAO.

Principal Investigator (PI) Perspective. Principal investigators will have less control over study protocol design, data collection, and data cleaning processes than they would outside of NCRA. Correspondingly, PIs will receive less credit from their institutions for bringing in research dollars. However, principal investigators will have more time to devote to research, presumably what they were trained to do best.

Institute Perspective. With NCRA, Institutes will have to redefine the way in which they control research studies and protocols in exchange for achieving a new level of efficiency. As with any large undertaking, there is always the risk of creating unnecessary bureaucracy. In this case, the basic necessity of NCRA is apparent. However, depending on the quality of the implementation, NCRA's bureaucracy could either end up exactly at the desirable level or, alternatively, could bloat unnecessarily and then require NIH's close attention. In any event, NCRA would create an additional layer of government that, even though recommended, depending on the personal interrelationships between government officials, could add frictions to the existing system.

It is important to realize that NCRA cannot be turned on and off according to the needs of the moment. The basic infrastructure needs to be maintained, even if no studies are run through the system. And to maintain the system and avoid the need to rebuild the infrastructure requires a minimum investment of approximately $10 million per year. This problem is inherent in any infrastructure project and would not surface as long as studies are continually channeled through the system.

Who Is Most Likely to Use NCRA and How?

The following section describes the stakeholders most likely to use NCRA and how.

What Types of Providers Are More Likely to Use NCRA? Three broad categories of providers are envisioned to participate in NCRA: physicians, dentists, and nurse practitioners. However, some provider types will be more eager to join NCRA than others. For example, providers with prior research experience may join NCRA earlier than those without such experience, because they may be more comfortable conducting research. These include providers affiliated with practice-based research networks who not only have research experience but also are familiar with the benefits of how common research-infrastructure elements related to coordination, methodological support, and administrative support can facilitate their successful participation in community-based research (Van Weel, Smith, & Beasley, 2000). Providers who currently are affiliated with research organizations may be more likely to join NCRA before other providers because it is easier for such organizations to identify these providers. However, as NCRA gains momentum, the profile of providers participating in clinical research is likely to change. Increasing numbers of community providers without research experience and without prior organizational affiliations are expected to take part in clinical research through NCRA.

In NCRA's initial stages, we should also expect to engage mainly providers associated with established provider groups, rather than those in solo practices. Members of these groups will find it most advantageous to join NCRA, and RAOs will probably find them easiest and cheapest to recruit. As the system becomes more established, we should observe increased numbers of providers from solo practices also participating.

What PIs Are More Likely to Use NCRA? The types of PIs who may be more likely to use NCRA will be those who are interested in conducting studies that can be conducted in community settings, since a core goal of NCRA is to incorporate into research a versatile network of qualified healthcare practitioner-researchers. Ideally, such studies would address the clinical and health services problems community-based providers face on a routine basis. Although community-based providers may participate in many different kinds of studies, they are likely to engage most enthusiastically in bedside and translational research pertinent to the most

prevalent conditions they see in their practices. Principal investigators who are interested in conducting research that requires highly specialized equipment or requires tertiary facilities, such as neonatal units or trauma centers, are unlikely to be interested in utilizing NCRA. Additionally, principal investigators of studies involving fewer than 500 patients may not want to use NCRA, because the administrative costs associated with making a study NCRA-compatible may outweigh the benefits.

What NIH Institutes Are More Likely to Use NCRA? NCRA-sponsored studies ideally should range across the full spectrum of diseases and types of patient-oriented research, including intervention studies, epidemiological and behavioral studies, outcomes research, and health services research. As such, most NIH institutes should be interested in using NCRA.

CONCLUSIONS

In view of the findings described in this report, RAND recommends that NIH proceed with building an NCRA-like entity.

Recommendations

NCRA is envisioned as a tool to be used by and shared across Institutes. Its goal is to establish and maintain a large, diverse network of NCRA Associates and the means to support the Associates. Once established, these network and support mechanisms can be used and reused by the Institutes to run multiple, large, national studies of their choosing. An evaluation of whether or not to pursue the National Clinical Research Associates Program involves understanding the extent to which NCRA achieves its stated goals of substantially increasing the number and diversity of providers and patients involved with clinical research. RAND recommends implementing NCRA as a safe, effective, and cost-saving mechanism for achieving its stated goal of introducing approximately 60,000 new providers from the community into clinical research in the next decade.

RAND has the following specific recommendations pertinent to optimizing NCRA use; extending the use of NCRA to other stakeholders; and conducting pilot evaluations to further understand how to best develop NCRA:

- Treat NCRA as a tool to be used across Institutes.
- Encourage Institutes and principal investigators to use NCRA.
- Populate NCRA with a steady and diverse stream of studies (i.e., at least 30 ongoing studies per year) to optimize efficiency and establish a predictable environment for providers.
- Reimburse providers at their market replacement value to recruit and maintain a satisfied and stable pool of providers.
- Consolidate data-coordinating centers to maximize cost savings and data quality through increased economies of scale and standardization.
- Extend efforts to develop reciprocal relationships by encouraging third-party payors to participate in clinical research. Given that third-party payors motivate cost savings by encouraging providers to practice evidence-based medicine, and given that NCRA will provide the science to expand the evidence basis for medicine, this seems a wise strategy.
- Encourage the development of an NCRA Code of Ethics.

With the full NCRA recommended by RAND, NIH should expect capacity to: (a) recruit upwards of 25,000 new providers per year; (b) maintain a stable network of almost 60,000 providers; (c) recruit over 1 million patients per year; (d) start up to 40 new studies annually; (e) run over 100 studies simultaneously; and (f) support studies that on average have more than 10,000 patients. After consideration of multiple alternative strategies, RAND still recommends this full implementation as most efficient and most likely to have the most desirable long-term effects on research. However, if, despite adequate funds for NCRA for the next several (i.e., five) years, uncertainties exist about the available funds for the period around Year 7 and beyond, then RAND recommends the initiation of the full NCRA as originally planned, but with a suspended expansion at Year 6 or 7. If it is clear that there will not be adequate funds to launch a full NCRA during the next decade, then RAND recommends beginning with a four-year demonstration project and following with a full implementation at a later date.

Why Do We Need NCRA? What Are Its Key Selling Points?

Decisions about NCRA should include an analysis of short-term and longer-term goals. In the longer term, which we define as ten or more years, potential financial savings and other important outcomes should be

considered. While some of the beneficial outcomes are easier to quantify because they are consistent with explicitly stated goals, others are more conceptual and likely to translate into highly valued goals with time. We expect that NCRA will improve the accountability among NIH, PIs, providers, recruiting sites, and data-coordinating centers. The development of the NCRA Registry of Providers and Studies, like the Registry of Clinical Trials that has been so strongly suggested by multiple medical journals (De Angelis et al., 2005), will allow NIH to better assess the costs and productivity of its clinical research programs. Clinical research will be conducted faster, with better documentation, improved measures of quality, and improved provider experiences. Collaboration among NIH representatives, principal investigators, RAOs, providers, and professional organizations will increase. Awareness of clinical research and the dissemination of research findings among principal investigators, providers and, ultimately, patients will increase. Participants in the research endeavor will better understand and appreciate what it costs to undertake various study designs.

Desired outcomes of the NCRA design described above are to increase the interactions among the different stakeholders and build a research system in which all participants in the research agenda are incentivized and rewarded for their efforts while being held explicitly accountable for the quality of their work. Another core feature is the building of a system to make explicit the productivity of research so that we can better assess what components of research should be enhanced or downsized, and where we should invest more or less in the future.

No one can estimate *a priori* the impact of NCRA on each of these and many other outcomes; no one knows in advance how many additional research findings or related products may be generated with the help of the NCRA. We only know that each of these will be positively affected.

Learning from History

We find it helpful to think about NCRA's long-term potential by taking some examples from history.

The consequences of building the transcontinental railroad offer one such example. The decision to build the rail system, at a time when it was economically unsustainable, was pursued because of political, security, or other reasons. The population on the West Coast in the 1860s and the limited business opportunities at that time did not support the enormous investment and spectacular engineering feats that ultimately allowed the railroad to extend from coast to coast. If the decisions regarding the building of rail or road systems were dependent only on the immediate estimates of costs and benefits, these projects would never have been started. No one could have anticipated at the time all the positive benefits that would follow. A recalculation, today, would show that all these projects have been extremely profitable when costs are weighed against benefits and were the engine that created the spectacular growth of 19th Century America (National Museum of American History, AOTM Team; last accessed February 25, 2006).

One should think about implementing an NCRA as if one were trying to decide whether or not to invest in the creation of the Internet. The Internet was an idea originally driven by the strategic need for a communications system that would not be shut down if central communication hubs were hit during a nuclear war. This system had strategic defense values (robustness and survivability) in the midst of the Cold War, including the capability to withstand losses of large portions of the underlying networks.[2] However, it probably would have never been initiated if it had been assessed solely on the basis of cost and the non-security economic benefits expected at the time. It would be hard to imagine today's world without the Internet.

One common element across these examples is that they each facilitated an essential flow—of physical entities by the railroad and of information and knowledge by the Internet. The NCRA, as well, has the potential to facilitate the flow of scientific information and knowledge as the result of a growing infrastructure for organizing and disseminating data, while efficiently linking providers in the community with scientists and funders. As with the examples above, NCRA has the capacity to facilitate the flow of knowledge and pertinent goods (those health interventions that will translate into improved patient outcomes) in a manner that will have far-reaching implications.

An additional shared component across the two examples above is the large infrastructure investment that resulted in equally large, but unanticipated, long-term payoffs. In relation to large investments in infrastructure,

[2]Historical accounts regarding the invention of the Internet identify a RAND researcher's (Paul Baran's) concept of packet switching as the technological seed on which the Internet is founded (Abbate, 2000).

some say, “If you build it, they will come.” We mention this because of the potential that a thriving NCRA will stimulate new mechanisms for collaboration across the government and private sector.

REFERENCES

Abbate J. (2000). *Inventing the Internet* (3rd ed.): MIT Press.

Asch S., Connor S. E., Hamilton E. G., & Fox S. A. (2000). Problems in recruiting community-based physicians for health services research. *J Gen Intern Med, 15*(8), 591-599.

Birkler J., Schank J., Smith G., Timson F., Chiesa J., Goldberg M., et al. (1994). *The U.S. submarine production base: an analysis of cost, schedule, and risk for selected force structures*. Santa Monica, CA: The RAND Corporation.

Campbell E. G., Weissman J. S., Moy E., & Blumenthal D. (2001). Status of clinical research in academic health centers. *JAMA, 286*(7), 800-806.

COPR. (2005). Public Trust in Clinical Research Report and Recommendations from NIH Director's Council of Public Representatives. Retrieved Aug, 2005

David B. R, Cutler J. A., & Gordon D. J. (1996). Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens, 9*, 342-360.

De Angelis C. D., Drazen J. M., Frizelle F. A., Haug C., Hoey J., Horton R., et al. (2005). Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Saudi Med J, 26*(12), 1857-1859.

Frist W. H. (2002). Federal funding for biomedical research. *JAMA, 287*(13), 1722-1724.

Heinig S. J., Quon A., Meyer R. E., & Korn D. (1999). The changing landscape for clinical research. *Acad Med, 74*(6), 725-745.

Hoyo C., Reid M. L., Godley P. A., Parrish T., Smith L., & Gammon M. (2003). Barriers and strategies for sustained participation of African-American men in cohort studies. *Ethn Dis, 13*(4), 470-476.

Institute of Medicine (January 1, 2003). *Unequal treatment*: National Academies Press.

Institute of Medicine (July 1, 2001). *Crossing the quality chasm*: National Academies Press.

Lenfant C. (2003). Clinical research to clinical practices—lost in translation? *N Engl J Med, 349*(9), 868-874.

Mamula K. B. NIH budget reduction could mean smaller, fewer grants for medical researchers. (http://pittsburgh.bizjournals.com/pittsburgh/stories/2006/01/09/story2.html. Accessed January 30, 2006).

Mathieu M. P. (2005). *PAREXEL's pharmaceutical R&D statistical sourcebook 2005/2006* (Vol. ISBN: 1-882615-69-7): Barnett Educational Services.

National Museum of American History, AOTM Team. *America on the Move: Transportation Infrastructure, 1800-1900.* Retrieved Aug, 2005, from http://americanhistory.si.edu/onthemove/themes/story_47_1.html.

Oinonen M. J., Crowley Jr., W. F., Moskowitz, J., & Vlasses, P. H. (2001). How do academic health centers value and encourage clinical research? *Acad Med, 76*(7), 700-706.

Osei K. (2003). *Recruitment and Retention of African Americans in Clinical Studies: Fiction, Myths, and Reality,* pp. 46-48, in Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance; Report of the Task Force by the NIH Office of Research on Women's Health, January 6-9, 2003, NIH Pub No. 03-5403.

Ross S., Grant A., Counsell C., Gillepsie W., Russell I., & Prescott R. (1999). Barriers to participation in randomised controlled trials, a systematic review. *J Clin Epidemiology, 52*(12), 1143-1156.

Snyderman R. (2000, Jan 13). *For the Health of the Public: Ensuring the Future of Clinical Research.* Paper presented at the Association of American Medical Colleges, Washington, D.C.

Sung N. S., Crowley W. F., Jr., Genel M., Salber P., Sandy L., Sherwood L. M., et al. (2003). Central challenges facing the national clinical research enterprise. *JAMA, 289*(10), 1278-1287.

Van Weel C., Smith H., & Beasley J. W. (2000). Family practice research networks: experiences from 3 countries. *J Fam Practice, 49*(10), 938-943.

Wilson S., Delaney B. C., Roalfe A., Roberts L., Redman V., Wearn A. M., et al. (2000). Randomised controlled trials in primary care: case study. *BMJ, 321*, 24-27.

Wright J. R., Whelan T. J., Schiff S., Dubois S., Crooks D., Haines P. T., et al. (2004). Why cancer patients enter randomized clinical trials: exploring the factors that influence their decision. *J Clin Oncol, 22*(21), 4312-4318.

Zerhouni E. (2003). The NIH roadmap. *Science, 302*, 63-72.

Appendix A

A Series of Pilot Evaluations for Consideration to Further Understand How to Best Develop NCRA

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Regardless of which NCRA strategy NIH selects, a series of pilot evaluations should be considered to further understand how to best develop NCRA. Appendix A presents brief synopses of several potential pilot studies.

A Pilot to Monitor the Effectiveness of Outreach Efforts to Increase Recruitment and Diversity of Providers/Associates and Patients. A key objective of NCRA is to increase both the number and diversity of providers and patients that engage in NIH-sponsored clinical research, thereby improving the representativeness of research findings. This representativeness will also enable a positive feedback loop, whereby the American public and their healthcare providers will see that research is based on more-representative samples of the population and thus be encouraged to participate in NIH-sponsored clinical research. The problem, however, is that most researchers have not systematically figured out ways to consistently recruit more-diverse populations. Even if they had, in most settings there is no effective mechanism for sharing recruitment strategies with community-based institutions and providers who are on the front line of patient recruitment. Thus, it is important to build into NCRA from the outset a study design that encourages RAOs to experiment with different ways to recruit diverse populations to participate in NCRA research studies. Effective ways to disseminate lessons learned from these experiments to providers will follow.

Undertaking an independent evaluation of each strategy for provider and patient recruitment would be prohibitively expensive and would serve to inhibit such experimentation from both the RAOs' and NCRA's perspectives. An alternative (albeit cruder) approach to evaluate the effectiveness of different outreach and recruiting strategies by RAOs is to set up an ongoing data-collection effort to monitor attitudes and perceptions about NCRA.

The Department of Defense sponsors an ongoing, attitudinal survey of youth attitudes and intentions to enroll in the military. This survey provides an important mechanism for predicting secular enlistment trends and for identifying which groups are most inclined to enlist, the value youths see in enlistment, and the real or perceived barriers to enlistment among those with weak or no intentions of enlisting. The Services use this information to inform their recruiting campaigns and compensation packages. NCRA might consider conducting a similar monitoring of attitudes and perceptions for both providers and patients. This monitoring would initially be set up in geographic areas representing the catchment areas of the RAOs selected in the initial years (Years 4 and 5), with very frequent random-digit-dialing (RDD) telephone surveys of households (perhaps quarterly in the first years) once the initial set of RAO sites is selected. The initial RAOs, working in consultation with the Community Relations Unit, would devise local advertising and outreach campaigns. Collection of local attitudes and perceptions of both the general population (broken down by subgroups of interest, such as race and ethnicity) and of providers could be used to crudely track the success of these local outreach efforts and to identify different strategies that seem to improve the perceptions of NCRA by different potential patient population groups and providers.

Once the full complement of initial RAOs is selected, NCRA might consider conducting the monitoring of the patient population (i.e., the RDD survey) on a national basis, or within the full geographic catchment area, with all RAOs.

A Pilot Pertinent to Providers: Internet-Connectivity Assistance. NCRA may want to consider establishing a pilot program to evaluate the effect on provider interest in and participation with NCRA of receiving assistance with Internet connectivity. For example, providers may randomly be assigned approximately $50 per month for their Internet connection. Making this a pilot project would enable NCRA to see who takes advantage of the opportunity and with what results.

A Pilot Pertinent to the RAO Unit. Currently, RAOs are structured so that they will provide intensive support to assist providers, from registration on ROPS through enrollment of patients and study completion. This type of support has been extended as a result of consistent reports from multiple stakeholders (including a broad set of practicing providers) indicating that providers would be inclined to participate in clinical research if the burden on them to carry out research-related tasks were minimized. At the same time, providers also stated

that they would need to have their time fairly compensated. Based on these comments, NCRA is currently designed to more heavily emphasize providing assistance to providers through all stages of the research process with some level of financial incentive.

The truth is that we do not know the correct balance of support (which could require substantial time on the part of the RAO staff) versus direct financial incentives. We recommend that RAOU undertake a pilot study, in Year 4 of the implementation, to empirically assess the best trade-off between hand-holding and financial incentives in motivating providers to be more likely to complete registration on ROPS, complete requisite training, and enroll their first patient. The small number of initial RAOs selected to participate in the pilot phase could randomly assign hand-holding versus financial incentives to providers to induce them to participate. The results from this experimental study could be used by RAOU to advise RAOs on the best way to recruit. Moreover, the pilot might explore which types of RAO-offered assistance are most useful to providers. Lessons learned from this pilot could be used by RAOs during the final scale-up to set up a structure that most encourages providers to become active NCRA Associates.

A Pilot Pertinent to the Training Unit. This pilot could examine the efficacy and user satisfaction of the clinical research training offered by the Drug Information Association (DIA), the professional association providing online training for clinical research certification. (The other professional organization offering this training, the Society of Clinical Research Association, provides only in-person courses, which are beyond the NCRA budget.) Existing training curricula are of interest because the NCRA's Training Unit may base its curriculum on those curricula. DIA's program also is the most appropriate for the NCRA Associates, given its content and length: DIA claims its online training takes approximately 6.75 hours to complete. Because the NCRA proposes that providers not only take training classes but that they pass an examination to improve the likelihood of their learning, this pilot would include a testing component. Using DIA's examination will require that providers travel to a DIA test site, because its examinations are conducted solely in person. Since such travel would be beyond NCRA's budget, NCRA's Training Unit would design online examinations subsequent to the pilot's completion.

This pilot could address the following three research questions:

1. What percentage of providers obtain a passing test score?
2. What are the Associates' satisfaction levels with these courses, and does that satisfaction differ by discipline or exam score?
3. Is this curriculum appropriate for persons with no clinical training? (The majority of people taking the DIA courses have prior research experience in meeting their certification examination requirements.)

Knowing the answers to these questions could help the NCRA develop more-efficient and more-effective Associate training.

A Study Operations Unit (SOU) Pilot: Structuring Payment Schemes. In the ALLHAT Study, several informants said that there was a problem with some providers who progressed all the way through the first patient visit, which came with a large reimbursement to the provider relative to the subsequent visits, and then dropped out of the study. This situation led some informants to recommend that provider reimbursements be better spread over the course of the study to reduce this problem. Yet, ALLHAT was a multiyear study that occurred during a period in which the way that health care was reimbursed to providers altered significantly. The ALLHAT payment schedule transitioned from reasonable, from the providers' perspectives, to what some assert nearly always meant that recruiting a patient cost the provider financially, and the payment schedule was not updated to reflect this reality. Consequently, it is difficult to interpret whether providers dropped out after the first patient visit as a way to purposefully game the system or because it was then that these providers realized that continuing the study would be too costly for them.

We recommend that the SOU carry out a pilot study to understand the most effective distribution of reimbursements over the course of the study. It may be that providers prefer and are most responsive to reimbursements that correspond to the amount of effort they must make across the course of the study or that they respond most favorably (i.e., enroll many patients and see them through the course of the study) if reimbursements are highest for the first and last payments. To our knowledge, no one has systematically assessed how well providers respond to pay-for-performance schemes within the context of clinical research.

Appendix B

Entities Used to Coordinate and Support Needed Services

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To motivate a stable cadre of providers to include research as a component of their professional lives will require implementing a system of support services for these busy practitioners of clinical care. NCRA will fund a set of service entities (shaded boxes in Figure B; mainly through subcontracts) that will provide certain services (unshaded boxes).

Figure B: NCRA-Funded Entities Used to Coordinate and Support Services Needed by NCRA Associates