DEPARTMENT of HEALTH and HUMAN SERVICES

FISCAL YEAR

2008

NATIONAL INSTITUTES OF HEALTH - Volume II

Overview -- Performance Detail

Justification of Estimates for Appropriations Committees

NATIONAL INSTITUTES OF HEALTH
FY 2008 PERFORMANCE DETAIL
VOLUME II

TABLE OF CONTENTS

NATIONAL INSTITUTES OF HEALTH
FY 2008 PERFORMANCE DETAIL
VOLUME II

OVERVIEW

Volume II of the National Institutes of Health FY 2008 President's Budget Submission contains the Performance Detail information for each of NIH's performance goals. This volume includes reporting requirements for the Government Performance and Results Act (GPRA) which includes representative trans-NIH performance goals and annual targets that are milestones in goal achievement. The selected goals also support a balanced research portfolio of extramural/ intramural and basic/clinical activities.

Volume II includes the Detail of Performance Analysis Tables which provides a summary of the NIH performance goals and annual targets with associated budgets. Volume II includes the Performance Goal Narratives which depicts the story of scientific discovery for each goal. An index, at the end of Volume II, provides a list of NIH's representative trans-NIH performance goals indexed by the functional area, disease/disorder category, IC lead, or topic/type of activity. The indices facilitate finding performance goals and/or information relate to a particular disease/ disorder or type of activity.

Functional Areas for NIH Activities

The NIH achieves its mission through a single program—**Research**. Under this program, NIH carries out activities in five functional areas presented below. The functional area, Scientific Research Outcomes (SRO), contains representative, trans-NIH, specific scientific research performance goals. The other four functional areas include performance goals which are representative of activities that enable research and its management. The graphic below the descriptions of the five functional areas shows the "drivers" or the components of each functional area. Each of the performance goals encompasses either intramural or extramural research activities or both, and they are all aligned with the agency mission.

- *Scientific Research Outcomes (SRO).* These goals are presented in a matrix that reflects low- to high-difficulty in achieving the goal by the number of years the agency estimates that it will take to attain the goal. NIH research encompasses the support and conduct of investigations across the full range of the health research continuum, including basic research, which may be disease oriented or related to the development and application of breakthrough technologies; observational and population-based research; behavioral research; prevention research; health services research; translational research; and clinical research. Clinical research includes research to understand both normal health and disease states, translational research which involves the application of laboratory findings to clinical interventions, as well as research on new treatments or prevention strategies.

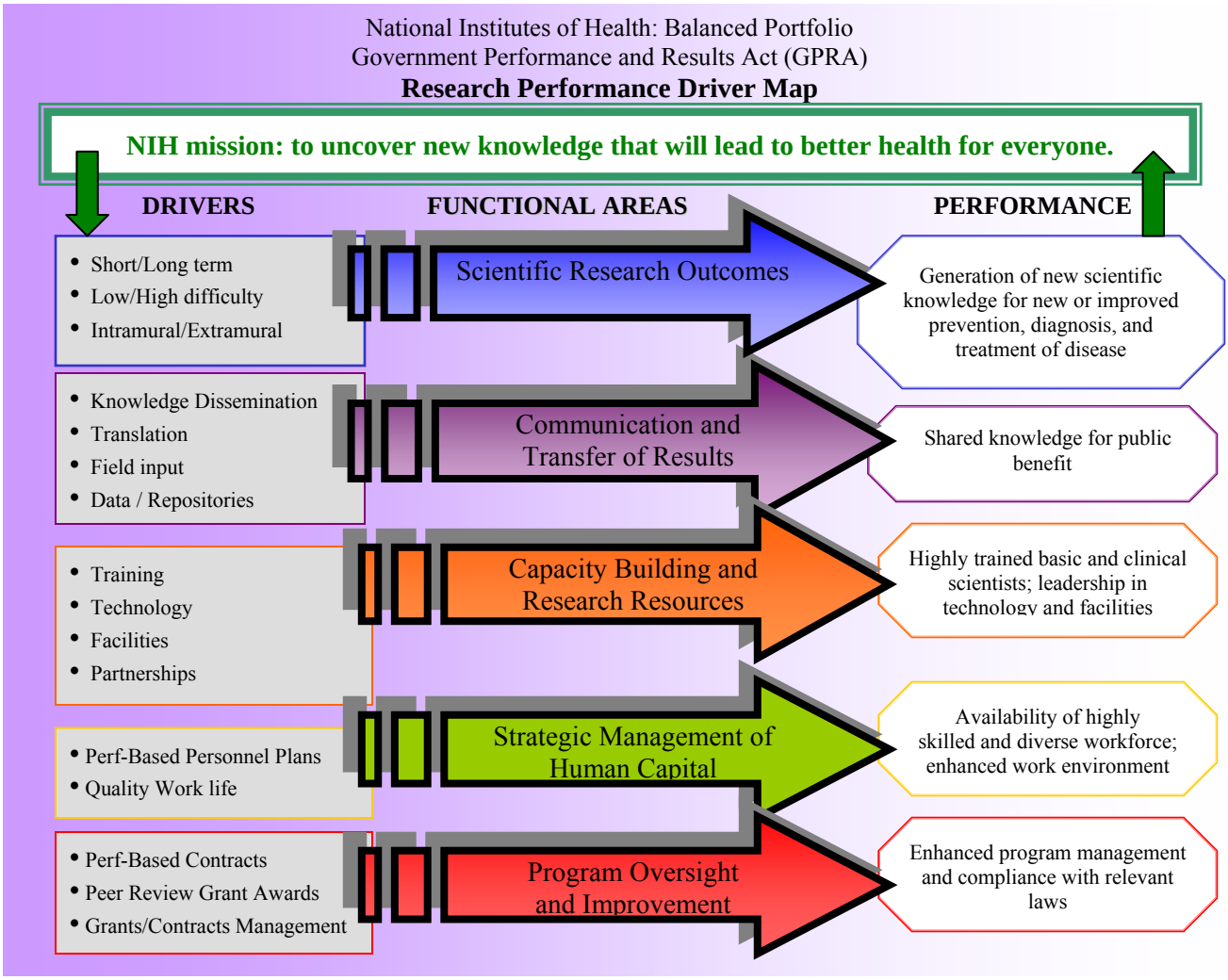
- *Communication and Transfer of Results (CTR).* The new knowledge resulting from NIH research activities cannot benefit human health unless the information is disseminated. Thus, a core NIH function is to facilitate the communication of research findings—both in the U.S. and

abroad—to clinicians, public health systems, voluntary health organizations, and the public at large. Scientific knowledge is the bedrock of evidence-based prevention and treatment programs. The diversity of the U.S. population means that effective communication requires varied approaches, such as the internet, community outreach projects, and tailored underserved population projects. Equally important is transferring knowledge to the private sector to be used in the development of new interventions, behavioral strategies, medications, biomedical technologies, and devices that lead to better health.

- *Capacity Building and Research Resources (CBRR).* The productivity of the research enterprise depends in large measure on the strength of the talent pool and on the technological and other research resources available for use in investigations. Support for pre-doctoral and postdoctoral research training replenishes and revitalizes the talent pool with new, highly trained investigators. Support for career development hones and expands the skills of those already performing research. In building capacity in the talent pool through training and career development, NIH particularly strives to augment the ranks of clinical researchers, enhance diversity, to ensure well-trained foreign collaborators, and to facilitate scientists' aptitude for multidisciplinary teamwork. Capacity building also encompasses improving and maintaining the Nation's biomedical research infrastructure. Also fundamental to the productivity of the research enterprise are the availability and accessibility of essential research tools, cutting-edge technologies, animal models, reagents, and databases and other information repositories. This is because optimal research resources set the boundaries for what questions can be investigated. Within research resources, information technology requires special notice. New technologies to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

- *Strategic Management of Human Capital (SMHC).* NIH recognizes human capital as one of the most important resources of the organization. A qualified workforce, working in an environment that utilizes its strengths, fosters the effective and efficient implementation of the NIH research program. NIH aims in this area include delayering, competitive sourcing, and developing a plan for strategic recruitment and retention, as well as planning for continuity and leadership succession.

- *Program Oversight and Improvement (POI).* Ensuring that NIH activities and strategies are carried out effectively and in compliance with all applicable laws and regulations requires careful oversight and thoughtful improvement in procedures, policies, and systems. Management systems need to be continually reviewed and updated to keep pace with advances in public administration, and mechanisms to ensure proper stewardship must evolve with the development of new requirements and rising thresholds for accountability. Meeting these challenges is a priority for NIH.



Budget Performance Integration

Medical research funded by NIH is conducted by extramural as well as intramural scientists. The majority of funds appropriated to NIH flows to the extramural scientific community at large—of which the lion's share supports individual scientists who are located at universities, hospitals, and other research facilities in the United States and points abroad. The extramural research community is funded through a variety of mechanisms of support including grants, cooperative agreements, and contracts. A smaller fraction of NIH funds supports research that is conducted by NIH's own physicians and scientists—the intramural research program.

The major funding instruments used by NIH to fund extramural research are financial assistance award grants, cooperative agreement grants, and acquisition awards or contracts. Grants are the most common funding mechanism. All grants are identified as either competing (for NIH support) or non- competing continuations (receiving support previously committed during the competing grant cycle). A research project grant (RPG) provides a commitment of support for an average of four years of funding. Thus, after the competing year, the grantee receives non-competing continuations each year for the specified length of the grant (subject to satisfactory progress as

documented to the NIH each year). Nearly three-quarters of funding allocated to RPGs supports non-competing continuations. Institutes and Centers developed budget projections based on committed levels for continuation projects, both extramural and intramural. By working closely with scientific program staff, IC budget identified planned Requests for Applications, Requests for Proposals, and Program Announcements. Costs of these initiatives were also included in total estimates for each program goal. Estimates also included the number and amount of investigator-initiated grants likely to be relevant to achieving each program goal, based on historical trends.

NIH strives to achieve effective and efficient management of the research portfolio as stewards of public health. Routine assessments are conducted to improve proficiency, to modernize processes and to sustain quality management. Some of these results are reported through other venues, such as the FMFIA and CJ, while others are used for internal management. These usual and customary assessments, as well as improvement strategies, are assumed under this label.

Summary of Full Cost*

(Dollars in Millions)

Performance Program Area	FY 2006	FY 2007	FY 2008
NIH Budget Authority	$28,516	$28,618	$28,849
NIH Full Cost Research Program	$28,516	$28,618	$28,849
SRO High Risk 1-3 Years	9	3	0
SRO High Risk 4-6 years	1,604	1,465	1,443
SRO High Risk 7-10 years	412	401	393
SRO Medium Risk 1-3 Years	790	734	5
SRO Medium Risk 4-6 years	117	133	146
SRO Medium Risk 7-10 years	24	22	22
SRO Low Risk 1-3 Years	50	63	0
SRO Low Risk 4-6 years	366	355	349
SRO Low Risk 7-10 years	3	3	3
Communication and Transfer of Results	3	2	1
Capacity Building and Research Resources	1,636	1,669	1,655
Strategic Management of Human Capital	10	5	5
Program Oversight and Improvement	7	184	146
Full Cost Total	$28,516	$28,618	$28,849

* Full cost data for the measures under each performance program area are shown as non-adds. The sum of full costs of performance measures does not equal the full cost of the performance program area, as NIH utilizes a representative sampling approach to report on program performance progress. Representative goals serve as proxies for performance of the larger research portfolio for each of the functional areas.

Methodology for Full Cost

NIH does not have an account or collection of accounts dedicated to program management. To allocate costs for program management, we selected the Research Management and Support (RMS) line item from the NIH mechanism display and Office of the Director Operations, a line item in the appropriation for the Office of the Director. Although these lines support some activities in addition to program management, they represent the majority of NIH program management activities. These totals were reduced by the direct costs of the performance goals that are funded through RMS or OD operations. This calculated level for Program Management was allocated across GPRA goals and the unsampled program on a pro-rata basis.

NIH Performance Goal Criteria

Although decisions regarding the development and implementation of performance goals are made at the NIH level, the development and administration of specific goals occur at the IC level. Consequently, budget and performance decisions are made at the IC level.

Overall GPRA management requires that each performance goal be based on Research and Development Investment (R&D) criteria; be representative, measurable and trans-NIH; be meaningful to researchers, public, and NIH stakeholders; have an estimated date of completion; and be reported annually. Also, the goal should enable linkage of budget with performance, be able to appear in managers' performance plans, and tie to one of the objectives found in Healthy People 2010 (http://www.healthypeople.gov/), the FY 2004-2009 HHS Strategic Plan (http://aspe.hhs.gov/hhsplan/), and/or the President's Management Agenda (http://www.whitehouse.gov/omb/budintegration/pma_index.html). Many of the NIH performance goals also support the HHS Secretary's 500-Day Plan (http://www.hhs.gov/500DayPlan/). The selection of performance goals and targets are guided by the following criteria:

- *Research and Development (R&D) Investment Criteria*. The NIH performance goals are consistent with the President's Management Agenda R&D Investment Criteria. These criteria – *relevance*, *quality*, and *performance* – are considered in the development of NIH performance goals and associated targets.

  The first criterion—relevance—is addressed in several ways as it relates to research. One way is in setting research priorities—by considering public health needs, as judged by the incidence, severity, and cost of specific disorders as a key factor in determining areas of research support. Relevance is also ensured by seeking the views of the public on NIH's research agenda(s). This occurs through meetings of advisory councils and/or boards that include representatives of the public, by publishing research plans for public comment, and by meeting with representatives of patient groups and presenting NIH research plans and seeking feedback. In addition, to help ensure that the results of research reach the hands of those who can put the information to practical use, relevance is also considered when developing and disseminating educational materials or implementing public education campaigns based on results from NIH-funded research.

  Quality—the second criterion—is embodied by a commitment on the part of NIH to support work of the highest scientific caliber. NIH ensures quality through the peer review process for grants, and the principles guiding this review for scientific merit are contained in the Public Health Service Scientific Peer Review regulations. Peer review takes place in multiple steps. The initial step of the peer review process takes place in Scientific Review Groups or study sections, and the second level of peer review is carried out by the National Advisory Councils. A major effort has been underway at NIH to reorganize many of these review groups to keep pace with the ever-changing landscape of science, thus helping to ensure the quality of peer review.

  The third criterion—performance—is key to each and every R&D goal set by NIH. Once priorities are set, peer review occurs, and funding decisions are made, performance on NIH

grants and contracts is monitored on a regular basis. For example, grantees must submit annual progress reports which are reviewed to assess their performance, and follow-up actions are taken when necessary. In addition, there are other oversight mechanisms for reviewing progress such as site visits conducted by NIH staff. NIH also conducts state-of-the-science reviews, workshops, and other scientific meetings where knowledge in a particular area of research is reviewed, and scientific progress and performance are assessed.

- *Balanced Portfolio of Goals (Difficulty and Time).* The continuum of scientific discovery affirms the need for a balanced portfolio of goals, ranging from low- to high-difficulty, and short- to long-term. NIH presents its scientific research outcome goals in a matrix framework (See GPRA Performance Goal Narratives by Five Functional Areas) to show the nature and extent of its portfolio.

- *Goal Selection Criteria*. NIH selected 35 specific, representative research goals as proxies for performance on the larger, research portfolio. As noted above, the goals were selected based on the following criteria:

    - The goals are representative, not comprehensive; that is, taken together the goals represent the breadth of NIH's portfolio. The goals address basic, prevention, diagnostic, and treatment research.

    - The goals are objective; that is, they permit a comparison between the actual achievement level and that targeted by the performance goal.

    - The goals are reportable; that is, they lend themselves to annual reporting, including incremental progress.

    - The goals are not obviously attainable; that is, they must be recognized as something that *could* be achieved in the future, but may not be reachable for any number of reasons—the unpredictable progress of science, funding, and/or development of new tools needed to achieve the goal.

    - The goals are as specific (e.g., to a disease or definable problem) as possible, with reference to a metric and/or a date for progress/completion, as appropriate.

    - The goals are meaningful; that is, they will be credible to the research community and the public; and they are important to the NIH and its research mission.

- *Adjusting Targets.* The target-based approach for science requires flexibility to reflect the discovery process. If a target is adjusted, it incorporates new knowledge and indicates enhanced performance to reflect progress in achieving the goal.

- *Budget/Performance Integration*. The required specific scientific focus of the performance goals does not lend itself to NIH level allocation of funds. Priority setting and funding occur below the NIH level penumbra. To achieve specificity, particular performance goals are created by program staff and funded at the Institute level with multiple contributors. Often, the

specificity of the goal is not captured at the level of the multiple contributing Institutes' penumbra either, since many are supported by grants and contracts. However, every performance goal is treated as a priority, performance is diligently monitored, and budgets are adjusted to facilitate the best possible outcome.

Once a goal is created, the lead and contributing Institutes/Centers (ICs) coordinate on performance monitoring and funding throughout the duration of the goal. The ICs work closely with the NIH Systemic Assessments Branch and Office of Budget to report annual performance and funding levels. Performance is monitored regularly with course corrections occurring as needed in order to achieve the goal. Programs that perform well are sustained if funding is available. Poorly performing programs are corrected to overcome deficiencies or cut to fund other high priority projects.

NIH Reporting Approach

NIH categorizes performance in the GPRA Plan under five functional areas with representative trans-NIH performance goals reported for six years increments.

PERFORMANCE GOALS BY FUNCTIONAL AREA SUMMARY TABLE						
FUNCTIONAL AREA	PERFORMANCE GOALS					
	FY03	FY04	FY05	FY06	FY07	FY08
Scientific Research Outcomes	27	28	36	35	32	28
Communication and Transfer of Results	1	4	5	5	3	3
Capacity Building and Research Resources	2	4	5	8	7	7
Strategic Management of Human Capital	3	2	3	3	3	3
Program Oversight and Improvement	3	3	7	7	7	6
Totals	36	41	56	58	52	47

A six year summary performance is described in the Detail Performance Analysis Tables. This section highlights the budget-performance integration. The goal narratives describe the impetus for the goal as well as the implementation plan to achieve the goal. Each GPRA goal contains the background/state-of-the-field, rationale for the goal, planned implementation strategies, an annual target table with baselines, a description of target performance, other advances, and options such as a section to report retrospective efficiencies and to describe if target or goal adjustments are needed. Scientific rationales for adjusted targets are presented if applicable. Given the unpredictable nature of scientific discovery, NIH adjusts its annual targets to reflect the latest developments in science and the most efficient path to goal achievement.

One new long-term, low-difficulty scientific research outcome goal, four Capacity Building and Research Resources goals, and one Program Oversight and Improvement goal were added to the plan. FY 2008 planned targets were added to each active 2008 goal. To simplify reporting, the goal becomes the expected annual target for the end year. The FY 2006 performance summary is provided with target achievements, and with highlights of implementation strategy advances. If a target is achieved efficiently, a short narrative description is provided and a subscript "e" on the performance summary table. Finally, at the end of the narrative, it indicates whether the goal was included in the Program Assessment Rating Tool (PART). Unless stated otherwise, NIH plans to

move forward with the proposed annual targets and implementation strategies within the context of the proposed budget.

Performance and budget information for each goal is collected through a centralized online reporting system called Visual Performance Suite (VPS). The system supports e-government as it provides an electronic systematic approach of collecting performance and budget information across ICs. The system provides an anthology of performance and associated budget information to facilitate communication and can be used to support organizational annual planning.

Specific accomplishments on current performance goals are highlighted below:

Scientific Research Outcomes

- *Publicly Accessible Collection of Reference Sequences Built to Serve as Basis for Medical, Functional, and Diversity Studies.* The Reference Sequence (RefSeq) Collection is a single, high-quality collection of reference sequences for multiple species that is richly annotated and highly connected to other information sources making it possible to undertake large-scale comparative analyses. The ability to make discoveries in one organism (such as mouse models of a human disease) and immediately apply them to another organism (such as humans) is one of the most powerful aspects of molecular biology. The academic and pharmaceutical research communities use reference sequences in this way to investigate basic molecular biological processes and medical problems, such as different disease susceptibilities for individuals or targeted individual drug treatment approaches. The availability of a RefSeq Collection means that time once spent identifying resources, gathering data, and reviewing its quality is freed for research. (See GPRA Goal SRO-7.8.3)

- *Directional Hearing Aid Microphone Developed to Help Hearing-Impaired Individuals*. NIH-supported scientists successfully completed a fabrication process to miniaturize the prototype of a low-power, highly directional hearing aid microphone so that it will fit into a hearing aid. This directional microphone mimics the auditory system of the parasitic fly *Ormia ochracea* that has mechanically coupled ears enabling it to detect the direction of sound. The scientists used silicon microfabrication technology to make a microphone that is small enough to be incorporated into a hearing aid. The directional microphone will ultimately help hearing aid users to better understand speech in a noisy background by "paying more attention to" or giving more weight to desirable sound(s) amidst noise. (See GPRA Goal SRO-1.2)

- *Significant Milestone in the Development of Salivary Diagnostic Tools.* NIH has developed a portable handheld diagnostic device to detect multiple substances in human saliva associated with oral and systemic diseases. Such a device has the potential to replace blood tests and make it easier and cheaper to monitor disease-specific biomarkers, such as C-reactive protein, an important biomarker for cardiovascular disease. Progress is now being made to advance this new device until a fully integrated system is ready for clinical trials and subsequent commercialization. (See GPRA Goal SRO-3.3)

- *Ongoing Efforts to Identify Genetic Variations Underlying Alcohol Dependence*. To better understand the cause of substance use disorders, NIH is conducting research to validate in different sample populations previously identified genes associated with an elevated risk for

alcohol dependence. Thus far, scientists have linked three genes to increased vulnerability to alcohol dependence in various groups: (1) one gene on chromosome 4 (GABRA2) was identified in European-American, Russian male, German, Irish, Plains Indian, and Finnish Caucasian male sample populations; (2) another gene on chromosome 4 (ADH4) was identified in European-American, European-Brazilian, and African-Brazilian sample populations; and (3) one gene on chromosome 7 (CHRM2) was identified in European-American and African-American sample populations. These results do not necessarily suggest that these sample populations are at increased risk for alcoholism but rather individuals possessing variants of these genes may be more vulnerable to developing alcohol dependence. (See GPRA Goal SRO-3.5)

- *Promising Applications of Nanotechnology in Early Cancer Detection.* A growing number of NIH-supported studies are demonstrating potential uses of nanotechnology in the early detection of cancer. Recent advances include: (1) the development of nanoparticle-based biobarcodes that can detect three different protein tumor markers: a prostate cancer marker (prostate specific antigen or PSA), a testicular cancer marker (human chorionic gonadotrophin or HCG), and a liver cancer marker (α-fetoprotein or AFP); (2) the successful melding of magnetic iron nanoparticles, the anticancer drug doxorubicin, and a polymer tagged with a tumor-targeted molecule into a stable nanoparticle that accumulates inside human tumor cells, thereby creating a single device that can image and treat tumors simultaneously; (3) the demonstration that dendrimer-based nanoparticles can deliver oligonucleotide-based drugs into breast cancer cells; and (4) the development of a polymer-coated bismuth nanoparticle that holds promise for improving the tumor-detecting capabilities of computed tomography X-ray imaging. (See GPRA Goal SRO-7.2)

- *Researchers Identified Small Molecules that Show Promise as Drugs, Diagnostic Agents, or Research Tools*. NIH-supported scientists have made significant progress in screening bioactive compounds for potential drugs, diagnostic agents, or research tools. In fact, three potential drugs have completed preclinical testing and are undergoing evaluation in clinical trials for treating amyotrophic lateral sclerosis (ALS), seizures, and anxiety, respectively. Two imaging agents for visualizing amyloid plaques, a characteristic feature of Alzheimer's disease, have also entered clinical stages of development. In addition, researchers have identified several new molecules that interact with various neurotransmitter systems and are developing a subset into new imaging agents in the human brain. (See GPRA Goal SRO-4.5.4)

- *Knowledge Base on Chemical Effects in Biological Systems*. NIH is creating the Chemical Effects in Biological Systems (CEBS) knowledge base, the first public repository that provides valuable experimental data relevant to environmental toxicology and disease to the scientific community. A recent enhancement allows CEBS to capture and integrate multiple data sets of different data types (biochemical measurements, toxicology/pathology outcomes, etc.) for a single compound (e.g., acetaminophen), thereby increasing its efficiency and usefulness. Additional enhancements to link outcomes of searches to existing literature databases are planned. Upon completion, CEBS will facilitate the characterization of toxicants and associated biological effects and help scientists predict the impact of suspected toxicants and estimate the hazard these toxicants posed to human and environmental health. (See GPRA Goal SRO-6.3)

- *New Mouse Model to Study Bone Formation Opens Avenues for Investigations into the Molecular Basis of Bone Diseases and Treatments*. When NIH-supported researchers who were investigating the role of fibronectin--a protein thought to be critical for bone development--engineered a strain of mice in which bone-forming cells (osteoblasts) could not produce this essential protein, they were surprised to observe that the change did not severely impair the animals' bone health. This recent finding is prompting researchers to hypothesize that other cells may be able to produce fibronectin if osteoblasts do not. Knowing where and when matrix proteins such as fibronectin are produced in mice gives insight into which cells must be targeted when designing a therapy for bone diseases such as osteoporosis. Therefore, studies are now underway to generate mice in which fibronectin production is eliminated in other cell types to test whether cells other than osteoblasts provide fibronectin during normal bone growth. (See GPRA Goal SRO-8.2)

Communication and Transfer of Results

- *Know Stroke Campaign Increased Stroke Awareness Across the U.S.* The NIH campaign, *Know Stroke. Know the Signs. Act in Time.* has increased stroke awareness in cities across the country by conducting outreach activities in a total of 25 communities. The campaign enlisted the aid of "Stroke Champions" who educated communities about the signs and symptoms of stroke. To date, 168 Champions have conducted 650 outreach events, reaching more than 150,000 individuals at health fairs, blood pressure screenings, and other community gatherings. In addition, NIH has distributed hundreds of thousands of *Know Stroke* brochures, developed television and radio public service announcements, and wrote feature articles which were targeted to the general public, African American and Hispanic communities. NIH has also disseminated more than 9,500 *Know Stroke* kits, leveraging its partnerships to plan and execute strategic, meaningful distribution of the materials, thus ensuring further reach of the *Know Stroke* messages. (See GPRA Goal CTR-2)

- *International Technology Transfer Training Program Strengthens the Capacity of Developing Countries.* NIH continues to provide technical assistance and training to scientific and administrative personnel in developing countries on Intellectual Property Management and Technology Transfer activities and operations. In FY 2006, NIH provided education and technical assistance to representatives of four developing counties (six institutions) to facilitate the development and expansion of technology transfer programs at their respective institutes and to assist in the identification of technologies for commercialization and development into products. (See GPRA goal CTR-3)

Capacity Building and Research Resources

- *NIH Trains More Than 17,000 in Biomedical Informatics, Bioinformatics, and Computational Biology in Two Years.* In an era of comparative genomics and personalized drug design, informatics training is very popular. All fields of biomedical research now employ sophisticated informatics tools to capture and analyze data. Both NIH's short-term training and pre- or post-doctoral training in informatics have proven very popular. In the short-term training, the three largest short courses each had more than 1,000 attendees. In one course, enrollment was more than 30% greater than expected; in another, it was nearly 3 times the expected enrollment; and in the third, nearly twice the expected number of people enrolled. Due to the strong interest and

need for informatics training, NIH will continue to offer both short-term and pre- or post-doctoral training in informatics and computational biology. (See GPRA Goal CBRR-5)

- *Integration of HHS OPDIVs to NIH electronic Research Administration (eRA) system.* This year saw NIH's full integration of eligible Health and Human Services (HHS) Operating Divisions (OPDIVs) as users of eRA, NIH's electronic research administration infrastructure for conducting interactive electronic transactions for the receipt and review of applications, and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. As a result of the OPDIV integration, five HHS OPDIVs are now using the same computer system to process their grants instead of having to maintain five separate computer systems. The OPDIVs have been provided access to all requested eRA modules and linked to the financial systems used by the Agencies. (See GPRA Goal CBRR-4)

- *NIH's National Research Service Award (NRSA) program trainees remain active in biomedical research.* NRSA predoctoral trainees and fellows from 1985 through 1995 were more likely to remain active in biomedical research, in contrast to other doctoral students at the same institution over the same time period and doctoral students at institutions not receiving NRSA support, as indicated by the greater percentage applying for and receiving NIH research project grant support within 10 years of completing their Ph.D.s. Similarly, NRSA postdoctoral fellows were more likely to remain active in biomedical research and receive NIH research grants following the completion of their training. This reflects the impact of NIH research training support on the ability of trainees and fellows to be competitive and sustain a research career. (See GPRA Goal CBRR-1)

Strategic Management of Human Capital

- *Competitive Sourcing Reviews on Commercial Functions Ensures Efficiency and Cost Effectiveness.* NIH identifies commercial activities for competitive sourcing reviews to ensure that they are subjected to the rigor and discipline of market competition. In FY 2006, the pre-planning step identified 4 potential functional areas for review, EEO administrative support, Clinical Center administrative support, IT network systems, and IT end user support & technical writers. All 4 were deemed appropriate for streamlined reviews each with a Most Efficient Organization (MEO) and were announced for competition in FY 2006. In addition, in FY 2006 NIH completed and won three reviews that were announced in FY 2005. These were: IT systems administration, food services, and patient care unit clerks. (See GPRA Goal SMHC-4)

Program Oversight and Improvement

- *Earned Value Analysis and Management System (EVAMS) Ensures Design and Construction Projects are Executed On Time, On Scope and On Budget.* In FY 2006, NIH fully launched the EVAMS and Earned Value Analyses (EVAs) were conducted for NIH major capital acquisition projects included in the NIH Real Estate Portfolio. The EVAMS uses a project data analysis framework to link cost and schedule estimates to actual results. It provides NIH Project

Managers with a management system, tools, and the information needed to improve their ability to manage, track, and report on, project performance, and intervene when the risk to successful completion of a project increases. The EVAs enabled better management and delivery of projects using the tracking and monitoring metrics to evaluate performance, control variances, and review business practices. (See GPRA Goal POI-1)

LINKS TO HHS STRATEGIC GOALS

The table below presents the NIH GPRA Goals support of the HHS Strategic Goals.

NIH GPRA Goals	HHS Strategic Goals							
	Goal 1: Reduce the major threats to the health and well-being of America	Goal 2: Enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health challenges	Goal 3: Increase the percentage of the Nation's children and adults who have access to health care services, and expand consumer choices	Goal 4: Enhance the capacity and productivity of the Nation's health science research enterprise	Goal 5: Improve the quality of health care services	Goal 6: Improve the economic and social well-being of individuals, families, and communities, especially those most in need	Goal 7: Improve the stability and healthy development of our Nation's children and youth	Goal 8: Achieve excellence in management practices
Scientific Research Outcomes (SRO)								
SRO-1.1: By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.	X			X				
SRO-1.2: By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.				X		X		
SRO-1.2.3: By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.				X				
SRO-2.2: By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.	X			X				
SRO-2.4: By 2009, the Laboratory of Symptom Management will develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress, to reduce related symptom burden and to increase functional status and quality of life.				X				
SRO-2.3.2: By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		X		X				
SRO-2.3.4: By 2010, develop an HIV/AIDS vaccine.	X			X				
SRO-3.1: By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).				X		X		
SRO-3.2.1: By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.				X				
SRO-3.3: By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.				X				
SRO-3.5: By 2013, identify and characterize at least 2 human candidate genes that mutually influence risk for substance use disorders and risk for comorbid psychiatric disorders using high-risk family, twin, and special population studies.	X			X				
SRO-3.6: By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.				X				
SRO-4.5.1: By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than current recommended HIV treatment regimens.				X				
SRO-4.5.4: By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.				X				
SRO-4.5.5: By 2008, develop and test new evidence-based treatment approaches for drug abuse in community settings.	X		X					
SRO-5.2: By 2009, determine the efficacy of statins in preventing the progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).				X				
SRO-5.3: By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.				X				
SRO-5.6: By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.	X			X				
SRO-5.6.2: By 2011, assess the efficacy of at least three new treatment strategies to reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.	X			X				
SRO-5.7: By 2010, validate and compare 4 imaging methods of assessing lung cancer response to therapy.				X				
SRO-5.8: By 2010, improve device(s) to measure hot flashes and test device(s) in clinical trials.				X				
SRO-5.9: By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.			X					
SRO-6.1: By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.				X		X		
SRO-6.3: By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.				X				
SRO-6.4: By 2014, identify and characterize two molecular pathways of potential clinical significance to serve as the basis for discovering new medications for preventing and treating asthma exacerbations.				X				
SRO-7.2: By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.				X				
SRO-7.8.1: By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.	X	X		X				
SRO-7.8.3: By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, nonredundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.				X				
SRO-8.2: By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.				X		X		
SRO-8.4: By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.				X				

SRO-8.5: By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.				X				
SRO-8.6: By 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).				X				
SRO-8.9.1: By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United States by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).				X		X		
SRO-8.9.2: By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.	X		X	X				
SRO-8.9.3: By 2012, create a database and analytical software that illustrates the progression of normal MRI measurement of brain development in a nationally representative sample of children in the United States.				X			X	
SRO-9.4: By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.				X			X	
Communication and Transfer of Results (CTR)								
CTR-1: By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).			X	X			X	
CTR-2: By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the National Institute of Neurological Disorders and Stroke campaign "Know Stroke. Know the Signs. Act in Time."	X			X				
CTR-3: By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.				X				
CTR-4: By 2008, increase the percentage of Small Business Innovation Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.				X				
CTR-5: By 2013, improve marketing and management of NIH intellectual property (IP) assets by building data mining capability.				X				X
Capacity Building and Research Resources (CBRR)								
CBRR-1: By 2012, recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.				X				
CBRR-2: Promote data sharing and provide information in real time by implementing the NIH Business System.								X
CBRR-3: By 2007, streamline business processes and automate data movement by implementing the Clinical Research Information System (CRIS).					X			X
CBRR-4: By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic research administration (eRA).								X
CBRR-5: By 2006, expand by 50% the pool of researchers trained in biomedical informatics by increasing the numbers of informatics-trained graduates in basic biomedical sciences, clinical medicine, and public health.				X				
CBRR-6: By 2010, build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.		X		X				
CBRR-7: By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.								X
CBRR-8: By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.								X
CBRR-9: By 2010, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.								X
Strategic Management of Human Capital (SMHC)								
SMHC-3: Improve the strategic management of NIH resources by developing a comprehensive human capital plan based on the Agency's programmatic objectives and projected future needs.								X
SMHC-4: Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory.								X
SMHC-5: Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal.								X
Program Oversight and Improvement (POI)								
POI-1: By 2007, ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing an Earned Value Analysis and Management System (EVAMS).								X
POI-2: Expand the use of Performance-Based Contracting (PBC).								X
POI-5: By 2010, enhance NIH's ability to demonstrate benefits for extramural research investments through changes to policy and information systems.								X
POI-6: Provide responsible stewardship over existing federally owned real property assets.								X
POI-7: Manage design and construction of capital facility projects funded by the building and facilities appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the appropriate budget.								X
POI-8: By 2010, protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements								X
POI-9: By 2012, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors								X

Note: New goals are in italics.

SUMMARY OF NIH MEASURES AND TARGET RESULTS

Six new performance goals were added to the GPRA FY 2008 performance plan. The new scientific research outcome goal, the four Capacity Building and Research Resources goals, and the one Program Oversight and Improvement goal began in FY 2006 due to the PART process. The annual targets for the new goal are included later in the Detail Performance Analysis Tables and the performance goal narrative. The new goals added to the plan last year create a crest in the total number of goals in FY 2006. However, many goals will be achieved in the next two years, and by FY 2008 the total number of goals will be back to the expected level seen in FY 2004. NIH continues to move in the direction of increasing the number of outcome goals while decreasing the number of output goals. NIH achieves a high level of "MET" measures. Measure not met has a sound scientific justification for the extended or not met rating. Sound science is expected to have some extended and not met annual targets.

SUMMARY OF MEASURES AND RESULTS TABLE								
FY	Measures				Target Results			
	Long Term Performance Goals	Annual Targets	Total Targets in Plan *	% Reported	Met	Extended	Not Met	% Met
2002	40	80	80	100%	66	12	2	97%
2003	36	45	47	104%	39	8	0	100%
2004	41	54	56	104%	52	3	1	98%
2005	56	79	82 (+3 FY04 extended)	104%	77	4	1	99%
2006	58	74	75 (+1 FY05 extended)	101%	69	5	1	99%
2007	52	65			Performance results will be reported in February 2008.			
2008	47	61			Performance results will be reported in February 2009.			

* Current year annual measures plus extended targets from prior year(s)

10 Percent Program Improvements

A large portion of NIH funds support grants to extramural investigators and institutions conducting high quality scientific research consistent with NIH's mission. Grants are the core means of supporting extramural research. It is essential that the processes relating to grants and peer review are unbiased, effective, and efficient so that scientific discovery is not impeded by administrative burdens.

As a means to gain efficiencies in the grants process, NIH will implement *grants.gov* as its form of direct electronic submission of grant proposals, replacing the current practice of paper submission and electronic scanning. The current process averages nine months from receipt to award notification and funding availability. This long process often delays the onset of research projects and further delays reapplication for those scientists who are denied funding. In 2007 a ten percent improvement is a one-month reduction in the application to award process, and the number of electronic submissions would increase by more than ten percent each year.

Electronic submission will reduce turn-around-time by reducing administrative burdens (including scanning, postage, photocopying) as well as enable NIH to categorize applications electronically, leading to more effective and rapid identification and assignment of appropriate reviewers. Thus, electronic submission will facilitate the peer review and grants management process to make more timely awards and enable supported scientists to begin important research more rapidly.

Strategies for improving program performance require a phased approach. NIH piloted and will incrementally phase-in electronic submission of grant applications by: 1) working with *grants.gov* to implement NIH specific forms and assure grants.gov functionality, 2) implementing the standard Federal grants application form (SF – 424) for NIH programs, 3) piloting additional programs using *grants.gov*, and 4) fully implementing electronic submission for all NIH funding types.

10% PROGRAM PERFORMANCE GOAL: Electronic grants submission reduces average application-to-award turn-around-time as a means to accelerate onset of scientific discovery.					
Measure	**Baseline**	**2005**	**2006**	**2007**	**2008**
Make available *grants.gov* as the method to submit NIH electronic applications in program areas	1 program area	Increase by 2 program areas	Increase by 2 program areas	Increase by 2 program areas	All NIH applications are submitted electronically
FY 2006 Actual Performance: (MET) NIH increased by 13 research program types: R36, R15, S10, X02, X01, R03, R21, R03/R21, R34, R18/U18, R25, C06/U06, and R01. NIH was able to exceed its goal because of successful initial e-submission programs that enabled the organization to more quickly apply technical fixes and to institute business processes in support of e-submission.					
Monitor the average application-to-award time for those programs having implemented electronic submission	9 months	9 months	9 months	8 months	Achieve 10% improvement
FY 2006 Actual Performance: (MET) 9 months					
Source Validation: eSubmission transition timeline at http://era.nih.gov/ElectronicReceipt/files/Electronic_receipt_timeline_Ext.pdf. Announcements in the NIH Guide for Grants and Contracts at http://era.nih.gov/ElectronicReceipt/guide_notices.htm. http://cms.csr.nih.gov/ http://grants.nih.gov/grants/partners/0906Nexus.htm#Appendix					

NIH is working to reduce the time from receipt to award by moving to electronic grant applications and by using various technologies to process those applications. Technologies being tested include the use of knowledge management systems to assist in the referral to a Scientific Review Group as well as to a funding Institute or Center. Such systems may ultimately help with the identification of peer reviewers and the identification of conflicts of interest. In some cases, electronic applications are sent to reviewers in advance of the meeting and special programs and interfaces allow reviewers to enter critiques in a secure fashion and to partially review applications in advance of the actual review meeting. In some cases, meetings can take place in secure webspace in order to reduce or avoid travel time. Some of the NIH Institutes and Centers use expedited second level review to accelerate the processing and approval of specific applications. The Center for Scientific

Review is also piloting a process that provides summary reports to applicants on an expedited basis so that they can revise and resubmit for the next receipt date. The NIH will continue to look for other approaches protect the integrity of the review process but reduce the time from receipt of an application until an award is made.

DETAIL OF PERFORMANCE ANALYSIS TABLES

Comprehensive summary tables covering all the FY 2006, 2007, and 2008 goals and targets in NIH's Research Program follow. These tables provide updated information on the status of all of the program's performance targets, as well as budget and performance integration. Due to the complexities of scientific discovery, the identified targets are subject to change to facilitate the prospect of achieving the best science. Detailed narratives for each goal, including a chart summarizing the performance results for each target, can be found later in this section following the NIH GPRA Scientific Research Outcomes Goals Matrix. Data source and validation information are provided to confirm achievement of annual targets. Healthy People 2010, PMA, HHS Strategic Plan, 500-Day Plan, One HHS Top 20 Objectives, outcome, output, efficiency, and PARTed goals are noted in the cross reference row in the table.

Program Performance Tables: FY 2006, 2007, 2008 Goals

SCIENTIFIC RESEARCH OUTCOMES

SRO - 1.1	By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Prepare clinical protocol for testing rimonabant in humans.	1. (FY02) Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	1. (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking.
2004	1. Complete a toxicologic evaluation of antalarmin.	1. (FY03) Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials	1. (MET) A toxicologic evaluation on antalarmin has been completed.
2005	1. Test antalarmin for relapse prevention in alcoholics.	1. (FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking	1. (EXT) For the drug antalarmin, the FDA requires further toxicology studies. Extended to 2007.
2006	1. Conduct toxicology studies of antalarmin in monkeys as required by FDA.	1. (FY05) Meetings with FDA to discuss initial toxicity study results in monkeys and dogs led to a new request from FDA for additional studies in monkeys	1. (MET) Toxicology studies of antalarmin in non-human primates were conducted as required by FDA.
2007	1. Complete goal of conducting medications development using animal models and beginning to conduct Phase I and II human trials of two potential treatments for alcoholism: rimonabant and antalarmin.	1. (FY06) Toxicology studies of antalarmin have been performed in monkeys and a phase IIa clinical trial of rimonabant has been conducted.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Hansson AC, Cippitelli A, Sommer WH, Fedeli A, Bjork K, Soverchia L, Terasmaa A, Massi M, Heilig M, Ciccocioppo R. Variation at the rat Crhr1 locus and sensitivity to relapse into alcohol seeking induced by environmental stress. Proc Natl Acad Sci U S A. 2006 Oct 10;103(41):15236-41. The antalarmin studies are supported by funding from the NIAAA Intramural Research Program (1Z01AA000487-02). Inquiries should be directed to Patricia Powell, Ph.D. (ppowell@mail.nih.gov, 301-443-5106).		
Cross Reference:	HP-26, SP-1.4, SP-4.1, Efficiency, Outcome		
SRO - 1.2	By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly "Ormia ochracea."	1. (FY02) Small insect model system exists and has hyperacute sound localization.	1. (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to

			the sound and is based on the ears of the parasitic fly 'Ormia ochracea'.
2004	1. Design and test the electronic circuitry to create a sound output from the diaphragm.	1. (FY03) Sound-responsive diaphragm based on an insect model system is available	1. (MET) NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal.
2005	1. Combine the diaphragm and the electronic output circuitry into a directional microphone. *Previous Target:* Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	1. (FY04) Diaphragm and electronic circuitry are available.	1. (MET) NIH-supported scientists successfully combined the diaphragm and circuitry into a directional microphone.
2006	1. Complete goal of developing one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	1. (FY05) Diaphragm and electronic circuitry combined into a directional microphone.	1. (MET) A prototype of a low-power, highly directional hearing aid microphone was developed to help hearing-impaired persons better understand speech in a noisy background.

Data Source & Validation:

Publications

Cui, W., Bicen, B., Hall, N.A., Jones, S.A., Degertekin, F.L., Miles, R.N., Optical sensing in a directional MEMS microphone inspired by the ears of the parasitoid fly, Ormia ochracea. Proceedings of the IEEE International Conference on Micro Electro Mechanical Systems, 614-617, Istanbul, January 22-26, 2006.

Homentcovschi, D., Miles, R.N., Viscous scattering of a pressure wave: calculation of the fluid tractions on a biomimetic acoustic velocity sensor. Journal of the Acoustical Society of America 119: 777-787, 2006.

Homentcovschi, D., Aubrey, M.J., Miles, R.N., A two-dimensional model of a directional microphone: calculation of the normal force and moment on the diaphragm. Journal of the Acoustical Society of America, 119: 756-768, 2006.

Miles, R.N., Hoy, R.R., The development of a biologically-inspired directional microphone for hearing aids. Audiology & Neurotology 11: 86-94, 2006.

Lockwood, M.E., Jones, D.L., Beamformer performance with acoustic vector sensors in air. Journal of the Acoustical Society of America 119: 608-619, 2006.

Hall, N.A., Bicen, B., Jeelani, M.K., Lee, W., Qureshi, S., and Degertekin, F.L., Micromachined microphones with diffraction-based optical displacement detection. Journal of the Acoustical Society of America 118: 3000-3009, 2005.

Younis, M.I., Miles, R.N., and Jordy, D., Investigation of the response of microstructures under the combined effect of mechanical shock and electrostatic forces. Journal of Micromechanics and Microengineering 16: 2463-2474, 2006.

Hall, N.A., Okandan, M., and Degertekin, F.L., Surface and Bulk Silicon Micromachined Optical Displacement Sensor Fabricated with SwIFT-Lite™. IEEE/ASME Journal of Microelectromechanical Systems 15: 770-776, 2006.

Patents and Patent Applications

Patent No. 6,963,653: High-order directional microphone diaphragm, 11-08-2005, R.N. Miles.

Patent application: Robust microphone for an acoustic device, filed 10-20-2003, R.N. Miles and W. Cui.

Patent application: Comb sense microphone, filed 08-05-2005, R.N. Miles.

Patent application: Optical microphone, filed 01-19-2006, R.N. Miles and F.L. Degertekin.

Patent application: Surface micromachined microphone, filed 01-31-2006, R.N. Miles,

	Patent application: Miniature, non-directional microphone, filed 10-18-2006, R.N. Miles.
Cross Reference:	HP-28, SP-4.1, SP-6.2, Outcome, PART

SRO - 1.2.3	By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	1. (FY02) 256 domain families curated; software to align domains by structure and class unavailable	1. (MET) Software was released which improved structure-based alignments of proteins and classification of protein domain families based on molecular evolution; software was used to annotate over 500 protein domain families.
2004	1. Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	1. (FY03) 800 domain families curated; 25% coverage of PubMed sequences	1. (MET) 1,674 domain families curated through enhancing software for molecular evolutionary classification and by bringing Conserved Domain Curator team to full strength.
2005	1. Obtain annotation for total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	1. (FY04) 1,500 protein domain families curated; 35% coverage of PubMed sequences	1. (MET) 2,814 expertly curated protein domain families curated by further developing the software and increasing the size of the Conserved Domain Curator team. 45% of PubMed sequences covered and, with first generation alignments, an estimated 75% covered.
2006	1. Complete goal of developing methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	1. (FY05) 2,800 protein domain families curated; 45% coverage of PubMed sequences	1. (MET) By the end of FY 2005, 75% of proteins from sequenced genomes according to evolutionary origin and biological structure had been classified and the goal had been met. In FY 2006, several enhancements were implemented beyond the goal of classifying 75% of proteins which enabled the team to produce a total of 3,904 expertly curated protein domain family models.

Data Source & Validation:	The conserved Domain database is publicly available via the PubMed / Entrez search engine: http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi. Sequence similarity searches are also supported via the available CD-Search utility: http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi. CDD is also described in: Marchler-Bauer et al. CDD: A conserved domain database for protein classification, Nucleic Acids Res. 33D, 192-6, 2005. This paper ranked number 28 among the top 40 most cited papers published in 2005, according to Thomson Corporation's ScienceWatch service: http://www.sciencewatch.com/march-april2006/sw_march-april2006_page1.htm
Cross Reference:	SP-4.1, Outcome

FULL COST (dollars in millions)	FY06	FY07	FY08
	$9	$3	$0

SRO - 2.2	By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	1. (FY02) No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	1. (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.
	1. Develop and launch at least two studies	1. (FY03) No programs for weight control	1. (MET) More than two studies to test the

2004	to test the effects of worksite interventions on weight control.	at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective	effects of worksite interventions on weight control were developed and launched.
2005	1. Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children 6 to 12 years.	1. (FY03) No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia	1. (MET) NIH scientists succeeded in enrolling 73 children in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.
2006	1. Enroll and randomize 240 predominantly minority pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain.	1. (FY04) Few effective community-based interventions are available to prevent weight gain in at risk children	1. (MET) Two hundred forty ethnically-diverse pre-adolescent girls were enrolled and randomized to test the efficacy of an after school dance program in reducing weight gain.
2007	1. Develop and launch at least three new clinical trials to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children.	1. (FY05) Few obesity intervention programs targeting children have been designed and tested to establish their effectiveness outside of small clinical settings.	1. Performance results will be reported in February 2008.
2008	1. Complete delivery of the 2-year interventions being tested in the preventing obesity using novel dietary strategies (POUNDS Lost) clinical trial, which is comparing four diets of different macronutrient composition for their effects on weight loss and weight loss maintenance in overweight and obese adults.	1. (FY06) Few trials have adequately tested the effects of diets differing in macronutrient composition.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Baseline data of the 240 preadolescent girls enrolled in the study can be found in Journal of Pediatrics 148 788-792 2006. Documentation that the study subjects have been randomized can be found in the Principal Investigator's Progress Report Summary which can be requested from Dr. Patrick Donohue in NIDDK's Office of Scientific Program and Policy Analysis.		
Cross Reference:	HP-19, 1HHS-13, 1HHS-19, SP-4.1, 5,000D-T1, 500D-A10, Efficiency, Outcome		

SRO - 2.3.2	By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	1. (FY02) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	1. (MET) Two different molecules with a common role in different classes of microbes were identified.
2004	1. Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	1. (FY03) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes.	1. (MET) A drug/metabolite transporter molecule from the malarial parasite Plasmodium falciparum, that is similar to transporter molecules in other protozoa, may serve as a target for drugs to increase responsiveness to drug therapies.
2005	1. Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections. *Previous Target:* Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development.	1. (FY04) NIH does not have a complete set of screening tools that can be used to test compounds for activity against both bacterial and viral pathogens.	1. (MET) A complete set of in vitro screening tools that can be used to test compounds for activity against bacterial and viral pathogens has been developed.
2006	1. Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases.	1. (FY04) Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed.	1. (MET) Screening tools were used to evaluate compounds for potential activity against multiple classes of organisms of infectious disease.
2007	1. Through medicinal and/or combinatorial chemistry, optimize several compounds for antimicrobial activity.	1. (FY05) Resources provided to the scientific community for development of medicinal and combinatorial chemistry capacity and assay optimization.	1. Performance results will be reported in February 2008.

2008	1. Begin determining safety and pharmacology profiles (e.g. bioavailability) of at least 1 candidate compound that has shown broad spectrum activity in vitro.	1. (FY07) NIH has not yet begun safety and pharmacology profile determinations for candidate compounds that have demonstrated broad spectrum activity in vitro.	1. Performance results will be reported in February 2009.
Data Source & Validation:	E. Barrow, et al. Newly developed colorimetric drug screening assay for Bacillus anthracis. International Journal of Antimicrobial Agents. 27 (2006) 178-180. P. Bourne, et al. High-throughput drug screening using the Biomek 2000 liquid handling system. Second Sitlington Infectious Disease Symposium. Stillwater, Oklahoma. April 24-25, 2006. B. Duncan, et al. Development of high-throughput in vitro screen for antimicrobial activity against Brucella abortus. Second Sitlington Infectious Disease Symposium. Stillwater, Oklahoma. April 24-25, 2006. K. Matsuyama, et al. Antimicrobial agents with activity against several BSL-2 and BSL-3 biodefense organisms. 2006 Annual Meeting of the Society for Industrial Microbiology. Baltimore, MD. July 30 - August 3, 2006. M. Stubbington, et al. A quantitative real-time PCR assay for antibiotic susceptibility testing of Francisella tularensis. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. September 27-30, 2006. Summary of 'Development of Broad Spectrum Therapeutics" workshop at http://www.niaid.nih.gov/dmid/meetings/bst.htm Refer to NIAID FY 2006 Biodefense Awards page for specific awards made under the initiative "Innate Immunity to Category B Protozoa" http://www3.niaid.nih.gov/Biodefense/Research/2006awards/innate_awards.htm Refer to NIAID FY 2006 Biodefense Awards page for specific awards made under the initiative "Cooperative Research Partnerships for Biodefense" http://www3.niaid.nih.gov/Biodefense/Research/2006awards/coop_awards.htm For all other NIAID FY2006 Biodefense awards, including ones related to development of broad-spectrum antimicrobials, please see: http://www3.niaid.nih.gov/Biodefense/Research/2006awards/		
Cross Reference:	HP-14, HP-24, SP-2.1, SP-4.1, 5,000D-A4, Outcome		

SRO - 2.3.4	By 2010, develop an HIV/AIDS vaccine.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Design and develop new or improved vaccine strategies and delivery/production technologies.	1. (FY02) Existing DNA and viral-vector vaccines strategies require further evaluation	1. (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.
2004	1. Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	1. (FY03) HIV Vaccine Trials Network currently supports clinical trials at 12 international sites	1. (MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.
2005	1. Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	1. (FY04) NIH has conducted 68 phase I and phase II HIV vaccine trials to date	1. (MET) NIH initiated five phase I trials for new products and six phase I and one phase II trials to further assess existing products. NIH expanded clinical trial capacity into 8 new international settings.
2006	1. Initiate 1 new phase IIb trial to determine if a third generation vaccine candidate has efficacy.	1. (FY04) NIH is conducting a phase III trial of a second generation vaccine (canarypox) in Thailand	1. (MET) NIH initiated a Phase IIb study (test of concept) to evaluate the safety and efficacy of Merck's Adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in high-risk adults.
2007	1. Initiate another Phase II/IIb trial(s) of the most promising third generation vaccine candidate.	1. (FY05) NIH is conducting Phase I trials of a second third generation candidate (6 plasmid DNA plus Adv boost).	1. Performance results will be reported in February 2008.
	1. Initiate a Phase IIb trial of a promising	1. (FY06) NIH is conducting 3 phase I/II	1. Performance results will be reported in

2008	vaccine candidate that may protect across viral clades (or subtypes).	trials (HVTN 502, HVTN 050, HVTN 204) of products that might be further tested for protection across viral clades (or subtypes).	February 2009.
Data Source & Validation:	www.HVTN.org and www.AIDSinfo.nih.gov for information and status of specific protocols. NIAID Planning and Reporting Process: Vaccine Clinical Research, HIV Vaccine Research and Development. For more information, contact Dr. Isaac R. Rodriguez-Chavez, VCRB Laboratory Team at icrodriguez@niaid.nih.gov http://www3.niaid.nih.gov/research/topics/HIV/vaccines/resources/simian/ for Simian Vaccine Evaluation Units (SVEU) http://www3.niaid.nih.gov/research/topics/HIV/vaccines/funding/pia.htm for the Vaccine Innovation Grant Program http://www3.niaid.nih.gov/research/topics/HIV/vaccines/funding/hivrad.htm for the HIV Research and Design (HIVRAD) Program		
Cross Reference:	HP-13, SP-1.2, SP-4.1, 5,000D-I2, Outcome		
SRO - 2.4	By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Integrate multidisciplinary approaches to investigate: 1) biological mechanisms of pain, fatigue, or psychological distress or 2) related potential therapeutic intervention(s) by establishing at least one intramural collaboration.	1. (FY05) Identification of potential intramural collaborations.	1. (MET) One intramural collaboration was established.
2006	1. Contribute to the identification of potential interventions for symptom/illness burden by identifying results from one study of symptom distress/quality of life.	1. (FY05) One study of symptom distress/quality of life completed.	1. (MET) Results from one study of symptom distress/quality of life were identified.
2007	1. Contribute to the identification of potential interventions for treatment-related oral complications and associated pain by analyzing the results of two (2) clinical research protocols relevant to cancer treatment.	1. (FY04) Two (2) IRB approved clinical research protocols addressing cancer treatment-related oral complications and associated pain are open to accrual.	1. Performance results will be reported in February 2008.
2008	1. Evaluate two interventions for reducing pain, fatigue, psychological distress, or other symptoms in patients undergoing treatment for cancer or other illness/chronic disease.	1. (FY06) Potential strategies for reducing symptom burden of patients with a chronic disease/illness identified.	1. Performance results will be reported in February 2009.
Data Source & Validation:	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16848906&query_hl=1&itool=pubmed_docsum Kim, H., Lee, H., Rowan, J., Brahim, J., Dionne, R.A. (2006).Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Molecular Pain 2(1):24. http://www.ninr.nih.gov/ResearchAndFunding/DivisionofIntramuralResearch/IRPublications.htm		
Cross Reference:	HP-2, HP-6, SP-1.1, Outcome		

FULL COST (dollars in millions)	FY06	FY07	FY08
	$1604	$1465	$1443

SRO - 3.1	By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	1. (FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	1. (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.
	1. Identify and implement effective strategies to facilitate drug discovery and	1. (FY03) Estimated 30 compounds are presently or will soon be tested in human	1. (MET) NIH continued a preclinical toxicology program and expanded a

2004	development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	AD clinical trials but additional targets are needed	program for pre-clinical drug discovery and development.
2005	1. Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	1. (FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression	1. (MET) The NIH launched the Alzheimer's Disease Neuroimaging Initiative in late 2004.
2006	1. Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	1. (FY04) The genetics initiative has identified 259 families, too few for researchers to identify the remaining risk factor genes.	1. (MET) Nearly 1000 new late-onset AD families have been identified and recruited to the AD Genetics Initiative.
2007	1. Identify and characterize molecular events that may prove to be targets for treating or preventing Alzheimer's disease through initiatives and projects focused on mechanistic and basic studies.	1. (FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.	1. Performance results will be reported in February 2008.
2008	1. For at least one promising drug candidate for the treatment of AD, complete at least one of the four preclinical steps necessary for regulatory approval: chemical optimization; proof of efficacy in an animal model relevant to the disease; pharmacokinetic profiling; and/or early toxicology screening.	1. (FY06) It is anticipated that 1-3 promising drug candidates will emerge from NIH's research programs by FY 2008; these have not completed the preclinical steps necessary for regulatory approval.	1. Performance results will be reported in February 2009.
Data Source & Validation:	'Genetics Study Makes Headway Toward 1,000 Family Goal.' Article in 'Connections' newsletter, vol. 14 #1-2 (2006), http://www.nia.nih.gov/Alzheimers/ResearchInformation/Newsletter/CurrentIssue.htm		
Cross Reference:	HP-18, SP-4.1, SP-6.2, Outcome		

SRO - 3.2.1	By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. (FY02) First trial of anti-CD52 to promote tolerance.	1. (NOT MET) Anti-CD52 was determined to be unsafe by a non-NIH supported trial of the agent in the target population. Therefore, the opening of the NIH-supported trial was cancelled.
2004	1. Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. (FY03) First trial of anti-CD3 to promote tolerance.	1. (NOT MET) The Phase I trial of the anti-CD3 antibody in patients who had undergone islet cell transplantation was cancelled because the amount of anti-CD3 antibody needed for the trial could not be obtained because the pharmaceutical company that owns the agent decided to use it for other clinical trials.
2005	1. Submit response to FDA addressing safety concerns about anti-CD3 antibody. *Previous Target:* Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	1. First trial of anti-CD3 to promote tolerance.	1. (MET) NIH submitted a response to the FDA addressing safety concerns about anti-CD3 antibody. The FDA removed the clinical hold on April 29, 2005.
	1. Establish uniform cGMP manufacturing	1. CIT established.	1. (MET) Uniform cGMP manufacturing

2006	process for preparation of pancreatic islet cells across CIT centers. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs. *Previous Target*: Analyze data from phase I trial(s); initiate development of efficacy trial(s); if appropriate.		process for preparation of pancreatic islet cells across CIT centers was developed.
2007	1. Develop 2 clinical protocols. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. Clinical protocols under development.	1. Performance results will be reported in February 2008.
2008	1. Initiate enrollment of individuals who have type 1 diabetes and who have severe hypoglycemic episodes and hypoglycemia unawareness into two Phase III clinical trials to evaluate the effectiveness of islet transplantation.	1. (FY07) Clinical trials under development.	1. Performance results will be reported in February 2009.
Data Source & Validation:	The Drug Master File, DMF 13072, was submitted to the FDA on June 6, 2006 International trial of the Edmonton protocol for islet transplantation. Shapiro AM et al. NEJM, 355:1318-30, 2006.		
Cross Reference:	HP-5, SP-4.1, Outcome		

SRO - 3.3	By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	1. (FY02) No integrated technologies to quickly and efficiently measure multiple substances in saliva	1. (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.
2004	1. Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	1. (FY03) Technology available to help identify salivary proteomes	1. (MET) Three research projects implemented to identify and catalog salivary proteomes.
2005	1. Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	1. (FY03) Systems to quantify C-reactive protein in saliva have not yet been developed.	1. (MET) Integrated microfluidic assay systems have been developed to measure C-reactive protein in saliva.
2006	1. Finalize the fabrication of a portable handheld diagnostic device that can detect C-reactive protein and other analytes associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization.	1. (FY04) Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation	1. (MET) A portable handheld diagnostic device has been fabricated.
2007	1. Establish a common proteome database that will include data from 2 subject groups that cover over 80 percent of the salivary proteome.	1. (FY05) Three groups of researchers are currently working to catalog the salivary proteome.	1. Performance results will be reported in February 2008.
2008	1. Complete the design of bioinformatics management systems for storing, searching, and disseminating salivary proteomics data.	1. (FY06) Scientists have begun efforts to design bioinformatics systems to store salivary proteomics data.	1. Performance results will be reported in February 2009.

Data Source & Validation:	Ramachandran et al, 'Identification of N Linked Glycoproteins in Human Saliva by Glycoprotein Capture and Mass Spectrometry', Journal of Proteome Research, 2006, 5(6), 1493-1503. Yang et al, 'Detection of Picomolar levels of interleukin-8 in Human Saliva by SPR', Lab on a Chip, 2005, 5 (10), 1017-1023.
Cross Reference:	SP-4.1, Outcome

SRO - 3.5 By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies.

FY	MEASURES/TARGETS	BASELINE	RESULTS
2006	1. Validate or replicate previously identified chromosome regions in different sample sources by one or more groups to identify genes.	1. (FY04) Regions have been previously mapped on chromosomes 1,4,7, and 15 by one or more independent groups.	1. (MET) Replicated the genetic associations of GABRA2, ADH4, and CHRM2 to alcohol dependence in different sample sources in multiple groups.
2007	1. Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek potential functional differences coming from these haplotypes.	1. (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.	1. Performance results will be reported in February 2008.
2008	1. Identify potential functional differences from fine mapping studies of specific haplotypes.	1. (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.	1. Performance results will be reported in February 2009.

Data Source & Validation:

Three independent studies replicated the initial findings of an association between GABRA2 and alcohol dependence:

Agrawal A, Edenberg HJ, Foroud T, Bierut LJ, Dunne G, Hinrichs AL, Nurnberger JI, Crowe R, Kuperman S, Schuckit MA, Begleiter H, Porjesz B, Dick DM. Association of GABRA2 with Drug Dependence in the Collaborative Study of the Genetics of Alcoholism Sample. Behav Genet. 2006 Sep;36(5):640-50.

Enoch MA, Schwartz L, Albaugh B, Virkkunen M, Goldman D. Dimensional anxiety mediates linkage of GABRA2 haplotypes with alcoholism. Am J Med Genet B Neuropsychiatr Genet. 2006 Sep 5;141(6):599-607.

Lappalainen J, Krupitsky E, Remizov M, Pchelina S, Taraskina A, Zvartau E, Somberg LK, Covault J, Kranzler HR, Krystal JH, Gelernter J. Association between alcoholism and gamma-amino butyric acid alpha2 receptor subtype in a Russian population. Alcohol Clin Exp Res. 2005 Apr;29(4):493-8.

The initial report of an association between CHRM2 and alcohol dependence was replicated by:

Luo X, Kranzler HR, Zuo L, Wang S, Blumberg HP, Gelernter J. CHRM2 gene predisposes to alcohol dependence, drug dependence and affective disorders: results from an extended case-control structured association study. Hum Mol Genet. 2005 Aug 15;14(16):2421-34.

The following studies were instrumental in replicating the initial study demonstrating an association of ADH4 with alcohol dependence:

Edenberg HJ, Xuei X, Chen HJ, Tian H, Wetherill LF, Dick DM, Almasy L, Bierut L, Bucholz KK, Goate A, Hesselbrock V, Kuperman S, Nurnberger J, Porjesz B, Rice J, Schuckit M, Tischfield J, Begleiter H, Foroud T. Association of alcohol dehydrogenase genes with alcohol dependence: a comprehensive analysis. Hum Mol Genet. 2006 May 1;15(9):1539-49.

Luo X, Kranzler HR, Zuo L, Lappalainen J, Yang BZ, Gelernter J. ADH4 gene variation is associated with alcohol dependence and drug dependence in European Americans: results from HWD tests and case-control association studies. Neuropsychopharmacology. 2006 May;31(5):1085-95.

Luo X, Kranzler HR, Zuo L, Yang BZ, Lappalainen J, Gelernter J. ADH4 gene variation is associated with alcohol and drug dependence: results from family controlled and population-structured association studies. Pharmacogenet Genomics. 2005 Nov;15(11):755-68.

Cross Reference:	HP-18, HP-26, SP-4.1, Outcome

SRO - 3.6	By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate stem cell labeling strategy.	1. (FY04) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.	1. (MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.
2006	1. Complete optical imaging probe development.	1. (FY05) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.	1. (MET) Researchers in the NIH intramural program have developed probes that are compatible with optical microscopy techniques developed by intramural scientists.
2007	1. Initiate validation and toxicity studies.	1. (FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.	1. Performance results will be reported in February 2008.
2008	1. Initiate preclinical studies on the nature of stem cell migration in adult tissue.	1. (FY06) Studies of the distribution of exogenously applied stem cells within a living organism are needed.	1. Performance results will be reported in February 2009.

Data Source & Validation:	For the optical imaging technique: Multi-photon excitation microscopy in intact animals. Rothstein EC, Nauman M, Chesnick S, and Balaban RS. Journal of Microscopy, Vol. 221, Pt 2 March 2006, pp. 00–00 For probe: Limited Utility of Acetoxymethyl (AM) Based Intracellular Delivery Systems, in vivo: Interference by Extracellular Esterases. Jobsis PD , Rothstein EC and Balaban RS. In press, Journal of Microscopy.
Cross Reference:	HP-12, SP-4.1, Efficiency, Outcome

FULL COST (dollars in millions)	FY06	FY07	FY08
	$412	$401	$393

SRO - 4.5.1	By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Increase the ability of resource-poor countries to conduct clinical trials for the treatment and prevention of HIV disease by providing training and capacity building at 4 sites.	1. (FY02) 12 AACTG sites and 10 PACTG sites.	1. (MET) Sites in resource-poor countries are better able to conduct HIV clinical trials as a result of training.
2004	1. Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	1. (FY03) 23 approved antiretroviral drugs exist for HIV infection treatment.	1. (MET) NIH has supported studies to develop treatments for three HIV-associated manifestations, hepatitis C virus (HCV), Cryptococcal meningitis (CM) and central nervous system (CNS)-associated neurological disease in individuals with HIV.
2005	1. Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	1. (FY03) Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed	1. (MET) NIH initiated 1 clinical trial of a new anti-HIV drug and 4 trials of anti-HIV drug regimens.
2006	1. Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	1. (FY04) Antiretroviral therapy has dramatically reduced MTCT in the developed world; many developing countries are implementing preventive MTCT programs using nevirapine and other antiretroviral regimens.	1. (MET) NIH completed 1 study of viral resistance in infants, 2 studies to determine antiretroviral dosing levels in pregnant women and 1 perinatal intervention study.
2007	1. Achieve goal of evaluating the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or	1. FY 2003 to FY 2006 results	1. Performance results will be reported in February 2008.

	simpler to use than the current recommended HIV treatment regimens.		
Data Source & Validation:	www.AIDSinfo.nih.gov for information on specific protocols identified and their status. NIAID Planning and Reporting Process, FY 2006: Pediatric HIV and Mother to Child Transmission, HIV Therapeutics Discovery and Development, Anti-HIV and Immune Based Therapy, Women's Health. Pharmacokinetics (PK) and Safety of Tenofovir Disoproxil Fumarate (TDF) in HIV-1 Infected Pregnant Women and their Infants. Rodman J, Flynn P, Shapiro D, Bardeguez A, Huang S, Fiscus S, Koen V, Rooney J, Mofenson L, Jean-Phillippe P, and PACTG 394 Study Team. 13th Conference on Human Retroviruses and Opportunistic Infections, Abstract #708, Denver, CO, February 5-8, 2006, Adequate lopinavir exposure achieved with a higher dose during the third trimester of pregnancy. Mirochnick M, Stek A, Capparelli E, Best B, Holland D, Connor J, Burchett SK, Hu C, Smith E, Read JS, and PACTG 1026s Protocol Team. 13th Conference on Human Retroviruses and Opportunistic Infections, Abstract #710, Denver, CO, February 5-8, 2006. Acquisition and Archiving of Non-Nucleoside Reverse Transcriptase Inhibitor-Resistant Human Immunodeficiency Virus Type 1 Variants during Mother-to-Child Transmission in U.S.-Born Infants. Persaud D, Palumbo P, Ziemniak C, Havens P, Chadwick E, and the PACTG P1030 Team. 13th Conference on Human Retroviruses and Opportunistic Infections, Abstract #617, Denver, CO, February 5-8, 2006. Shapiro RL, Thior I, Gilbert PB, Lockman S, Wester C, Smeaton LM, Stevens L, Heymann SJ, Ndung'u T, Gaseitsiwe S, Novitsky V, Makhema J, Lagakos S, Essex M. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. AIDS. 2006 Jun 12;20(9):1281-8. Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, Gilbert PB, Stevens L, Peter T, Kim S, van Widenfelt E, Moffat C, Ndase P, Arimi P, Kebaabetswe P, Mazonde P, Makhema J, McIntosh K, Novitsky V, Lee TH, Marlink R, Lagakos S, Essex M, and the Mashi Study Team. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. JAMA. 2006 Aug 16;296(7):794-805.		
Cross Reference:	HP-13, SP-4.1, 5,000D-I2, Outcome		

SRO - 4.5.4	By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	1. (FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	1. (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.
2004	1. Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	1. (FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened	1. (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.
2005	1. Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	1. (FY03) Known bioactive compounds require further evaluation of activity and improved availability	1. (MET) Compounds selected based on evaluation of properties; collection assembled for public use.
2006	1. Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	1. (FY04) SMA program established; 3 promising compounds identified in screens; SMA mouse models available	1. (MET) Three promising compounds, trichostatin A and two indoprofen analogs, were tested in SMA mouse models.
	1. Complete goal of identifying 20 small	1. (FY06) Compounds identified in screens	1. Performance results will be reported in

2007	molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	and advanced to various stages of preclinical development	February 2008.

Data Source & Validation:	A paper about trichostatin has been submitted to a peer-reviewed scientific journal and is currently under review: Avila AM, Burnett BG, Taye AA, Knight MA, Hartenstein P, Cizman Z, Di Prospero NA, Fischbeck KH, Sumner CJ: Trichostatin A increases SMN gene expression and survival in spinal muscular atrophy mice. Submitted. The mouse testing results are summarized in the 12th Quarterly report for the SAIC SMA Project contract (period of July 1-September 30, 2006). Contract number N01-NS-3-2356. Contract progress reports are confidential and not publicly available. Identification and preclinical studies of ceftriaxone are described in: Rothstein JD, et al. (2005) Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433: 73-7. ICA-69673 and YPK3089 were developed through the NINDS Anticonvulsant Screening Program. This program is described at http://www.ninds.nih.gov/funding/research/asp/index.htm. Press releases announced the initiation of industry clinical trials: http://ir.icagen.com/phoenix.zhtml?c=178443&p=irol-newsArticle_Print&ID=816316&highlight= http://kron.com/Global/story.asp?S=3785346 Imaging agent IMPY (for amyloid plaques) was developed under NIH grants P30AG010124, R21AG021868, and R01EB00360. Advances are described in the following papers: - Kung MP et al. (2004) Characterization of IMPY as a potential imaging agent for beta-amyloid plaques in double transgenic PSAPP mice. Euro J Nuc Med Molec Imaging 31(8): 1136-45. - Newberg AB et al. (2006) Safety, biodistribution, and dosimetry of 1231-IMPY: a novel amyloid plaque-imaging agent for the diagnosis of Alzheimer's disease. J Nucl Med 47(5): 748-54. Imaging agent Pittsburgh Compound-B (for amyloid plaques) was developed under NIH grants K02AG01039, P50AG05133, R01AG18402, R01AG20226. Advances are described in the following papers: - Mathis CA et al. (2003) Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothizaoles as amyloid imaging agents. J Med Chem 46(13): 2740-54. - Klunk WE et al. (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 55:306-19. For more information about this goal, please contact: Paul A. Scott, Ph.D. Director Office of Science Policy and Planning National Institute of Neurological Disorders and Stroke National Institutes of Health 31 Center Drive, Room 8A03 Bethesda, MD 20892; MSC 2540 Phone: 301-496-9271 scottp@ninds.nih.gov
Cross Reference:	HP-18, HP-26, SP-4.1, Outcome

SRO - 4.5.5	By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	1. (FY03) No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations	1. (MET) Three treatments have been adapted for community-based settings.
2005	1. Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	1. (FY03) Fewer than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings	1. (MET) The Clinical Trials Network has trained 184 providers (94 more than planned) in BSFT, MET, or Seeking Safety, which are being tested in community settings.

2006	1. Recruitment will be completed of approximately 1000 patients from specialized populations to test the efficacy of community-based treatments.	1. (FY04) Enrollment of subjects for Seeking Safety, BSFT, and MET was initiated.	1. (MET) The Clinical Trials Network has enrolled more than 1,200 patients in BSFT, MET, and Seeking Safety interventions which are being tested in community settings. Treatments are being delivered to diverse communities that are 20%, 34%, and 41% African American, respectively, and 43%, 7%, and 14% Hispanic, respectively.
2007	1. Analyze data from completed behavioral protocols and report initial findings from data analysis.	1. (FY05) Providers trained, subjects being recruited for intervention.	1. Performance results will be reported in February 2008.
2008	1. Complete development and testing of two new evidence-based treatment approaches for drug abuse in community settings.	1. To be determined by FY07 results.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Information from the Trial Progress Report, October 24, 2006, prepared by the Data and Statistics Center for NIDA's Clinical Trials Network (Duke Clinical Research Institute, Duke University Medical Center). The data are current as of September 30, 2006. These reports are submitted monthly. Upon completion and issue of scientific publications, released data are available at http://www.drugabuse.gov/CTN/Data.html. The following PR brochures/notices/information were issued: Each protocol, including enrollment status and contact information for the Lead Investigator, is described on our public website found at http://www.nida.nih.gov/CTN/Research.html. Clinical brochures describing the purpose for each study are found as PDF files under the name of each protocol. The relevant protocols are NIDA-CTN-0014, NIDA-CTN-0015 and NIDA-CTN-0004.		
Cross Reference:	HP-26, 1HHS-19, SP-1.4, SP-3.4, Outcome		

FULL COST (dollars in millions)	FY06	FY07	FY08
	$790	$734	$5

SRO - 5.2	By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	1. (FY02) Standard operating procedures are being completed but training not yet done	1. (MET) Training of all appointed sonographers has been completed.
2004	1. Launch patient enrollment in at least 10 of the 20 planned sites.	1. (FY03) Protocol for patient enrollment established	1. (MET) There are currently 16 sites actively recruiting patients into the study.
2005	1. Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	1. (FY03) One ancillary study approved to assess the effect of statins on blood cells	1. (MET) The ancillary studies are underway. One example is a study that explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus in pediatric patients.
2006	1. Complete baseline data analysis on the enrolled patients, including any adverse events.	1. (FY04) 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events	1. (MET) Baseline characteristics of the study population as of August 2006 have been analyzed and the results were shared with the Study Data and Safety Monitoring Board.
2007	1. All clinical sites will be actively enrolling/following pediatric lupus patients, to result in an overall average recruitment rate of 3 new patients per month.	1. (FY06) Number of Clinical Sites: 20	1. Performance results will be reported in February 2008.
2008	1. Implement two strategies to attain study medication compliance rate of at least 80 percent.	1. (FY06) Previous research suggests that compliance among pediatric patients receiving treatment for chronic illness can be as high as 70% due in part to factors such as family support and severity of symptoms	1. Performance results will be reported in February 2009.

Data Source & Validation:	A description of the APPLE study (ClinicalTrials.gov identifier number NCT00065806) is available online at www.clinicaltrials.gov. The analysis of baseline data is described in the September 2006 DSMB report. The DSMB records are part of the official files on N01AR22265, which is maintained by the NIAMS Extramural Research Program. Information about the ancillary investigations is contained in the Grant Progress Report submitted by Duke University as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant AR51307, which is maintained by the NIAMS Extramural Research Program. For more information about the study, please contact: Anita Linde Director, Office of Science Policy and Planning National Institute of Arthritis and Musculoskeletal and Skin Diseases 31 Center Dr, Room 4C13 Bethesda, MD 20892 Phone: 301-496-8271
Cross Reference:	HP-12, HP-16, SP-4.1, 500D-P1, Outcome

SRO - 5.3	By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	1. (FY02) Prior to FY 2003, only two centers existed.	1. (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.
2004	1. Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.	1. (FY03) High throughput methods for making chemical libraries for drug development are limited.	1. (MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.
2005	1. Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	1. (FY03) CMLD centers are currently being established; screening of their libraries has not yet begun.	1. (MET) Support for CMLD centers provides facilities to validate new methodologies used to synthesize chemical libraries. These new methods are being made available to the scientific community.
2006	1. Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	1. (FY03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs.	1. (MET) Supported the development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).
2007	1. Begin development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds.	1. (FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.	1. Performance results will be reported in February 2008.
2008	1. Use chemical libraries in high-throughput biological screens.	1. (FY06) CMLD libraries under development.	1. Performance results will be reported in February 2009.

Data Source & Validation:	New Methodologies for Natural Products Chemistry, RFA Number: RFA-RM-05-013 http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-013.html The Chemical Methodologies and Library Development Centers

	http://www.nigms.nih.gov/Initiatives/CMLD/Centers/ Rediscovering Natural Products http://pubs.acs.org/cen/coverstory/8141/8141pharmaceuticals.html Medicines by Design: Tweaking Nature http://publications.nigms.nih.gov/medbydesign/drugs/tweaking/
Cross Reference:	SP-4.1, Outcome

SRO - 5.6	By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify 1-2 promising compounds as candidate medications for tobacco addiction.	1. (FY05) Current medications inadequate to address tobacco addiction.	1. (MET) Four candidate medications, instead of two, have been identified for tobacco addiction, and research is continuing on these candidates.
2006	1. Begin at least one clinical trial of a candidate medication for tobacco addiction.	1. (FY05) NicVAX shows promise in pre-clinical or early clinical trials.	1. (MET) Three candidate medications are being tested in: Phase II clinical trials, multi-site trials, and human laboratory studies.
2007	1. Develop and test 1-2 potential new compounds for tobacco addiction in animal models.	1. (FY06) Preclinical work on compounds that target nicotinic or GABA receptors is continuing based on preliminary positive results.	1. Performance results will be reported in February 2008.
2008	1. Analyze results from the FY 2006 clinical trial (Phase II) to determine whether an additional clinical trial should be initiated.	1. To be determined by results in FY06 and FY07.	1. Performance results will be reported in February 2009.

Data Source & Validation:	**References related to selegiline, the enzyme inhibitor for MAO:** - Fowler JS, Volkow ND, Wang GJ, Pappas N, Logan J, MacGregor R, Alexoff D, Shea C, Schlyer D, Wolf AP, Warner D, Zezulkova I, Cilento R. Inhibition of monoamine oxidase B in the brains of smokers. Nature 1996;379:733-6. - Berlin I, Said S, Spreux-Varoquaux O, Launay JM, Olivares R, Millet V, Lecrubier Y, Puech AJ. A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin Pharmacol Ther 1995;58:444-52. - George TP, Vessicchio JC, Termine A, Jatlow PI, Kosten TR, O'Malley SS. A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. Biol Psychiatry 2003;53:136-43. - Biberman R, Neumann R, Katzir I, Gerber Y. A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. Addiction 2003;98:1403-7. **Reference related to tiagabine, a GABA agonist for smoking cessation:** Sofuoglu, M, Mouratidis, M, Yoo, S, Culligan, K, and Kosten, T. Effects of tiagabine in combination with intravenous nicotine in overnight abstinent smokers. Psychopharmacology (Berl) 2005; 181(3):504-10. **Validation source for NicVax vaccine:** http://clinicaltrials.gov/ct/show/NCT00318383?order=1
Cross Reference:	HP-26, HP-27, 1HHS-13, SP-1.4, SP-1.5, Outcome

SRO - 5.6.2	By 2011, assess the efficacy of at least three new treatment strategies to reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	1. (FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	1. (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.
2004	1. Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to	1. (FY03) Look AHEAD had recruited about half (2,500) of its patients	1. (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145

	compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.		participants by May 2004.
2005	1. Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	1. (FY03) ACCORD had recruited 1,184 participants in a Vanguard phase	1. (MET) The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005.
2006	1. Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	1. (FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population	1. (MET) Initial findings from Look AHEAD were presented at the annual Society of Behavioral Medicine meeting in March 2006. One-year results from Look AHEAD on reduction in weight and cardiovascular disease (CVD) risk factors in type 2 diabetes were presented at the annual American Diabetes Association meeting in June 2006.
2007	1. Complete at least 90% of the total enrollment for the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial which aims to determine whether reduction of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in atherosclerotic CVD.	1. (FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.	1. Performance results will be reported in February 2008.
2008	1. Review and evaluate collectively, indicators of Look AHEAD's progress to date (measures such as safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends) in order to determine whether the science is progressing appropriately--in accord with the clinical trial's protocol--and whether the trial will be continued.	1. (FY07) Human clinical trials require periodic review and evaluation to assess progress.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Society of Behavioral Medicine meeting: http://www.sbm.org/meeting/2006/final_program.pdf see page 47 American Diabetes Association meeting: http://scientificsessions.diabetes.org/index.cfm?fuseaction=Locator.DisplayAtAGlanceSearch &ShowAll=Yes&CalledByID=1031#06/13/2006 see Tuesday, June 13 → Clinical Diabetes / Therapeutics → Click on Symposium for Late Breaking Clinical Studies (copy into browser if needed)		
Cross Reference:	HP-4, HP-5, HP-12, 1HHS-13, SP-1.1, SP-4.1, Outcome, PART		
SRO - 5.7	By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Convene workshops of relevant experts on PET and MRI scanning to develop consensus standards and quantitative tools for image assessment.	1. (FY05) Workshop planned.	1. (MET) FDG-PET and DCE-MRI workshops have been held. Consensus guidelines are on the Cancer Imaging Program web site: imaging.cancer.gov.
2006	1. Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial.	1. (FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.	1. (EXT) Launch of the public-private partnership responsible for conducting the lung cancer therapy trial was delayed, which led to delays in initiating the study and collecting test-retest repeatability data. Preliminary analysis of the test-retest repeatability data will be conducted in early 2007.
	1. Perform additional analysis of test-retest	1. (FY05) Trial not complete.	1. Performance results will be reported in

2007	repeatability data from 1st year of trial. *Previous Target:* Complete accrual in lung cancer therapy trial and perform final analysis of test-retest reproducibility of functional imaging scans.		February 2008.
2008	1. Correlate patient outcome data from the lung cancer therapy trial with serial functional imaging scan results to determine the efficacy of this imaging technique.	1. (FY06) Performed preliminary analysis of test-retest repeatability data from 1st year of trial.	1. Performance results will be reported in February 2009.
Data Source & Validation:	A press conference was held on October 5, 2006 to announce the Biomarker Consortium, and this FDG-PET lung cancer trial was announced as one of the Biomarker Consortium's first projects (http://www.fnih.org/Biomarkers%20Consortium/Press_Release.shtml).		
Cross Reference:	HP-3, SP-4.1, Outcome		
SRO - 5.8	By 2011, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate at least 3 research projects to improve objective measures of hot flash frequency.	1. (FY04) Currently available monitors are not suitable for multiple day ambulatory studies.	1. (MET) NIH initiated seven research projects.
2006	1. Develop and validate improved devices to measure hot flash frequency.	1. (FY05) Improved devices not yet available.	1. (MET) NIH funded three projects to further validate new sternal skin conductance monitors.
2007	1. Continue validation of at least 2 devices to measure hot flash frequency.	1. (FY06) Prototype device from FY05 target should be available for additional validation testing.	1. Performance results will be reported in February 2008.
2008	1. Initiate 1 clinical study that includes a treatment for hot flashes in which the investigators would use a sternal skin conductance monitor to measure hot flash frequency.	1. (FY06) No clinical studies of hot flashes using user-friendly sternal skin conductance monitors exist.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Grant Numbers of Funded Projects: R43AT004071-01 R43AT004075-01 R43AT004070-01 Abstracts available through CRISP at http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen		
Cross Reference:	SP-4.1, 5,000D-T1, 500D-P1, Outcome		
SRO - 5.9	By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Collect a cumulative total of 5.8 million genotypes from the FUSION study.	1. (FY04) 3 million genotypes collected in the FUSION study.	1. (MET) The FUSION study collected 3.0 million genotypes, making a cumulative total of 6.0 million genotypes collected for this study of genetic variants that predispose to common type 2 diabetes. The cumulative total exceeded the projected target by 200,000 genotypes.
2006	1. Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community.	1. (FY05) No FBPP data publicly available to the scientific community.	1. (EXT) The pooled data with documentation and web utility were made publicly available in September 2006. Public data training is scheduled for March 2007.
2007	1. Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study.	1. (FY06) Scientific infrastructure established and RFP for initial scan released.	1. Performance results will be reported in February 2008.

2008	1. HapMap III: Analyze data from samples from additional populations to assess how well the genome-wide HapMap applies to additional populations, as well as to figure out how to choose HapMap SNPs to make them most useful for additional populations.	1. (FY07) HapMap III not started	1. Performance results will be reported in February 2009.
Data Source & Validation:	The website for the data release/web utility can be viewed at http://www.biostat.wustl.edu/fbpp/FBPP.shtml.		
Cross Reference:	SP-3.4, SP-4.1, Outcome		

FULL COST (dollars in millions)	FY06	FY07	FY08
	$117	$133	$146

SRO - 6.1	By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	1. (FY02) 31,000 human gene sequences; 12,000 unique human eye-expressed genes	1. (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.
2004	1. Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	1. (FY03) No consensus descriptions on AMD phenotypes exist	1. (MET) A consensus was reached on a manual of classification standards for use by fundus photograph and reading centers that will aide in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections.
2005	1. Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	1. (FY04) DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available	1. (MET) Collected samples from over 4,000 well-characterized patients with either AMD or glaucoma. Created the National Eye Disease Genotyping Network (EyeGENE).
2007	1. Conduct studies in animal models to identify potential modifier genes.	1. (FY05) Modifier genes for AMD and glaucoma have not yet been identified.	1. Performance results will be reported in February 2008.
2008	1. Conduct haplotype analysis to identify common risk haplotype for genes associated with primary open-angle glaucoma (POAG) through single-nucleotide polymorphism (SNP) genotyping.	1. (FY06) A dozen genes associated with glaucoma have been mapped and half a dozen genes have been cloned.	1. Performance results will be reported in February 2009.
Data Source & Validation:			
Cross Reference:	HP-28, SP-4.1, SP-6.2, Outcome		

SRO - 6.3	By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	1. (FY02) Intramural databases and commercial software to build ProtoCEBS available	1. (MET) ProtoCEBS launched, tested, and implemented.
2004	1. Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	1. (FY03) CEBS object model to capture molecular expression data (only) designed but not tested	1. (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.
	1. Create and provide public access to a	1. (FY03) CEBS version 1.0 launched in	1. (MET) CEBS versions 1.5 and 1.6 have

2005	global molecular expression and toxicology/pathology database of both chemicals found in the environment and drugs that have an effect on biological systems (CEBS), featuring simple query download capability.	August 2003 contains only microarray data.	been made available to the public. These programs provide simple query download capability of global molecular expression and toxicology/pathology data on a select number of studies of chemicals found in the environment and drugs that have an effect on biological systems.
2006	1. Enhance the CEBS to allow the capture and integration of transcriptomics, proteomics, and toxicologic data for the same compound.	1. (FY04) The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound	1. (MET) CEBS has been enhanced. Version 2.0.7 is the first public repository designed to capture and fully integrate with 'omics data, toxicological, histopathological and other biological measures.
2007	1. Enhance electronic sharing of 'omics and biology endpoint data.	1. (FY06) Initial integration of microarray and toxicologic/histopathologic data achieved	1. Performance results will be reported in February 2008.
2008	1. Complete goal of developing a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	1. (FY07) CEBS currently does not link outcomes of searches to existing literature databases.	1. Performance results will be reported in February 2009.
Data Source & Validation:	The publication by Fostel, J., et al., Chemical effects in biological systems - data dictionary (CEBS-DD). A compendium of terms for the capture and integration of biological study design description, conventional phenotypes and 'omics data. Toxicological Sciences 88(2) 585-601 (2006) is a description of the CEBS study design, toxicology/pathology and other metadata elements. PMID: 16150882 The publication by Xirasagar, S. et al., CEBS Object Model for Toxicology Data, SysTox-OM, Design, Implementation, and Application. Bioinformatics 22(7) 874-82 (2006) is a technical description of the CEBS toxicology/pathology object model. PMID: 16410321 The CEBS website: http://cebs.niehs.nih.gov/ may be consulted to confirm the content and functionality of CEBS as required to meet the FY06 Performance Target.		
Cross Reference:	HP-8, SP-4.1, Outcome		
SRO - 6.4	By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate study of molecular, cellular, and genetic causes in AE.	1. (FY05) Little is known about the factors that predispose asthmatics for exacerbation.	1. (MET) Developed and funded a program consisting of twelve studies which will examine the molecular, cellular, and genetic causes of AE.
2006	1. Initiate study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history.	1. (FY05) Little is known about the role glycosidase activity may play in modification of airway glycans and the promotion of virus-induced AE.	1. (MET) A study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history was initiated in July 2005.
2007	1. Analyze data from studies of molecular, cellular, and genetic causes in AE.	1. (FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.	1. Performance results will be reported in February 2008.
2008	1. Use advanced radiological and molecular imaging techniques to increase understanding of changes in pulmonary physiology associated with asthma exacerbations.	1. (FY06) Limits of imaging methods have made it difficult to understand how AEs affect pulmonary physiology.	1. Performance results will be reported in February 2009.
Data Source & Validation:	http://www.clinicaltrials.gov/ct/show/NCT00201266?order=1		
Cross Reference:	HP-24, SP-4.2, 5,000D-T1, Outcome		

FULL COST (dollars in millions)	FY06	FY07	FY08
	$24	$22	$22

SRO - 7.2	By 2006, integrate nanotechnology-based components into a system capable of detecting specific

	biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	1. (FY02) Lack of relevant collaborations.	1. (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.
2004	1. Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	1. (FY03) No current core laboratory with needed capacity	1. (MET) The national Nanotechnology Characterization Laboratory (NCL) has been established and will enable development of essential data about the profiles of nanoparticles in biological systems.
2005	1. Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	1. (FY03) Existing nanosensors and nanoparticles not integrated into a common platform.	1. (MET) Nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings.
2006	1. Complete goal of integrating nanotechnology-based components into a system capable of detecting specific biomarkers to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	1. (FY05) Nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings.	1. (MET) Nanotechnology-based components have been integrated into systems capable of detecting specific biomarkers (molecular signatures), serving as proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. Goal completed.
Data Source & Validation:	Savka I. Stoeva, Jae-Seung Lee, Jennifer E. Smith, Steven T. Rosen, and Chad A. Mirkin. Multiplexed detection of protein cancer markers with biobarcoded nanoparticle probes. JACS 2006; 128, 8378-8379. Norased Nasongkla, Erik Bey, Jimin Ren, Hua Ai, Chalermchai Khemtong, Jagadeesh Setti Guthi, Shook-Fong Chin, A. Dean Sherry, David A. Boothman, Jinming Gao. Multifunctional polymeric micelles as cancer-targeted, MRI-ultrasensitive drug delivery systems. Nano Lett. 2006; 6(11), 2427 -2430. Chen AM, Santhakumaran LM, Nair SK, Amenta PS, Thomas T, He H, Thomas TJ. Oligodeoxynucleotide nanostructure formation in the presence of polypropyleneimine dendrimers and their uptake in breast cancer cells. Nanotechnology 2006; 17 5449-5460. Rabin O, Manuel Perez J, Grimm J, Wojtkiewicz G, Weissleder R. An X-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. Nat Mater. 2006; 5(2):118-22.		
Cross Reference:	HP-3, SP-4.1, SP-4.2, Efficiency, Outcome		
SRO - 7.8.1	By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Complete the genomic sequences for at least five bacteria and two protozoa that cause infectious disease.	1. (FY02) Genome sequences for 32 bacterial pathogens, 1 protozoan parasite, and 1 insect completed.	1. (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.
2004	1. Complete the genomic sequences of at least five bacterial pathogens, two protozoa, and three fungal pathogens that cause infectious disease.	1. (FY03) Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed	1. (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.
2005	1. Complete the genomic sequences of at least five bacterial pathogens, four protozoa, two fungal pathogens that cause infectious disease.	1. (FY04) Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi and 1 insect completed	1. (MET) Genomic sequencing projects for 30 bacteria, 1 protozoan, 1 insect and 3 fungi were completed.
2006	1. Complete the genome sequence of at least six bacterial pathogens, two protozoan parasites, and one invertebrate vector of infectious diseases.	1. (FY05) Genome sequences for 88 bacterial pathogens, 9 protozoan parasites, 6 fungi, and 2 invertebrate vectors of infectious diseases completed	1. (MET) Genomic sequencing projects of 44 bacteria, 6 protozoa, 1 parasitic worm, 2 fungi, 1 invertebrate vectors of disease and 1 plant were completed in FY 2006. One additional invertebrate

			vector which was completed in FY2005 ahead of schedule also counts toward meeting/exceeding the FY06 target.
2007	1. Complete goal of determining the genome sequences of 45 human pathogens and 3 invertebrate vectors	1. (FY06) Genome sequences for 132 bacterial pathogens, 15 protozoan parasites, 8 fungi, 1 parasitic worm, 1 plant, and 3 invertebrate vectors of infectious diseases completed	1. Performance results will be reported in February 2008.
Data Source & Validation:	Organism followed by Genbank database accession number Aspergillus clavatus NRRL 1 AAKD00000000 761 Aspergillus terreus NIH2624 AAJN01000000 Entamoeba dispans AANV00000000 970 Entamoeba invadens AANW00000000 972 Burkholderia cenocepacia AAKX01000000 Burkholderia dolosa AAKY01000000 Burkholderia mallei FMH shotgun sequencing AAIQ00000000 656 Burkholderia mallei JHU shotgun sequencing AAIR00000000 655 Burkholderia mallei 721280 AANX00000000 971 Burkholderia pseudomallei 1106a AAMA00000000 651 Burkholderia pseudomallei 1106b AAMB00000000 641 Burkholderia pseudomallei 1655 AAHR00000000 657 Burkholderia pseudomallei 406e AAMM00000000 719 Campylobacter concisus 13826 AAQZ00000000 Campylobacter curvus 525.92 AARA00000000 Campylobacter fetus subsp. fetus 82-40 AANR00000000 904 Campylobacter jejuni subsp. jejuni 260.94 AANK00000000 902 Campylobacter jejuni subsp. doylei 269.97 AARB00000000 Campylobacter jejuni subsp. jejuni 81-176 AANY00000000 975 Campylobacter jejuni subsp. jejuni 84-25 AANT00000000 906 Campylobacter jejuni subsp. jejuni CF93-6 AANJ00000000 899 Campylobacter jejuni subsp. jejuni HB93-13 AANQ00000000 901 Coxiella burnetii Dugway 7E9-12 AAQI00000000 1210 Coxiella burnetii RSA 331 AAQO00000000 1259 Escherichia coli 101-1 AAMK00000000 654 Listeria monocytogenes * FSL F2-515 AARI00000000 Listeria monocytogenes * FSL J1-194 AARJ00000000 Listeria monocytogenes * FSL J1-175 AARK00000000 Listeria monocytogenes * FSL J1-208 AARL00000000 Listeria monocytogenes* FSL J2-003 AARM00000000 Listeria monocytogenes * FSL J2-071 AARN00000000 Listeria monocytogenes * FSL J2-064 AARO00000000 Listeria monocytogenes * FSL N1-017 AARP00000000 Listeria monocytogenes * FSL N3-165 AARQ00000000 Listeria monocytogenes * FSL R2-503 AARR00000000 Listeria monocytogenes * F6900 AARU00000000 Listeria monocytogenes * J2818 AARX00000000 Listeria monocytogenes * LO28 AARY00000000 Listeria monocytogenes * Aureli1997 AATL00000000 Listeria monocytogenes J0161 AARW01000000 Listeria monocytogenes 10403S AARZ01000000 Mycobacterium tuberculosis C AAKR01000000 Mycobacterium tuberculosis F11 AAIX01000000 Shigella dysenteriae 1012 AAMJ00000000 653 Pseudomonas aeruginosa PA7 AAQE00000000 1209 Pseudomonas aeruginosa 2192 AAKW01000000 Pseudomonas aeruginosa C3719 AAKV01000000 Plasmodium falciparum Dd2 AASM01000000 Plasmodium falciparum HB3 AANS01000000 Ricinus communis AASG00000000 1564 Rickettsiella grylli AAQJ00000000 1211 Yersinia pestis IP275 AAOS00000000 1019 Toxoplasma gondii type I AAQM00000000 1255		

	Trichomonas vaginalis AAHC010000000 Organism followed by trace archive URL Pediculus humanus (body louse) http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?&cmd=retrieve&val=species_code%3D%27 PEDICULUS%20HUMANUS%27&dopt=fasta&size=1480551&dispmax=5&page=2&prev=%3C%3C Trichinella spiralis http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?&cmd=retrieve&val=species_code%3D%27 TRICHINELLA%20SPIRALIS%27&dopt=fasta&size=4302527&dispmax=5&page=1
Cross Reference:	HP-10, HP-14, HP-24, HP-25, SP-1.2, SP-2.1, SP-4.1, Efficiency, Outcome

SRO - 7.8.3	By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	1. (FY02) At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	1. (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.
2004	1. Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	1. (FY03) RefSeq collection includes sequence data from 2124 species; only a limited database is available	1. (MET) The RefSeq collection is now fully available via the online resource Entrez Gene.
2005	1. Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	1. (FY04) About 40 collaborations in place for obtaining annotated RefSeq records and other functional data	1. (MET) The RefSeq project was expanded through the deployment of a database and web site that both tracks the submission of genome sequencing projects and supports the generation of RefSeq records from those submissions. Collaborations were established at multiple levels to support the expansion and curation of the project.
2006	1. Complete goal of building a publicly accessible RefSeq Collection to serve as the basis for medical, functional, and diversity studies	1. (FY05) Database and website deployed. Collaborations established at multiple levels.	1. (MET) The goal was completed by building a publicly accessible RefSeq Collection to serve as the basis for medical, functional, and diversity studies.

Data Source & Validation:	1. RefSeq: • RefSeq web site announcements: http://www.ncbi.nlm.nih.gov/RefSeq/ • RefSeq FTP site: ftp://ftp.ncbi.nih.gov/refseq/release/ • RefSeq announce email archive: http://www.ncbi.nlm.nih.gov/mailman/pipermail/refseq-announce/ • Written descriptions: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=handbook.chapter.ch18 2. Entrez Gene: • Statistics: http://www.ncbi.nlm.nih.gov/projects/Gene/gentrez_stats.cgi • FTP release: ftp://ftp.ncbi.nih.gov/gene/ • Written descriptions:: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=handbook.chapter.ch19 3. Collaborations: Growth of collaborations is indicated by increased numbers of Genome Resource pages and Genome Sequencing projects • Genome Project DB web site: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj • Status of eukaryotic genome sequencing projects: http://www.ncbi.nlm.nih.gov/genomes/leuks.cgi • Status of prokaryotic genome sequencing projects: http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi • Genomic Biology Overview: http://www.ncbi.nlm.nih.gov/Genomes/ • Conserved CDS collaboration expanded to include the mouse genome: http://www.ncbi.nlm.nih.gov/projects/CCDS/

Cross Reference:	SP-4.1, Efficiency, Outcome		
FULL COST (dollars in millions)	FY06	FY07	FY08
	$50	$63	$0

SRO - 8.2	By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	1. (FY02) Information on the role of thrombospondin-2 in bone generation is incomplete.	1. (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.
2004	1. Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	1. (FY03) Biochemical pathways that mediate cell survival are unknown.	1. (MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.
2005	1. Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	1. (FY03) Information is incomplete on where thrombospondin-2 is produced; mouse model can provide this data.	1. (EXT) The FY05 target was extended to FY 2007. The stromal cells of bone marrow appear to be the key producers of thrombospondin-2. Technical difficulties have delayed construction of the fluorescent reporter mouse.
2006	1. Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor.	1. (FY04) Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown.	1. (MET) Researchers produced a mouse in which only bone-forming cells are deficient in fibronectin and identified integrin alpha v beta 5 as the cell surface molecule that mediates interactions between the cells and connective tissue growth factor.
2007	1. Determine the characteristics of the skeleton in mice deficient in dentin matrix protein 1 (DMP-1), and assess the consequences of DMP-1 deficiency for bone cell function.	1. (FY06) The skeleton of a mouse lacking DMP-1 exhibits complex defects. It is unknown how this is related to bone cell function.	1. Performance results will be reported in February 2008.
2008	1. Determine the properties of bone-forming cells and bones from mice in which fibrillin-2 is absent.	1. (FY06) Although fibrillin proteins have been studied as structural components of the matrix, it has only recently been recognized that they may influence the function of bone cells.	1. Performance results will be reported in February 2009.

Data Source & Validation:

The generation and characterization of the fibronectin-deficient mouse is described in the Grant Progress Report submitted by the University of Missouri, Kansas City, as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant AR51517, which is maintained by the NIAMS Extramural Research Program.

The identification of integrin alpha v beta 5 as the cell surface molecule mediating interaction between osteoblasts and CTGF is described in the Grant Progress Report submitted by the Temple University School of Medicine, as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant AR47432, which is maintained by the NIAMS Extramural Research Program. The work has been submitted for publication in a major peer-reviewed journal.

The discovery of the role of DMP1 in bone mineralization has been published in a leading international journal: Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, Yu X, Rauch F, Davis SI, Zhang S, Rios H, Drezner MK, Quarles LD, Bonewald LF, White KE. 2006. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet. 38:1310-5.

The description of the mechanical properties of bones from biglycan deficient mice has been published in a major peer-reviewed journal: Wallace JM, Rajachar RM, Chen XD, Shi S, Allen MR, Bloomfield SA, Les CM, Robey PG, Young MF, Kohn DH. 2006. The mechanical phenotype of biglycan-deficient mice is bone- and gender-

	specific. Bone 39:106-16.		
Cross Reference:	HP-2, SP-4.1, Outcome		
SRO - 8.4	By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	1. (FY02) Indictors from Pre-COBRE analysis and previous evaluations.	1. (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.
2004	1. Assessment Methodology for IDeA Program (Step 1): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. -Develop a data collection system for BRIN.	1. (FY03) Data collection and management system to evaluate impact of IDeA/COBRE in place. (FY04) Indicators from IDeA/COBRE evaluation design.	1. (MET) The COBRE evaluation design, which includes a confirmed list of target indicators, is complete. Data collection and management system is in place for BRIN.
2005	1. Assessment Methodology for IDeA Program (Step 2): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. -Assess results of COBRE evaluation design study.	1. (FY04) Data collection and management system to evaluate impact of IDeA/BRIN in place. (FY04) COBRE evaluation design completed but not evaluated.	1. (MET) The IDeA/INBRE evaluation design was completed in September 2005 and the final report included a confirmed list of target indicators to measure INBRE impact. The results of the COBRE evaluation design study were assessed.
2006	1. Full-Scale Assessment of the IDeA Program (Step 1): - Initiate the full-scale evaluation for IDeA/COBRE.	1. (FY04) COBRE evaluation design	1. (MET) The full-scale evaluation for IDeA/COBRE was initiated when the contract to conduct the COBRE evaluation was awarded on September 28, 2006.
2007	1. Full-Scale Assessment of the IDeA Program (Step 2): - Initiate the full-scale evaluation for IDeA/INBRE.	1. (FY05) INBRE evaluation design.	1. Performance results will be reported in February 2008.
2008	1. Full-Scale Assessment of the IDeA Program: --Complete the IDeA/COBRE evaluation and analyze preliminary results.	1. (FY06) IDeA/COBRE evaluation initiated.	1. Performance results will be reported in February 2009.
Data Source & Validation:	The contract award number is: 263-MJ-613400. The official file is located in the National Heart, Lung and Blood Institute (NHLBI) contracting office files. The office is located on the 6th floor of the Rockledge Two building. For more information, please contact Debra Hopkins at 301-435-0367.		
Cross Reference:	HP-23, SP-4.3, Outcome		
SRO - 8.5	By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify specific domains to be measured, evaluate existing measures and items, and develop instrument(s) and assessment methods for use in diverse chronic disease patient samples.	1. (FY04) Highly valid, reliable, and broadly usable assessment tools are needed to enhance clinical research on patient-reported chronic disease outcomes.	1. (MET) Preliminary item pools to measure the chosen domains (Pain, Fatigue, Physical Functioning, Emotional Distress, and Social Role Participation) have been created based on exhaustive review of existing measures. Initial instruments and methodologies have been developed.
	1. Initiate administration of instrument(s) to a large demographically diverse patient sample representing a wide range of chronic disease type and severity.	1. (FY05) An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 05 target.	1. (MET) Administration of the PROMIS item pool to a diverse sample representing a wide range of conditions was initiated in July, 2006.

2006			
2007	1. Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and social role participation.	1. (FY06) Preliminary data analyses undertaken.	1. Performance results will be reported in February 2008.
2008	1. Conduct primary data analyses of item responses in pain, fatigue, physical functioning, emotional distress, and social role participation domains obtained from large, diverse samples of the general population and chronic disease patients to calibrate items and refine item banks for the PROMIS instrument.	1. (FY07) More data needed from large, diverse samples of chronic disease patients using the test item pool.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Regular updates on item testing progress are available at: http://www.nihpromis.org/network_activities/NetworkTesting.asp.		
Cross Reference:	SP-4.1, 500D-A8, Outcome		

SRO - 8.6	By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2007	1. Extend NHANES and survey approximately 3,500 people.	1. (FY06) Very little reliable data on the prevalence of visual impairment in the U.S.	1. Performance results will be reported in February 2008.
2008	1. Continue collecting data for the vision component of NHANES to reach a target of surveying approximately 7,000 people in total.	1. (FY07) Approximately 3,500 people surveyed in FY 2007.	1. Performance results will be reported in February 2009.
Data Source & Validation:			
Cross Reference:	HP-28, SP-4.1, SP-4.4, Outcome		

SRO - 8.9.1	By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify at least one biological (gene-environment) interaction that has high probability of contributing to depression.	1. (FY02) Known that stress linked to depression but interaction not known.	1. (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.
2004	1. Determine whether vascular changes related to aging contribute to depression.	1. (FY03) Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression.	1. (MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.
2005	1. Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	1. (FY04) A series of clinical trials are currently underway that match patients' responses to different treatments.	1. (MET) Characteristics that influence the efficacy of pharmacological and behavioral treatment for depression have been identified. The characteristics range from genetic variation to psychosocial factors.
2006	1. Identify at least one effective strategy for treating depression in the elderly in a variety of settings.	1. (FY05) A number of interventions to treat depression in the elderly are currently being developed and tested.	1. (MET) Several new effective strategies for treating depression in the elderly have been identified.
2007	1. Determine the relative efficacy of combined treatment strategies or sequential treatment algorithms in treating chronic depression.	1. (FY05) Studies are underway to test the efficacy of differing treatment combinations or sequences for depressed patients.	1. Performance results will be reported in February 2008.
	1. Identify at least two methodologies for	1. (FY07) New methodologies may be	1. Performance results will be reported in

2008	examining interactions between depression and other comorbid physical disorders.	applied to address interactions of depression with co-morbid physical disorders.	February 2009.
Data Source & Validation:	Bruce ML, Ten Have TR, Reynolds CF III, Katz IR, Schulberg HC, Mulsant BH, Brown GS, McAvay GJ, Pearson JL, Alexopoulos GS. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: A randomized controlled trial. JAMA 2004; 291:1081-1091. Alexopoulos GS, Katz IR, Bruce ML, Heo M, Ten Have T, Raue P, Bogner HR, Schulberg HC, Mulsant BH, Reynolds CF III, PROSPECT Group. Remission in depressed geriatric primary care patients: A report from the PROSPECT study. Am J Psychiatry 2005; 162:718-724. Bogner HR, Cary MS, Bruce ML, Reynolds CF III, Mulsant B, Ten Have T, Alexopoulos GS. The role of medical comorbidity in outcome of major depression in primary care: The PROSPECT study. Am J Geriatr Psychiatry 2005; 13:861-868. Lyness JM, Heo M, Datto CJ, Ten Have TR, Katz IR, Drayer R, Reynolds CF III, Alexopoulos GS, Bruce ML. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Ann Intern Med 2006; 144:496-504. Reynolds CF III, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, Schlernitzauer MA, Whyte EM, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ. Maintenance treatment of major depression in old age. New Engl J Med 2006; 354:1130-1138.		
Cross Reference:	HP-5, HP-12, HP-18, SP-4.1, SP-6.2, Outcome		

SRO - 8.9.2	By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Establish a 5-year program to create about 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	1. (FY02) Piloted programs to build nursing center research capacity focused on health disparities	1. (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.
2004	1. Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	1. (FY03) Acute stroke center exists but is not focused on stroke disparities or in a minority community	1. (MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.
2005	1. Establish the infrastructure for a Stroke Prevention and Intervention Research Program (SPIRP) at a minority institution.	1. (FY03) Minority institution research /training programs exist but not on stroke prevention/intervention	1. (MET) Established research infrastructure and advisory committees, and hired director for SPIRP.
2006	1. Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives.	1. (FY04) Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke	1. (MET) Established the infrastructure for the Alaskan Native Stroke Registry, began enrolling patients.
2007	1. Initiate at least two collaborative, community-based prevention projects at the Stroke Prevention and Intervention Research Program (SPIRP).	1. Cooperative agreement awarded establishing SPIRP infrastructure, but stroke prevention projects have not yet begun	1. Performance results will be reported in February 2008.
2008	1. Establish a database of stroke patients and collect data for the purposes of identifying new stroke risk factors and developing effective stroke prevention strategies.	1. WHC lacks patient data needed to identify stroke risk factors, evaluate stroke prevention programs	1. Performance results will be reported in February 2009.

Data Source & Validation:	The website for the Alaskan Native Stroke Registry can be found at http://alaskastroke.com/. Enrollment information was taken from the most recent grant progress report, which is not publicly available (grant number U01NS048069).
Cross Reference:	HP-7, HP-12, 1HHS-13, 1HHS-19, SP-1.1, SP-3.4, SP-4.1, SP-4.4, 5,000D-T1, Efficiency, Outcome

SRO - 8.9.3	By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Prepare and disseminate the first of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	1. (FY04) First of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.	1. (MET) Enrolled 504 children, and prepared and disseminated the first stage of scans, demographic, medical, cognitive, and behavioral data collected from 430 children, age 4.5 to 18, to the research community.
2006	1. Complete the second of three stages of neuroimaging scans and data collection of approximately 500 children across the United States.	1. (FY05) The first of three stages of scans, demographic, medical, cognitive, and behavioral data were collected from 500 children and disseminated to research community.	1. (MET) A total of 514 children have been enrolled in the study. Ninety-five percent of the children between the ages of 4.5 to 20 years old who completed the first stage of data collection have completed the second stage of neuroimaging scans, demographic, medical, cognitive, and behavioral data collection.
2007	1. Complete preliminary analyses of changes of brain growth in children over time and share findings with research community.	1. (FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.	1. Performance results will be reported in February 2008.
2008	1. Prepare and disseminate all three stages of anatomical neuroimaging scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	1. (FY07) Preliminary analyses of changes of brain growth in children over time completed.	1. Performance results will be reported in February 2009.

Data Source & Validation:	Almli, C.R., Rivkin, M.J., McKinstry, R.C., and Brain Development Cooperative Group. The NIH MRI Study of Normal Brain Development (Objective-2): Newborns, Infants, Toddlers, and Preschoolers. NeuroImage (in press).
Cross Reference:	HP-16, SP-4.1, SP-4.4, 500D-A7, Efficiency, Outcome

FULL COST (dollars in millions)	FY06	FY07	FY08
	$366	$355	$349

SRO - 9.4	By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2006	1. Design and develop clinical protocols and other needed study documents.	1. (FY05) Previous studies have strongly suggested that congenital CMV infection is a leading cause of sensorineural hearing loss in children.	1. (MET) NIH-supported scientisists designed and developed needed clinical protocols and other needed study documents, such as patient brochures for the CMV & Hearing Multicenter Screening (CHIMES) Study.
2007	1. Compile Manual Of Procedures (MOP) and distribute to all hearing screening sites.	1. (FY06) Clinical protocols and other needed study documents are available.	1. Performance results will be reported in February 2008.
2008	1. Initiate patient enrollment at 7 hearing screening sites.	1. (FY07) Manual of Procedures (MOP) delivered to all hearing screening sites.	1. Performance results will be reported in February 2009.

Data Source & Validation:	The logo, study documents, and clinical protocols are included in the appendices of the CHIMES study Semi-Annual Progress Reports for 2006. Press Release entitled 'UAB to Lead National Study of CMV, Hearing Loss in Children' can be seen at

	http://main.uab.edu/show.asp?durki=84831. For more information, please contact Laura Cole at 301-402-2313.
Cross Reference:	HP-28, SP-4.1, 5,000D-A5, Outcome

FULL COST (dollars in millions)	FY06	FY07	FY08
	$3	**$3**	**$3**

COMMUNICATION AND TRANSFER OF RESULTS

CTR - 1	By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	1. (FY02) No regional summit meetings were held prior to 2003	1. (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.
2004	1. Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in FY 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	1. (FY03) No interviews have been conducted for this purpose	1. (MET) Interviews were held with participants from each summit and 150 outreach activities resulted from each of the summits.
2005	1. Continue to extend 'Back to Sleep' campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	1. (FY03) Three participating national organizations	1. (MET) NIH extended the 'Back to Sleep' campaign messages to African American populations through community-based collaborations with eight national organizations in SIDS training and educational activities.
2006	1. Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the Back to Sleep campaign messages.	1. (FY03) There are no known efforts to systematically educate the nursing community on a national level about SIDS risk reduction.	1. (MET) The Nurses Continuing Education Program was presented at eight national and four regional nurses conferences. Approximately 5,250 nurses participated in the training.
2007	1. Extend the continuing education module for nurses in appropriate community-based clinical settings in African American communities in the Mississippi Delta region.	1. (FY05) There are no known efforts to systematically educate nurses on a community level about SIDS risk reduction.	1. Performance results will be reported in February 2008.
2008	1. Achieve goal of reducing the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).	1. (FY06) TBD Baseline disparity between African American and white infants in back sleeping.	1. Performance results will be reported in February 2009.
Data Source & Validation:	Nurse Continuing Education Program on Sudden Infant Death Syndrome Risk Reduction: Final Report August 2006, and updated through November 30, 2006 in discussions with principals. To obtain a copy of the report, please contact John McGrath, Ph. D. at the National Institute of Child Health and Human Development at (301) 496-5133.		
Cross Reference:	HP-11, HP-16, 1HHS-13, 1HHS-19, SP-3.4, 5,000D-T1, 500D-P1, 500D-T3, Efficiency, Outcome		

CTR - 2	By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the campaign, '*Know Stroke. Know the Signs. Act in Time.*'		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Work with partners in five communities with at least 15 percent African American audiences to extend the Know Stroke campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 Know Stroke community education kits and 100,000 Know Stroke brochures (25,000 will be distributed to African American audiences).	1. (FY03) National partnerships developed; no current comprehensive local partnerships	1. (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.
2005	1. Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 Know Stroke community education kits (1,000 will be through African American partners).	1. (FY03) Five Partnerships developed in FY 2004.	1. (MET) Planned outreach programs in 5 U.S. cities. An additional 5,686 Know Stroke community education kits are being distributed (approximately 1,000 through African American partners). Distribution efforts are under budget by $142,000 and 686 kits over the projected target.
2006	1. Complete goal of increasing awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least 5 communities and extending the impact of the campaign, "*Know Stroke. Know the Signs. Act in Time.*"	1. (FY05) Extended outreach program to five additional communities nationwide.	1. (MET) Exceeded goal of increasing awareness among the general public in 5 communities by conducting *Know Stroke* outreach activities in a total of 25 communities. These activities were executed through NIH *Know Stroke in the Community* training sessions in 3 cities, as well as 14 presentations through local GFWC chapters and 8 stroke-related presentations conducted at GFWC regional meetings.
Data Source & Validation:	Validation sources for the reported distribution quantities of materials include: • NINDS Warehouse Inventory, Quarterly Cost Recovery Report • NINDS Warehouse Inventory, Quarterly Know Stroke Materials Report Information about the Know Stroke campaign materials is available online: https://ice.iqsolutions.com/ninds/strokepubs.asp For information about this goal, please contact: Marian Emr, Director, Office of Communications and Public Liaison, NINDS, NIH, at (301)496-5924.		
Cross Reference:	HP-11, HP-12, 1HHS-13, 1HHS-19, SP-1.1, SP-3.4, SP-4.4, 5,000D-T1, 500D-P1, 500D-T3, Output		
CTR - 3	By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	1. (FY03) No known needs assessment studies exist for developing technology TA program.	1. (MET) Developed a 'needs' assessment study for a technical assistance program.
2005	1. (Target 2) Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	1. (FY03) No personnel.	1. (MET) Personnel joined OTT to design and implement the TA program based on the results of the needs assessment study.
	2. (Target 3) Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the	2. (FY03) Limited access to targeted training in developing countries.	2. (MET) OTT identified and targeted appropriate institutions in seven developing countries for participation in either an educational and technical assistance internship program (China,

	bedside.		South Africa, India, and Brazil) or an on-site training seminar (Ghana, Zambia and Korea).
2006	1. (Target 4) Complete goal of through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.	1. (FY05) OTT identified and targeted appropriate institutions in seven developing countries.	1. (MET) OTT efficiently achieved the FY2006 goal of strengthening capacity of developing countries to identify technologies and pursue their development, through education/technical assistance.
Data Source & Validation:	For supporting documentation related to completion of the FY06 target and the goal, including information related to international technology transfer internships, workshops, and on-site training sessions; website materials; and educational materials, please contact: Luis A. Salicrup, Ph.D. Senior Advisor for International Technology Transfer NIH's Office of Technology Transfer 6011 Executive Boulevard, Suite 325 Rockville, MD 20852 Telephone: (301) 496-7057 For additional information related to OTT website materials, please refer to www.ott.nih.gov.		
Cross Reference:	1HHS-02, SP-4.4, 5,000D-I1, Output		
CTR - 4	By 2008, increase the percentage of Small Business Innovation Research (SBIR) program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing Assistance (extended to FY 07) (FY 07) Manufacturing Assistance	1. No current programs.	1. (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs (FY04) CAP 1st Yr. (FY 05) CAP 2nd Yr., Niche 1st Yr. (FY 06) CAP 3rd Yr., Niche 2nd Yr. (FY 07) Niche 3rd Yr., Manufacturing 1st Yr. (FY 08) Manufacturing 2nd Yr.	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. (MET) Initiated trans-NIH CAP with 130 participants.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program (FY 04) None (FY 05) CAP 1st Yr. (FY 06) CAP 1st Yr., CAP 2nd Yr., Niche 1st Yr. (FY 07) CAP 1st Yr., CAP 2nd Yr., CAP 3rd Yr., Niche 2nd Yr., Manufacturing Pilot (FY 08) Niche 3rd Yr., Manufacturing 1st Yr.	3. Pilot programs converted to program implementation.	3. (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.
2005	1. (Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing Assistance	1. No current program.	1. (MET) Completed pilot Niche Assessment Program with 100 participants.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. (MET) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at

			an investment forum.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program.	3. Pilot programs converted to program implementation.	3. (MET) Pilot CAP -- 40% of forum presenters received additional private investments or sales. Cumulative private sector funding/sales received was $37,764,520 with most received by five firms.
2006	1. (Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing Assistance	1. No current program.	1. (EXT) Pilot test for MAP has been extended to FY2007
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs (FY04) CAP 1st Yr. (FY 05) CAP 2nd Yr., Niche 1st Yr. (FY 06) CAP 3rd Yr., Niche 2nd Yr. (FY 07) Niche 3rd Yr., Manufacturing 1st Yr. (FY 08) Manufacturing 2nd Yr.	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. (MET) 122 awardees participated in the second year trans-NIH CAP program and 72 presented their business opportunities at an investment forum. All 150 participants in Niche Assessment Program received their TNA™ reports.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program (FY 04) None (FY 05) CAP 1st Yr. (FY 06) CAP 1st Yr., CAP 2nd Yr., Niche 1st Yr. (FY 07) CAP 1st Yr., CAP 2nd Yr., CAP 3rd Yr., Niche 2nd Yr., Manufacturing Pilot (FY 08) Niche 3rd Yr., Manufacturing 1st Yr.	3. TBD in FY04 CAP pilot conversion to program implementation.	3. (MET) First Year CAP -- 87% of participants showed commercialization progress. Contacts with investors increased 18%, negotiations 68%, and deals 87%. Second Year CAP -- 88% of participants showed commercialization progress.
2007	1. (Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization. (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing Assistance (FY 07) Manufacturing Assistance	1. No current programs.	1. Performance results will be reported in February 2008.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs.	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. Performance results will be reported in February 2008.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program.	3. TBD in FY04 CAP pilot conversion to program implementation.	3. Performance results will be reported in February 2008.
2008	1. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs	1. Piloted assistance programs (i.e., CAP, Niche, etc.)	1. Performance results will be reported in February 2009.
	2. (Target 3) Report critical elements to assess advances of each technical assistance program Pilot programs converted to program implementation.	2. Pilot programs converted to program implementation.	2. Performance results will be reported in February 2009.
	3. (Target 4) Complete goal of increase the percentage of Small Business Innovation Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.	3. Results of pilot programs converted to program implementation	3. Performance results will be reported in February 2009.
Data Source & Validation:	(Targets 2 & 3) Implement effective piloted programs and report critical elements: 1. Contract N01-LM-4-5509 with Larta Institute		

	2. Contract N01-LM-5-5510 with Foresight Science and Technology 3. NIH-CAP 2004-05 First Interval Tracking Report (July 1, 2005 - March 31, 2006) 4. NIH-CAP 2005-06 Baseline Tracking Report (Sept 1, 2005 - June 30, 2006) Contact: Kay Etzler SBIR/STTR Program (301) 435-2713
Cross Reference:	1HHS-18, SP-4.2, SP-4.4, Outcome

CTR - 5	By FY 2013, improve marketing and management of NIH intellectual property assets by building text mining capability.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify and text mine at least four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	1. (FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.	1. (MET) Identified and text mined five relevant data sources: TechTracS, CRISP, PubMed, Science News Wire, and the USPTO's patent database (2001-present).
2006	1. Identify and text mine an additional four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	1. (FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.	1. (MET)Identified and text mined an additional four data sources, comprising RaDUIS, NIH Office of Rare Diseases, USPTO patent applications, and industry leads databases. The target was met efficiently by accomplishing task with minimal cost and expanded scope.
2007	1. Establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually.	1. To be determined by results of FY06 target.	1. Performance results will be reported in February 2008.
2008	1. To further refine the automated computer system by exploring other relevant data sources and developing portfolio synthesis and visualization tools to assist in the identification of prospective licensees and matching of technologies to those potential licensees, and by continuing to beta-test the system to allow for it eventually to be more widely distributed.	1. To be determined by results of FY07 target.	1. Performance results will be reported in February 2009.

Data Source & Validation:	For source validation information, including Synapse information, please contact: Bonny Harbinger, Ph.D., J.D. Deputy Director Office of Technology Transfer National Institutes of Health 6011 Executive Boulevard, Suite 325 Rockville, MD 20852 Telephone: (301) 496-7057
Cross Reference:	SP-4.2, SP-4.4, SP-8.5, Efficiency, Output

FULL COST (dollars in millions)	FY06	FY07	FY08
	$3	**$2**	**$1**

CAPACITY BUILDING AND RESEARCH RESOURCES

CBRR - 1	By 2012, recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	1. The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	1. (MET) Award rate to comparison groups exceeded by 12%
	2. (Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	2. The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	2. (MET) Award rate to comparison groups exceeded by 14%.
2005	1. (Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups.	1. The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data	1. (MET) Award rate to comparison groups exceeded by at least 14%

	(FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	
	2. (Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	2. The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	2. (MET) Award rate to comparison groups exceeded by at least 13%
2006	1. (Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	1. The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	1. (MET) Award rate to comparison groups exceeded by at least 13%

	(FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%		
	2. (Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	2. The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	2. (MET) Award rate to comparison group exceeded by at least 13%
2007	1. (Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	1. The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	1. Performance results will be reported in February 2008.
	2. (Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups.	2. The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined	2. Performance results will be reported in February 2008.

	(FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	
2008	1. (Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12%	1. The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	1. Performance results will be reported in February 2009.
	2. (Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12%	2. The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	2. Performance results will be reported in February 2009.
Data Source & Validation:	"Analyses of career outcomes for predoctoral and postdoctoral NRSA participants, compared to individuals that did not receive NRSA support," using the Doctorate Records File and the NIH Intermediate Trainee and Fellow and Combined Grant Applicant Files. Conducted under PO # 467-FZ-700074. Contact: Jennifer Sutton Research Training Coordinator Office of Extramural Programs (301) 435-2686		

Cross Reference:	HP-23, 1HHS-02, SP-4.3, Output, PART		
CBRR - 2	Promote data sharing and provide information in real time by implementing and monitoring the NIH Business System. (By FY 2010, the NBS will be in an ongoing status.)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	1. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	1. (MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.
	2. (Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	2. (FY03) NBS without service and supply fund activities module	2. (MET) Identified solutions for automated amortization for Real Property and Agency Agreements.
2005	1. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07) *Previous Target:* Deploy the property module.	1. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	1. (EXT) The program steps a-g 'Integration' is being re-planned. Extended to 2006.
	2. (Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	2. (FY03) NBS without service and supply fund activities module	2. (EXT) The program steps a-g 'Integration' deployment for service and supply fund modules are being extended to 2008.
2006	1. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	1. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	1. (MET) Completed CRPs 2 and 3, user acceptance testing (UAT) and production of training materials is underway. The program steps a-g 'Integration' has been completed.
	2. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	2. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	2. (EXT) The program steps h-I 'Final review' is being extended to 2007.
	3. (Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	3. (FY03) NBS without service and supply fund activities module	3. (EXT) The program steps h-I 'Final review' is being extended to FY 2009.

	4. (Target 3) Report critical elements of General Ledger and Travel Module performance.	4. (FY04) NBS performance with General Ledger and Travel Modules deployed	4. (MET) Performance metric mapping directly to the HHS strategic goals and objectives were reported against FY2004 baseline.
2007	1. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	1. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	1. Performance results will be reported in February 2008.
	2. (Target 3) Report critical elements of General Ledger and Travel Module performance.	2. (FY04) NBS performance with General Ledger and Travel Modules deployed	2. Performance results will be reported in February 2008.
	3. (Target 4) NBS roll-out and post deployment support.	3. (FY05) NBS without contracts/acquisition/accounts payable and receivable /supply modules	3. Performance results will be reported in February 2008.
	4. (Target 5) Commencement of NBS/UFMS migration activities.	4. (FY06) NBS without the UFMS migration	4. Performance results will be reported in February 2008.
2008	1. (Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	1. (FY03) NBS without service and supply fund activities module	1. Performance results will be reported in February 2009.
	2. (Target 3) Report critical elements of General Ledger and Travel Module performance.	2. (FY04) NBS performance with General Ledger and Travel Modules deployed	2. Performance results will be reported in February 2009.
	3. (Target 5) Commencement of NBS/UFMS migration activities.	3. (FY06) NBS without the UFMS migration	3. Performance results will be reported in February 2009.
	4. (Target 6) Continue to provide NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules.	4. (FY06) No NBS post deployment support currently exist	4. Performance results will be reported in February 2009.
Data Source & Validation:	All project performance metrics and associated communications are stored in the NBS project database. Contact: Eric Cole NBS Program Management Office (301) 451-0052		
Cross Reference:	PMA-3, 1HHS-06, SP-8.4, SP-8.5, Output		
CBRR - 3	By 2007, streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Implement a core hospital system.	1. (FY03) 28 year old legacy system	1. (MET) The core hospital system, CRIS, went live and the legacy system was retired.
2005	1. Implement a surgery and anesthesia management system.	1. (FY03) No current system exists	1. (MET) Surgery and anesthesia management system implemented; project is on task and within budget.
	2. Implement a clinical data warehouse.	2. (FY03) No trans-NIH clinical data warehouse currently exists	2. (MET) Implemented a clinical data warehouse; project is on task and within budget.
2006	1. Integrate clinical systems across the NIH Clinical Center.	1. (FY04) Multiple clinical systems exist, but information is not retrievable in a central system.	1. (MET) CRIS has interfaced clinical systems across NIH Clinical Center and has gone from 3 integrated systems in 2000 to 19 integrated systems.
	1. Complete goal of streamlining business processes and automation of data	1. FY06 results	1. Performance results will be reported in February 2008.

2007	movement by implementing , monitoring and updating the clinical research information system (CRIS).		
Data Source & Validation:	The CRIS OMB 300 filing: http://prosight.hhs.gov/prosight/Portfolios/View.htm?window=form&itemID=1405&formID=1055&tabID=1215 Contact: Elaine Ayres Assistant Director for Ethics and Technology Clinical Center (301) 594-3019		
Cross Reference:	PMA-4, PMA-3, 1HHS-07, 1HHS-08, SP-5.1, SP-5.2, SP-5.5, SP-8.5, 500D-A7, Output		
CBRR - 4	By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic Research Administration (eRA) system.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. (Target 1) Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership[1].	1. (FY99) No institutions using electronic reporting	1. (MET) Electronic reporting available to the 65 FDP participating institutions.
	2. (Target 2) Begin pilot-testing of progress reporting for multi-project mechanisms.	2. (FY99) 14 simple competing grant applications received	2. (EXT) XML development needed. Extended to 2007.
2004	1. (Target 3) Expand availability of electronic progress reporting to all grantee institutions	1. (FY02) 145 FDP institutions given access to electronic reporting.	1. (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.
	2. (Target 4) Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	2. FY03) Need for system to conform with OMB/Federal Enterprise Architecture	2. (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.
	3. (Target 5) Develop plan to integrate OPDIV's	3. No plans in place for OPDIV Integration.	3. (MET) eRA has developed plans for adding the FDA and components of the CDC.
2005	1. (Target 6) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. Goals: FY05 - 50% of eligible HHS OPDIV's FY06 - 100% of eligible HHS OPDIV's	1. Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's AHRQ and CDC/NIOSH	1. (MET) The Target was exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) are using eRA to process new grants.
	2. (Target 7) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing FY07 - 55% electronic business processing FY08 - 80% electronic business processing	2. 10% of business processes being done electronically	2. (MET) Approximately, 33% of business processes & financial status reports are done electronically.
	3. (Target 8) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 - 50% code conversion FY06 - 75% code conversion FY07 - 100% code conversion	3. (FY03) Migration plan developed. Current architecture is client-server mix with web	3. (MET) 60%of the code has been converted. This efficiency was accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.
2006	1. (Target 6) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. Goals:	1. Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIVs, AHRQ and CDC/ NIOSH	1. (MET) 100% of the eligible HHS OPDIVs (AHRQ, CDC, FDA, and SAMHSA) are using eRA for administration of research grants.

[1] Target was carried over from previous eRA goal and was met for FY 2003.

	FY05 - 50% of eligible HHS OPDIV's FY06 - 100% of eligible HHS OPDIV's		
	2. (Target 7) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing FY07 - 55% electronic business processing FY08 - 80% electronic business processing	2. 10% of business processes being done electronically	2. (MET) Approximately 40% of the transactions in the business processes are now being done electronically.
	3. (Target 8) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 - 50% code conversion FY06 - 75% code conversion FY07 - 100% code conversion	3. (FY03) Migration plan developed. Current architecture is client-server mix with web	3. (MET) The target was met and exceeded. 100% of the code was converted before the end of FY06, and all of the Web-based applications were deployed by the end of FY06
2007	1. (Target 7) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing FY07 - 55% electronic business processing FY08 - 80% electronic business processing	1. 10% of business processes being done electronically	1. Performance results will be reported in February 2008.
2008	1. (Target 7) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing FY07 - 55% electronic business processing FY08 - 80% electronic business processing	1. 10% of business processes being done electronically	1. Performance results will be reported in February 2009.
Data Source & Validation:	Operational reports generated by the eRA system will show the number of applications accepted and the number of grants awarded by NIH and the other OPDIVs for FY06. Progress for this target is documented in the Clear Quest change requests, project plans, deployment announcements and bi-weekly status reports. System queries and reports provide the data to determine the percentage of electronic transactions in the system. Deployment records and communications to eRA users will verify the deployment of the web-based applications, and minutes of status meeting will verify the completion of the code conversion. Contact: Thomas Boyce Interim eRA Program Manager Office of Extramural Research and Reports Management (301)-594-4490		
Cross Reference:	PMA-4, 1HHS-08, 1HHS-18, SP-8.5, Efficiency, Output		
CBRR - 5	By 2007, expand by 15,000 the pool of researchers and clinicians NIH has trained in biomedical informatics, bioinformatics, or computational biology.		

FY	MEASURES/TARGETS	BASELINE	RESULTS
2005	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY05) 8,716 people received short-term training in informatics or computational biology.	1. (MET) NIH provided short-term training for 8,716 people in informatics or computational biology.
	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY05) 365 trainees enrolled in pre- or post-doctoral training in informatics or computational biology.	2. (MET) NIH enrolled 365 people in pre or post-doctoral training in informatics or computational biology.
2006	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY05) 8,716 people received short-term training in informatics or computational biology.	1. (MET) NIH provided short-term training for 8,028 people in informatics or computational biology.
	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY05) 365 trainees enrolled in pre- or post-doctoral training in informatics or computational biology.	2. (MET) NIH enrolled 358 people in pre or post-doctoral training in informatics or computational biology.
2007	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY06) Determined by FY06 results	1. Performance results will be reported in February 2008.
	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY06) Determined by FY06 results	2. Performance results will be reported in February 2008.
Data Source & Validation:	(Target 1) Data come from the attendance statistics at each course, or from the program coordinator who arranges for short rotations. Each IC compiles and tracks these activity statistics separately, as these activities are not grant projects and, hence, are not available via IMPAC. Contact: Valerie Florance, Deputy Director for Extramural Programs at the National Library of Medicine. (Target 2) Trainee appointment forms and fellowship notices of grant awards, IMPAC records for NRSA awards, plus report from program coordinator for visiting faculty program. Contact: Valerie Florance, Deputy Director for Extramural Programs at the National Library of Medicine.		
Cross Reference:	HP-23, 1HHS-02, SP-4.3, Output		
CBRR - 6	By 2010, build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2006	1. (Target 1) Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research. (FY06) 44 to be completed (FY07) 48 to be completed (FY08) 30 to be completed (FY09) 22 to be completed (FY10) 9 to be completed	1. Number of projects proposed to be completed annually: (FY06) 0 (FY07) 44 (FY08) 92 (FY09) 122 (FY10) 144	1. (MET) 43 of the 44 construction grants were completed either early or on time. One site was unable to begin construction due to unforeseen circumstances, and NIH is seeking a legal opinion regarding final disposition of the funds.
2007	1. (Target 1) Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research. (FY06) 44 to be completed	1. Number of projects proposed to be completed annually: (FY06) 0 (FY07) 44 (FY08) 92 (FY09) 122	1. Performance results will be reported in February 2008.

	(FY07) 48 to be completed (FY08) 30 to be completed (FY09) 22 to be completed (FY10) 9 to be completed	(FY10) 144	
	2. (Target 2) Completion of 15 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. (FY07) complete 2 facilities (FY08) complete 4 facilities (FY09) complete 8 facilities (FY10) complete 1 facility	2. Number of biocontainment facilities proposed to be completed annually: (FY06) 0 (FY07) 2 (FY08) 6 (FY09) 14 (FY10) 15	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research. (FY06) 44 to be completed (FY07) 48 to be completed (FY08) 30 to be completed (FY09) 22 to be completed (FY10) 9 to be completed	1. Number of projects proposed to be completed annually: (FY06) 0 (FY07) 44 (FY08) 92 (FY09) 122 (FY10) 144	1. Performance results will be reported in February 2009.
	2. (Target 2) Completion of 15 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. (FY07) complete 2 facilities (FY08) complete 4 facilities (FY09) complete 8 facilities (FY10) complete 1 facility	2. Number of biocontainment facilities proposed to be completed annually: (FY06) 0 (FY07) 2 (FY08) 6 (FY09) 14 (FY10) 15	2. Performance results will be reported in February 2009.
Data Source & Validation:	The completion dates are located in the NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864. Information regarding a specific grant may be found using the NIH CRISP database.		
Cross Reference:	1HHS-12, Output, PART		

CBRR - 7	By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Initiate redesign of ARIS by hiring a contractor.	1. Existing ARIS, a 15-year-old mainframe system used to track and monitor AIDS research expenditures.	1. (MET) Contractor was hired to initiate the redesign and reformatting from a mainframe to a web-based system with improved data entry and reporting capability to more efficiently accommodate evolving scientific priorities and needs for information.
2005	1. Improve existing ARIS by converting its mainframe system into a web-based system designed by OAR and IC representatives in consultation with a contractor.	1. Mainframe system allows coding of each project according to functional categories and the 7 original scientific categories of the NIH AIDS strategic plan. Periodic monitoring of the portfolio utilizing ARIS system with limited capability to allow comprehensive trans-NIH portfolio assessment. Strategic planning process determined that AIDS vaccine research is highest scientific priority.	1. (MET) Assessed existing coding system to determine necessary changes to collect program and budget data to meet reporting needs; established the ARIS Working Group, including OAR and key IC staff, to better coordinate development and implementation of converted system.
2006	1. Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research.	1. (FY06) 723 expiring grants eligible for renewal/recompetition	1. (MET) 100% of the 723 expiring grants eligible for renewal or recompetition were reviewed.
	1. Track, monitor, and budget for trans-	1. (FY07) 100% of expiring grants eligible	1. Performance results will be reported in

2007	NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research.	for renewal/recompetition will be reviewed (number of grants expiring will be determined annually).	February 2008.
2008	1. Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research.	1. (FY08) 100% of expiring grants eligible for renewal/recompetition will be reviewed (number of grants expiring will be determined annually).	1. Performance results will be reported in February 2009.
Data Source & Validation:	http://www.oar.nih.gov/about/oarac/oaracmin_10_05.html#DirectorsReport		
Cross Reference:	1HHS-08, Output, PART		
CBRR - 8	By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2008	1. By 2012, ensure that 100% of trainee appointment forms are processed electronically. (FY08) 5% (FY09) 25% (FY10) 50% (FY11) 75% (FY12) 100%	1. (FY07) 0% processed electronically	1. Performance results will be reported in February 2009.
Data Source & Validation:			
Cross Reference:	1HHS-08, Output, PART		
CBRR - 9	By 2010, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2006	1. Achieve average annual cost of managing construction grants	1. Proposed annual costs: (FY06) $35,643 per grant (FY07) $35,837 per grant (FY08) $36,419 per grant (FY09) $36,530 per grant (FY10) $36,703 per grant	1. (MET) Achieved average annual cost of $35,643 per grant.
2007	1. Achieve average annual cost of managing construction grants	1. Proposed annual costs: (FY06) $35,643 per grant (FY07) $35,837 per grant (FY08) $36,419 per grant (FY09) $36,530 per grant (FY10) $36,703 per grant	1. Performance results will be reported in February 2008.
2008	1. Achieve average annual cost of managing construction grants	1. Proposed annual costs: (FY06) $35,643 per grant (FY07) $35,837 per grant (FY08) $36,419 per grant (FY09) $36,530 per grant (FY10) $36,703 per grant	1. Performance results will be reported in February 2009.

Data Source & Validation:	Data used to calculate cost savings are maintained in internal databases. For more information, please contact Karin Lohman, Ph.D. at (301) 496-6752.
Cross Reference:	1HHS-08, Output, PART

FULL COST (dollars in millions)	FY06	FY07	FY08
	$1636	**$1669**	**$1655**

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

SMHC - 3	Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the agency's programmatic objectives and projected future needs. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	1. (FY01) NIH Workforce plan, June 2001	1. (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.
	2. (Target 2) Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.	2. (FY02) Administrative Restructuring Advisory Committee	2. (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.
2005	1. (Target 1) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	1. Practices related to recruitment, retention and succession planning	1. (MET) Methods were implemented that addressed recruitment, retention and succession planning for key IRP positions.
	2. (Target 2) Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	2. Practices related to recruitment, retention and succession planning	2. (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.
2006	1. (Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.	1. (FY 05) Performance indicators that addresses recruitment, retention and succession planning established	1. (MET) Recommendations developed for improving the effectiveness of recruitment, retention and succession planning for key ERP positions.
	2. (Target 2) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)	2. (FY 05) Performance indicators that addresses recruitment, retention and succession planning established	2. (MET) Implemented leadership training for tenure-track and senior investigators and assessed the impact of utilizing adopted methods through surveys.
2007	1. (Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.)	1. (FY 04) Performance indicators to be determined from FY 2006 results	1. Performance results will be reported in February 2008.
	2. (Target 2) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program.	2. (FY 04) Performance indicators to be determined from FY 2006 results	2. Performance results will be reported in February 2008.
	3. (Target 3) Establish performance indicators with baselines related to recruitment, development and succession planning for the NIH Extramural Research Program.	3. Performance indicators to be determined from FY 2006 results	3. Performance results will be reported in February 2008.
2008	1. (Target 1) Evaluate and modify performance indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	1. Performance indicators to be determined from FY 2007 results	1. Performance results will be reported in February 2009.
	2. (Target 2) Continue performance and report on performance indicators related	2. Performance indicators to be determined from FY 2007 results	2. Performance results will be reported in February 2009.

	to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.		
	3. (Target 3) Assess the impact of utilizing newly adopted methods and processes for recruitment, development and succession planning for key scientific positions within the NIH Extramural Research Program. Report on performance indicators.	3. Performance indicators to be determined from FY 2007 results	3. Performance results will be reported in February 2009.
Data Source & Validation:	OIR Website, OIR Mentoring and Training Guide Contact: Dan Dupuis, Acting Deputy Director Office of Strategic Management Planning (301)-402-0622		
Cross Reference:	PMA-1, HP-23, 1HHS-02, SP-8.2, Output		
SMHC - 4	Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the agency's commercial inventory. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.
2004	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Nine streamlined and two standard studies conducted in FY 2004.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. (MET) Career transition services provided for out-placed staff as a result of competitive assessments/studies.
2005	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Thirteen streamlined and one standard studies conducted in FY 2005.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. (MET) Career transition services were provided to employees displaced.
	4. (Target 4) Evaluate transition services provided to employees.	4. (FY03) Career transition services provided to employees impacted by one of the FY 2003 studies	4. (MET) Evaluation conducted during FY 2005.
2006	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Identified 4 potential functional areas for review, all 4 were deemed appropriate for streamlined reviews.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET)Four functional areas identified for reviews were announced for competition.
	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2008.

2007			
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2009.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. Performance results will be reported in February 2009.
Data Source & Validation:	President's Management Agenda scorecards for NIH and HHS: • "NIH Scorecard Q4 2006.doc" • "HHS FY06-Q4 Final Scorecard 10-18-06.cs.doc" Contact: Name: Michael Tulenko Title: Director, Office of Competitve Sourcing Office:HHS/OS/ASAM Phone: 202-690-5803 Federal Business Operations announcements of the four FY 2006 competitive sourcing reviews: http://www2.fbo.gov/spg/HHS/NIH/OoA/Reference%2DNumber%2DN06LM04/listing.html http://www2.fbo.gov/spg/HHS/NIH/OoA/Reference%2DNumber%2DN06LM01/listing.html http://www2.fbo.gov/spg/HHS/NIH/OoA/Reference%2DNumber%2DN06LM02/listing.html http://www2.fbo.gov/spg/HHS/NIH/OoA/Reference%2DNumber%2DN06LM03/listing.html		
Cross Reference:	PMA-2, PMA-3, 1HHS-04, SP-8.3, SP-8.4, Efficiency, Output		

SMHC - 5	Improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	1. (FY04) Multiple means of access to HR systems; multiple websites for HR information and resources.	1. (MET) Developed HR Community on the NIH Portal as primary site for accessing HR information and resources
	2. (Target 2) Identify HR critical elements and tools to monitor use and quality of the HR information.	2. Inconsistent quality and currency of HR information.	2. (MET) Worked with CIT to evaluate products for measuring usage of HR information on HR Community Portal.
2006	1. (Target 3) Establish baselines for the HR critical elements to monitor over time.	1. (FY05) HR critical elements and tools identified.	1. (MET) The critical elements to be monitored are: freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools.
	2. (Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information.	2. (FY05) HR Community established.	2. (MET) A Corrective Strategies Plan was developed to address improved usability and quality of HR information.
2007	1. (Target 5) Implement corrective strategies with subject matter experts and customers.	1. (FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.	1. Performance results will be reported in February 2008.
2008	1. (Target 6) Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline.	1. Quality management plan established.	1. Performance results will be reported in February 2009.
Data Source & Validation:	NIH network users can access statistics on the NIH Portal by logging into the portal at http://my.nih.gov. Navigate to the 'Portal Info Center', to view statistics on the Top Portal Communities and Top Portal Searches of which the HR Community Portal is part. • URL for NIH Portal Top Communities https://my.nih.gov/portal/server.pt?space=CommunityPage&cached=true&parentname=CommunityPage&parentid=2&in_hi_userid=1321966&control=SetCommunity&CommunityID=247&PageID=502# • URL for Top Portal Searches		

	https://my.nih.gov/portal/server.pt?space=CommunityPage&cached=true&parentname=CommunityPage&parentid=2&in_hi_userid=1321966&control=SetCommunity&CommunityID=247&PageID=504# An article on the HR Portal at the NIH was published in the IPMA-HR News in September 2006 - http://www.ipma-hr.org/files/IPMANews09-06.pdf
Cross Reference:	PMA-4, SP-8.5, Efficiency, Output

FULL COST (dollars in millions)	FY06	FY07	FY08
	$10	**$5**	**$5**

PROGRAM OVERSIGHT AND IMPROVEMENT

POI - 1	By 2007, ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an earned value analysis and management system (EVAMS).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Evaluate and assess existing project management systems and implement into a proof-of-concept version of the NIHs Earned Value Management System (EVAMS).	1. (FY03) Policies and procedures in place to identify data needed for evaluation	1. (MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts.
2005	1. Implement a revised project management system that incorporates earned value analysis and management.	1. (FY03) EVAMS proof-of-concept version	1. (MET) Project Management System was modified to reflect management and contracting procedures suitable for the project acquisition method used.
2006	1. Fully launch the Earned Value Management System (EVMS) and conduct Earned-Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio.	1. (FY05) Earned Value Management System (EVMS) is incorporated into the project management system	1. (MET) EVAMS has been fully launched and was used to evaluate on time, on scope and on budget delivery of NIH major capital projects.
2007	1. Complete goal of ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an Earned Value Analysis and Management System (EVAMS).	1. FY06 results	1. Performance results will be reported in February 2008.
Data Source & Validation:	Office of Research Facilities Development and Operations Division of Capital Project Management Director's Briefing on Capital Projects Contact: Clarence Dukes Program Manager, Federal Programs Office of Reserach Facilities, Division of Policy and Program Assessment Building 13, Room 201 (301) 496-5078		
Cross Reference:	PMA-5, 1HHS-12, SP-8.5, Output, PART		

POI - 2	Utilize performance-based contracting (PBC). (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	1. (FY02) $207 million projected for contracted work with requirements tied to performance	1. (MET) Obligated $557 million of eligible service contracting dollars through performance-based contracting.
2004	1. Obligate 40% of eligible service contracting dollars through PBC.	1. Obligate 40% of eligible service contracting dollars through performance-based contracting	1. (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.
2005	1. Obligate 40% of eligible service contracting dollars through PBC.	1. Obligate 40% of eligible service contracting dollars through performance-based contracting	1. (MET) Obligated 44% of eligible service contracting dollars through performance-based contracting.
2006	1. Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	1. FY 2006 OMB/OFPP Goal	1. (MET) Obligated 55% of the total eligible service contracting dollars through performance-based contracting.
2007	1. Obligate the FY 2007 OMB/OFPP goal of eligible service contracting dollars to PBC.	1. FY 2007 OMB/OFPP Goal	1. Performance results will be reported in February 2008.
2008	1. Obligate the FY 2008 OMB/OFPP goal of eligible service contracting dollars to PBC.	1. FY 2008 OMB/OFPP Goal	1. Performance results will be reported in February 2009.

Data Source & Validation:	Obligations to PBC eligible service contracts as reported in DCIS. These obligations are reported throughout the fiscal year as monies were committed to various contracts throughout NIH. Contact: Ms. Sherley Mizzell Director, Division of Acquisition Policy and Evaluation, OAMP/OA/OM/OD 301-496-6014
Cross Reference:	PMA-5, PMA-1, 1HHS-02, SP-8.4, Output

POI - 5	By FY 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI. (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	1. In FY 2004, all research grants had only one Principal Investigator	1. (MET) Addressed signature and regulatory issues, and develop plans for application forms and data systems associated with multiple PIs.
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) Mock Pilot 424-R&R forms using 'dead data' to assess utilization of common data sets. (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements. (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.	2. Paper grant applications currently received	2. (MET) A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use.
	3. (Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) ' Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) ' Expand NIHMS system	3. (FY 04) No mechanism exists to receive manuscripts	3. (MET) NIH developed and launched the NIHMS system was May 2, 2005.

	capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.		
2006	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI. (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	1. In FY 2004, all research grants had only one Principal Investigator	1. (MET) The data structure of the system was modified to maintain data for multiple Principal Investigators (PIs) for a single application and grant in the spring of 2006. Both paper and electronic applications involving multiple PIs were received and processed by NIH.
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) Mock Pilot 424-R&R forms using 'dead data' to assess utilization of common data sets. (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements. (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.	2. Paper grant applications currently received.	2. (MET) NIH required electronic submission of applications through Grants.gov on the new form set for 19 research programs. Over 13,000 applications were accepted and processed electronically in FY06.
	3. (Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) ' Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) ' Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	3. (FY 04) No mechanism exists to receive manuscripts	3. (MET) Receiving third party manuscript uploads met 12/05; Linking submissions met 2/06.
2007	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for	1. In FY 2004, all research grants had only one Principal Investigator.	1. Performance results will be reported in February 2008.

	application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI. (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.		
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) Mock Pilot 424-R&R forms using 'dead data' to assess utilization of common data sets. (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements. (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.	2. Paper grant applications currently received.	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI. (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	1. In FY 2004, all research grants had only one Principal Investigator.	1. Performance results will be reported in February 2009.
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) Mock Pilot 424-R&R forms using 'dead data' to assess utilization of common data sets. (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data	2. Paper grant applications currently received.	2. Performance results will be reported in February 2009.

	elements. (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.		
	3. (Target 4) Better balance workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications (FY 2008 accomplished) (FY08) – Implement changes to standing application receipt dates	3. (FY07) Peak receipt dates involving up to 8,000 applications.	3. Performance results will be reported in February 2009.
Data Source & Validation:	Announcements of NIH plans, policies, and solicitations involving multiple-PIs are posted on the NIH Guide for grants and Contracts. See: http://grants.nih.gov/grants/guide/notice-files/ (NOT-OD-06-074), http://grants.nih.gov/grants/guide/notice-files/ (NOT-OD-06-069), http://grants.nih.gov/grants/guide/notice-files/ (NOT-OD-06-036). Progress for this target is documented on NIH's Electronic Submission website at http://era.nih.gov/ElectronicReceipt/ and in daily eSubmisison reports generated by the eRA system. Progress can also be tracked through Grants.gov Agency submission reports. Bulk Submission http://www.nihms.nih.gov/publishers.html#q2 http://www.nihms.nih.gov/faq.html#q15 Linkage See "time savings links" at http://publicaccess.nih.gov/overview.htm#benefits		
Cross Reference:	1HHS-07, SP-8.5, Output		

POI - 6	Provide responsible stewardship over existing federally owned real property assets.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY04) CIwa = 85	1. (MET) The condition of the portfolio was maintained so that the average CI was 85.
	2. (Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)	2. (FY04) 86.0%	2. (MET) 86% of occupied GSF had a CI greater than 65.
2005	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY05) 54.0%	1. (MET) The condition of the portfolio improved so that the average CI for 2005 was 87 which met and exceeded the 2005 target of 85.
	2. (Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65	2. (FY05) 87.0%	2. (MET) 87% of the occupied space had a CI greater than 65.

	FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)		
2006	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY05) 54.0%	1. (MET) The condition of the portfolio was maintained so that at least the average CI was 85.
	2. (Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)	2. (FY05) 87.0%	2. (MET) The FY06 target of 88.5% occupied GSF was met and exceeded by 2.5%. 91% occupied space (GSF) had a CI greater than 65.
2007	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY05) 54.0%	1. Performance results will be reported in February 2008.
	2. (Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)	2. (FY05) 87.0%	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY05) 54.0%	1. Performance results will be reported in February 2009.
	2. (Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)	2. (FY05) 87.0%	2. Performance results will be reported in February 2009.
Data Source & Validation:	Vanderweil Facility Advisory (VFA) Inc. facility summary website (http://nih.vfafacility.com) for the National Institutes of Health Contact: Clarence Dukes Program Manager, Federal Programs Office of Research Facilities, Division of Policy and Program Assessment (301) 496-5078		
Cross Reference:	PMA-5, 1HHS-12, SP-8.4, Efficiency, Output, PART		

POI - 7	Manage design and construction of capital facility projects funded by the Building and Facilities Appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the approved budget. (Ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 20 active projects (FY07) TBD active projects (FY08) TBD active projects *Previous Target:* (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 24 active projects (FY07) TBD active projects (FY08) TBD active projects	1. (FY06) 20 active projects	1. (MET) All 19 projects were managed within the approved budget.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 20 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD *Previous Target:* (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 24 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	2. (FY06) ≤ 2	2. (MET) No projects required scope adjustments.
2005	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 24 active projects (FY07) TBD active projects (FY08) TBD active projects	1. (FY04) 19 active projects (FY05) 21 active projects	1. (MET) All twenty-one (21) projects were managed within the approved budget.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 24 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	2. (FY04) ≤ 2 (FY05) ≤ 2	2. (MET) All projects were managed within the approved scope.
2006	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 20 active projects (FY07) TBD active projects (FY08) TBD active projects *Previous Target:* (Target 1) Manage all	1. (FY06) 20 active projects	1. (MET) All twenty (20) active projects were managed within the approved budget.

	B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 24 active projects (FY07) TBD active projects (FY08) TBD active projects		
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 20 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD *Previous Target:* (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 24 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	2. (FY06) ≤ 2	2. (MET) All twenty (20) of the active projects were managed within the approved scope.
2007	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 20 active projects (FY07) TBD active projects (FY08) TBD active projects	1. (FY06) 20 active projects	1. Performance results will be reported in February 2008.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 20 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	2. (FY06) ≤ 2	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 20 active projects (FY07) TBD active projects (FY08) TBD active projects	1. (FY06) 20 active projects	1. Performance results will be reported in February 2009.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 20 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	2. (FY06) ≤ 2	2. Performance results will be reported in February 2009.
Data Source & Validation:	GPRA Capital Portfolio Performance Reports: DPPA Database Contact: Clarence Dukes Program Manager, Federal Programs Office of Research Facilities, Division of Policy and Program Assessment (301) 496-5078		

Cross Reference:	PMA-5, 1HHS-12, SP-8.4, Output, PART		
POI - 8	By 2010, protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (MET) 100% of projects under construction have approved design and construction documents or are implementing corrective strategies, and 100% of projects ensured the Notice of Federal Interest has been recorded or are implementing corrective strategies.
	2. (Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (FY05) 95% of 117 projects are in compliance (FY06) 95% of 123 projects are in compliance (FY07) 95% of 143 projects are in compliance (FY08) 95% of 164 projects are in compliance (FY09) 95% of 179 projects are in compliance (FY10) 95% of 196 projects are in compliance	2. No. of Projects occupied in past 20 years: (FY05) 117 prjs (FY06) 123 prjs (FY07) 143 prjs (FY08) 164 prjs (FY09) 179 prjs (FY10) 196 prjs	2. (MET) 100% of projects monitored the use of grant-supported space or are implementing corrective strategies.
2006	1. (Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (NOT MET) 66% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. Corrective strategies have been taken to ensure that the remaining projects will meet the construction requirements.
	2. (Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (FY05) 95% of 117 projects are in compliance (FY06) 95% of 123 projects are in compliance (FY07) 95% of 143 projects are in compliance (FY08) 95% of 164 projects are in compliance (FY09) 95% of 179 projects are in compliance	2. No. of Projects occupied in past 20 years: (FY05) 117 prjs (FY06) 123 prjs (FY07) 143 prjs (FY08) 164 prjs (FY09) 179 prjs (FY10) 196 prjs	2. (MET) 97% of the extramural construction projects were in compliance with the post award 20 year usage requirement.

	(FY10) 95% of 196 projects are in compliance		
2007	1. (Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. Performance results will be reported in February 2008.
	2. (Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (FY05) 95% of 117 projects are in compliance (FY06) 95% of 123 projects are in compliance (FY07) 95% of 143 projects are in compliance (FY08) 95% of 164 projects are in compliance (FY09) 95% of 179 projects are in compliance (FY10) 95% of 196 projects are in compliance	2. No. of Projects occupied in past 20 years: (FY05) 117 prjs (FY06) 123 prjs (FY07) 143 prjs (FY08) 164 prjs (FY09) 179 prjs (FY10) 196 prjs	2. Performance results will be reported in February 2008.
2008	1. (Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	1. Performance results will be reported in February 2009.
	2. (Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (FY05) 95% of 117 projects are in compliance (FY06) 95% of 123 projects are in compliance (FY07) 95% of 143 projects are in compliance (FY08) 95% of 164 projects are in compliance (FY09) 95% of 179 projects are in compliance (FY10) 95% of 196 projects are in compliance	2. No. of Projects occupied in past 20 years: (FY05) 117 prjs (FY06) 123 prjs (FY07) 143 prjs (FY08) 164 prjs (FY09) 179 prjs (FY10) 196 prjs	2. Performance results will be reported in February 2009.

Data Source & Validation:	NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864.
Cross Reference:	PMA-5, Output, PART

POI - 9	By 2012, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources.	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	1. (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.
2004	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources.	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	1. (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.
2005	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	1. (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.
2006	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	1. (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.
2007	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	1. Performance results will be reported in February 2008.
2008	1. Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	1. BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments	1. Performance results will be reported in February 2009.

Data Source & Validation:	The NIH Manual Issuance 3005 - Review and Evaluation of Intramural Programs describes policy for the scientific review process for Principal Investigators within the intramural programs. For additional information, contact Linda Adams at (301) 496-1828.
Cross Reference:	Output, PART

FULL COST (dollars in millions)	FY06	FY07	FY08
	$7	**$184**	**$146**

Data Limitations Affecting Performance Targeting or Reporting

NIH's scientific research outcome goals are representative of the agency's goals. Almost all of the goals involve scientific and/or financial contributions of more than one IC; most goals involve several ICs. This representative trans-NIH approach enables performance assessment of NIH's broad and complex research program. In laying the groundwork for reporting on prospectively defined targets, NIH presents linkages among inputs, processes, outputs, and outcomes in science, taking into account the following factors:

- The representative approach and specific scientific research outcome goals results in reporting on projects that are components of, but are not budget line items.

- Research outcomes are challenging to predict with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the goal. Although outcomes may encompass the proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.

- The full value of any given research finding may not be apparent at the time of discovery, and often reaches a state of fruition after many years or in combination with other advances.

- NIH supports the discovery of scientific knowledge; knowing that the downstream impact of basic research is usually dependent on substantial further development of new knowledge by private industry, other public sector researchers, and economic factors.

Each of these factors will need to be considered in interpreting research performance reports.

GPRA PERFORMANCE GOAL NARRATIVES BY FIVE FUNCTIONAL AREAS

SCIENTIFIC RESEARCH OUTCOMES

NIH conducts and sponsors investigations in this country and abroad across the full range of the health research continuum, including basic research, which may be disease oriented or lead to the development and application of breakthrough technologies, observational and population-based research, behavioral research, prevention research, health services research, translational research, and clinical research. Clinical research includes research to understand both normal health and disease states, move laboratory findings into clinical interventions, and assess new treatments or compare different treatment approaches.

Each NIH Institute and Center (IC) maintains an extensive portfolio of research activities in its area of focus. In addition to providing grant support to the extramural research community through a competitive proposal process, most of the ICs also conduct their own research in NIH's intramural laboratories. Each year, NIH supports approximately 50,000 awards made to the most promising and productive scientists at universities and research centers throughout the country and, where special opportunities exist, to scientists abroad.

The vastness of the NIH portfolio presents a challenge in terms of articulation of goals. NIH has selected 35 specific, representative research goals, as proxies for performance on the larger, research portfolio. The goals were selected based on the following criteria:

- **Representative.** The goals are a sampling of NIH aims that, as a set, represent the NIH mission. NIH has abandoned the previous approach of goals that, collectively, embody the NIH mission comprehensively.
- **Meaningful.** The goals must be credible to the research community, as well as to the public and NIH stakeholders.
- **Specific.** Goals should be as specific to a disease or definable problem as possible, with reference to a metric and/or a date for progress/completion, as appropriate.
- **Objective.** Objective goals are self-measuring; that is, they permit a comparison between the actual achievement level and that targeted by the performance goal.
- **Reportable.** Goals must lend themselves to annual reporting. Reports of incremental progress are fine.
- **Not obviously attainable.** The goal must be recognized as an outcome that could be achieved in the future, but may not be reachable for any number of reasons.

Central to this approach is a framework that characterizes goals on the basis of risk (i.e., likelihood of attaining the goal) and time. One way of visualizing this framework is to use a three-by-three matrix (see next page). Following presentation of the goals in the matrix format, the goals are presented with accompanying background information. Baseline information provides the current state of the field upon which the goal was developed. The implementation strategies provide the key building blocks of science for a three year range. These strategies will be adjusted from year to year to adapt to scientific discoveries and advancements that facilitate progress toward the goal. Since scientific discovery is complex, the annual target selected represents only one critical step in the process of achieving the final outcome.

NIH GPRA SCIENTIFIC RESEARCH OUTCOMES GOALS MATRIX

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
High	**1.1** By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin. **1.2** By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background. **1.2.3** By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	**2.2** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2.3.2** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **2.3.4** By 2010, develop an HIV/AIDS vaccine. **2.4** By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.	**3.1** By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD). **3.2.1** By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials. **3.3** By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. **3.5** By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies. **3.6** By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.
Medium	**4.5.1** By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens. **4.5.4** By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools. **4.5.5** By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings. **6.3** By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	**5.2** By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus). **5.3** By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs. **5.6** By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction. **5.6.2** By 2011, assess the efficacy of at least three new treatment strategies to	**6.1** By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. **6.4** By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
		reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease. **5.7** By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy. **5.8** By 2011, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies. **5.9** By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.	
Low	**7.2** By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. **7.8.1** By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases. **7.8.3** By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.	**8.2** By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals. **8.4** By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding. **8.5** By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. **8.6** By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). **8.9.1** By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).	**9.4** By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
		8.9.2 By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities. **8.9.3** By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software.	

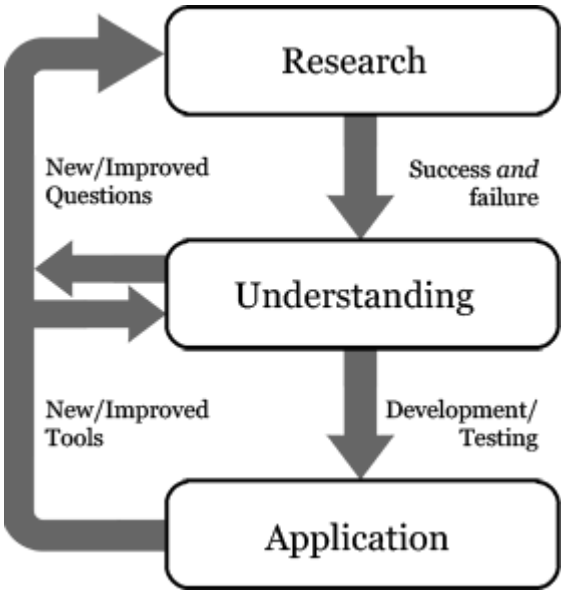
The matrix of goals selected by NIH reflects the challenges of complex biological systems. They range across a continuum of low to medium to high risk, and they have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes high-risk goals that reflect the start of a scientific journey, which often means that the knowledge is limited and pathways to success are primarily unknown. Achievement of a high-risk goal in the early stages cannot be guaranteed. In contrast, NIH low-risk goals usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-risk goals, only a few steps remain to translate the knowledge into an application that could lead to improved public health. NIH also utilizes performance goals that span the middle of the continuum. For the latter, a foundation of knowledge has been set but not extensively developed. Yet the goal is pursued because achievement is deemed probable. The elements used to determine the level of risk/ambition/difficulty include predictability of outcomes, absence of clear pathways, delivery time, and needed resources.

This continuum of scientific discovery affirms the need for a balanced portfolio with high-risk/ambitious goals as well as low-risk/probable goals and all those in between. NIH recognizes that all of its goals involve some degree of uncertainty because of the risk factor inherent in the nature of scientific discovery. NIH promotes ambitious goals because they hold promise to address a critical need and improve the health of the Nation. Goals that are ambitious and/or involve risk will by nature be difficult: The pathway to discovery may not be linear, and the building blocks needed to make a scientific breakthrough still have to be determined. Through utilizing goals that span the range of the continuum, NIH is making progress toward its mission of uncovering new knowledge leading to better health for everyone.

NIH's scientific research outcome goals in the matrix represent NIH as a whole. Almost all of the goals involve the scientific and/or financial contributions of more than one IC; most goals involve several ICs. This representative approach enables an approximate performance assessment of NIH's vast and complex research program. In laying the groundwork for reporting on prospectively defined targets, NIH presents linkages among inputs, processes, outputs, and outcomes in science as unique and nonlinear in the sense that:

- Outcomes are challenging to foresee with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the end goal.
- The full value of any given research finding can be visible at the time of discovery, and often reaches a state of fruition after many years or in combination with other advances.
- Although outcomes may encompass the proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.
- NIH supports the discovery of scientific knowledge; knowing that the downstream impact of basic research usually is dependent on substantial further development of new knowledge by private industry, other public sector researchers, and economic factors.

Each of these factors will need to be considered in interpreting research performance reports.



The typically circuitous course of progress in science is depicted above. The graphic illustrates that gaps in scientific knowledge drive the development of hypotheses for research studies. Yet, the findings from those studies may unveil roadblocks that will further narrow or redirect the research efforts. Often considerable time will pass before a new approach to the problem (a new scientific opportunity) emerges. In addition, findings that did not validate a specific hypothesis may be used in other research efforts leading to new scientific knowledge. Thus, each NIH research result has merit and may prove critical in the realm of scientific discoveries.

Research is an inherently collaborative endeavor and partnerships are crucial to achieving

scientific research outcome goals. The role of the extramural research community (the scientists at universities and hospitals across the country and even around the world) as NIH's partner in research is well known. However, of increasing importance are partnerships with private companies, not-for-profit institutions, non-governmental organizations, and state and foreign governments. Joint research and training activities and other exchanges with such groups leverage NIH resources. Moreover, such partnerships facilitate valuable information feedback loops that identify emerging needs, suggest important new research questions, and otherwise inform priority setting. Partnerships also provide access to populations that are key in advancing knowledge.

All scientific research carried out through NIH support is subjected to a rigorous and consistently applied review process. For example, the Extramural Program, which oversees the largest category of NIH-funded research, utilizes two levels of peer review. The first level consists of chartered scientific groups composed of experts in particular scientific disciplines. The second level is the National Advisory Boards of the various Institutes. For the Intramural Program, an outside Board of Scientific Counselors participates in evaluating entire laboratory programs. The latter occurs once every 4 years, which allows ongoing assessments of all intramural labs and the accomplishments of the scientists who contribute to them. It is through this well-honed system of peer review that NIH can maintain its focus on supporting research of the highest possible quality.

SRO-1.1	**By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.**

BACKGROUND

Prevalence/Incidence

The 2002 World Health Organization report lists alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension. In the United States, alcohol is the third leading root cause of death not attributable strictly to genetic factors, after tobacco and diet/activity patterns. Almost 16 million American adults are alcoholic (physically dependent on alcohol) or abuse alcohol (dysfunctional, but not dependent). Children also are at risk. Almost 30 percent of 9th to 12th graders report having had five or more drinks, in a row, at least one day of the previous month.

Disease Burden

Alcohol use disorders cost U.S. society almost $185 billion each year through injury, lost wages, property damage, death, and other factors. Unlike other drugs of abuse, alcohol can have toxic effects on any organ in the body. Heavy alcohol use can cause brain damage, contributes to cardiovascular disease, and is a leading cause of liver cirrhosis and pancreatitis. Alcohol also is linked to some kinds of cancer.

Rationale

Alcoholism is a chronic disease subject to relapse; sustaining abstinence is the goal of treatment. However, current medications work for some people but not others. Different factors contribute to abusive drinking and to subtypes of alcoholism. Some alcoholics have a genetic predisposition that affects specific brain systems, such as those regulating stress or rewarding sensations, resulting in molecular and cellular variations. Others are vulnerable to environmental stimuli. Developing more widely effective medications requires (1) understanding and targeting the different biological and environmental variations that underlie alcoholism, and (2) the availability of a wide array of candidate medications for testing. Animal models enabling the testing of compounds in different biological and environmental scenarios are making this goal possible.

Two recently identified classes of compounds with treatment potential are antalarmin and rimonabant. By blocking a brain cell receptor (CRH1) for a hormone that elicits anxiety in response to stress, antalarmin reduced drinking in monkeys going through alcohol withdrawal. Rimonabant blocks another receptor (CB1) that otherwise would stimulate biological pathways in specific areas of the brain that result in rewarding sensations. In mice, this medication reduced drinking by young animals. Researchers must continue to cast a wide net to identify compounds with therapeutic potential for the different subtypes of alcoholism. This involves identifying molecular targets and new and existing compounds that act on them, conducting screenings that predict the utility of these compounds, and confirming their utility with animal and human studies.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Three strategies have been identified. First, NIH prepared a clinical protocol to test rimonabant for its ability to reduce alcohol drinking and obtain approval to proceed. Such testing should lead to enhanced techniques for treating alcoholism. Second, NIH contracted for toxicology studies of antalarmin for the purpose of obtaining approval by FDA of an Investigational New Drug (IND) application. This toxicologic evaluation should be completed by 2007. Third, NIH designed a protocol to be used for testing antalarmin in alcoholics for relapse prevention and reduced alcohol drinking. The protocol would be implemented in Phase I/II clinical trials to begin in 2007. Therefore, both rimonabant and antalarmin will be in clinical trials in 2007. While scientific in nature, this step is ambitious because of the normal risks associated with any medications development program.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Prepare clinical protocol for testing rimonabant in humans.	(FY02) Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	◆e					
FY03	*Actual Performance:* (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking.						
Complete a toxicologic evaluation of antalarmin.	(FY03) Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials		◆e				
FY04	*Actual Performance:* (MET) A toxicologic evaluation on antalarmin has been completed.						
Test antalarmin for relapse prevention in alcoholics.	(FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking			→	→	→	
FY05	*Actual Performance:* (EXT) For the drug antalarmin, the FDA requires further toxicology studies. Extended to 2007.						
Conduct toxicology studies of antalarmin in monkeys as required by FDA.	(FY05) Meetings with FDA to discuss initial toxicity study results in monkeys and dogs led to a new request from FDA for additional studies in monkeys				◆		
FY06	*Actual Performance:* (MET) Toxicology studies of antalarmin in non-human primates were conducted as required by FDA.						
Complete goal of conducting medications development using animal models and beginning to conduct Phase I and II human trials of two potential treatments for alcoholism: rimonabant and antalarmin.	(FY06) Toxicology studies of antalarmin have been performed in monkeys and a phase IIa clinical trial of rimonabant has been conducted.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was MET. Toxicology studies of antalarmin in monkeys are expected to be completed in December 2006 and the results should be available by January 2007. These studies are required by the FDA before an Investigational New Drug application can be submitted for a phase I clinical trial. These efforts were supported by a consortium of the NIH institutes.

Implementation Strategy Advances or Other Highlights

Preliminary results of the toxicology studies show that antalarmin causes only small changes in the bone marrow of non-human primates, the species that is likely to be most similar to humans in its response to the drug. If the final results show promise, then phase I trials are expected to begin in 2007. Recently, researchers demonstrated a strong preclinical validation of antalarmin for the treatment of alcoholism in animals, further validating the corticotrophin releasing hormone receptor as a treatment target. A phase IIa study on the cannabinoid antagonist rimonabant has been completed and data analysis should begin soon. In addition, NIH is collaborating with the pharmaceutical industry to screen proprietary compounds in the preclinical models for alcoholism. Compounds showing positive results will move to early human trials.

SRO-1.2	**By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.**

BACKGROUND

Prevalence/Incidence

Approximately 32.5 million American adults report some degree of hearing difficulty, making it one of the most prevalent disabling conditions in the United States. As Baby Boomers age, this number is expected to increase significantly. Hearing aids continue to be the only form of remediation for most people with permanent hearing loss. Only about 20% of Americans with hearing loss have hearing aids and only about half of those are satisfied with their aids. Hearing aids are not typically effective in restoring the ability to listen only to the desired speech source from among competing sound sources. This makes it difficult to hear speech in public venues such as meetings, banquets and sporting events.

Disease Burden

Sensorineural hearing loss affects people of all ages, in all segments of the population, and across all socioeconomic levels. It can interfere with an individual's physical, cognitive, behavioral, and social functions and is caused by a problem in the cochlea or the auditory nerve, the parts of the ear that help sound impulses reach the brain.

Rationale

Hearing aid users want devices that enable them to better understand speech. Two recent surveys demonstrate this desire. Poor benefit in noisy situations was listed among the top 20 reasons why hearing aid owners don't use their hearing aids. Another survey of 2,428 hearing aid owners found that improved understanding of speech in noise was among the top 10 desired changes. Of all the available technologies, directional microphones have shown the most promise for addressing this problem, as demonstrated by clinical studies of individuals with hearing loss.

In spite of their promise, many engineering challenges stand in the way of achieving the full potential of directional microphones. The tremendous recent advances in signal processing have not produced marked improvements in speech intelligibility for the hearing impaired. Part of the reason for this is that processing technology has outpaced sensing technology. A primary premise of this project (SRO-1.2) is that processing must be integrated with significantly improved directional microphone technology. The combined result will improve the lives of hearing-impaired individuals.

NIH-supported scientists have been studying the tiny fly Ormia ochracea, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultra sensitive time coding and localization of sound, provide a model for scientists and engineers to use in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has identified four strategies toward developing a directional microphone prototype using improved technology. First, NIH researchers designed and tested a device (diaphragm) that responds to sound based on the ears of the fly *Ormia ochracea*. Second, NIH designed and tested the electronic circuitry needed to create a sound output from the diaphragm. Third, NIH combined the diaphragm and the electronic output circuitry into a directional microphone. Fourth, NIH miniaturized the prototype directional microphone so that it is small enough to fit into a hearing aid worn behind the ear. By developing a hearing aid that mimics the sound localization abilities of the fly, NIH anticipates transferring the same sound localization abilities to hearing-impaired individuals who use hearing aids.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly "Ormia ochracea."	(FY02) Small insect model system exists and has hyperacute sound localization.	◆					
FY03	*Actual Performance:* (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to the sound and is based on the ears of the parasitic fly 'Ormia ochracea'.						
Design and test the electronic circuitry to create a sound output from the diaphragm.	(FY03) Sound-responsive diaphragm based on an insect model system is available		◆				
FY04	*Actual Performance:* (MET) NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal.						
Combine the diaphragm and the electronic output circuitry into a directional microphone. *Previous Target:* Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	(FY04) Diaphragm and electronic circuitry are available.			◆			
FY05	*Actual Performance:* (MET) NIH-supported scientists successfully combined the diaphragm and circuitry into a directional microphone.						
Complete goal of developing one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	(FY05) Diaphragm and electronic circuitry combined into a directional microphone.				◆		
FY06	*Actual Performance:* (MET) A prototype of a low-power, highly directional hearing aid microphone was developed to help hearing-impaired persons better understand speech in a noisy background.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target has been MET and the goal has been ACHIEVED. NIH-supported scientists successfully completed a fabrication process to miniaturize the prototype of a low-power, highly directional hearing aid microphone so that it will fit into a hearing aid. This directional microphone mimics the auditory system of the parasitic fly Ormia ochracea. The fly's system is an excellent model to imitate because its mechanically coupled ears enable it to detect the direction of sound and because it suggests a way to miniaturize a microphone for use in hearing aids. The scientists used silicon microfabrication technology to make a

directional microphone that is small enough to be incorporated into a hearing aid. The directional microphone developed in FY 2006 will ultimately help hearing aid users to better understand speech in a noisy background, such as in a crowded room. The microphone is able to do this by 'paying more attention to' or giving more weight to desirable sound(s) amidst noise.

Implementation Strategy Advances or Other Highlights

During FY 2006, NIH-supported scientists were able to successfully use silicon microfabrication to create a new type of microphone diaphragm to detect sound. Since the typical microphone diaphragm consists of a very thin plate, stress (from pressure or twisting) nearly always has significant detrimental effects on microphone performance. However, the design approach of the NIH-supported scientists avoids many of the difficulties caused by stress in silicon microphones. A miniature version of the optical sensor electronics has been fabricated and modified so that it does introduce noise into the system. In addition, the research team used SLA (stereolithography) technology to design a microphone package based on a 3-dimensional scan of the ear. The microphone is suitable for integration into a hearing aid.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-1.2.3	**By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.**

BACKGROUND

Classification of domains by computational sequence analysis is a powerful means to deduce the function of newly discovered proteins. In the context of proteins associated with human disease, this analysis can generate hypotheses concerning the metabolic pathways in which proteins act and greatly accelerate research into the molecular basis of disease and therapy. Domain analysis identifies regions of high sequence similarity with respect to other proteins from a variety of organisms. Conserved domains, as these regions are called, have been shown to be fundamental units of biological function; they adopt similar three-dimensional (3-D) structures and interact with other molecular components of living cells in similar ways. Thus, a comprehensive domain database, searchable over the Internet, is a powerful research tool for academic and industrial scientists with diverse interests.

Rationale

A comprehensive database was achievable because proteins contain only a few thousand domain families. Maintaining an up-to-date collection with respect to current knowledge nonetheless represents a challenge that was met only by the development of new methods for large-scale comparative analyses of molecular data that allow curators to focus on functional annotation. The continuing investment by Federal agencies and other organizations in genome sequencing and structural genomics will yield the greatest return when combined with efforts to organize these data in useful ways. Results of related research in comparative genomics and methodology for protein classification assisted in achieving this goal. The conserved domain database represents an advance over previous efforts because it applies structure-based alignment and molecular evolutionary classification in a systematic and ongoing manner.

This resource is particularly valuable to researchers such as medicinal chemists who require a synthesis of information on protein biological function, 3-D structure, and sequence conservation. Effective antiviral drugs have been designed by targeting the conserved regions of viral proteins; for example, the virus is unable to develop resistance to these drugs because sequence changes that block drug binding also block the normal function of the protein. By describing conserved regions in detail, this resource provides information that is directly useful to the medicinal chemist undertaking this research.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Production and maintenance of a classification database demand intensive intellectual effort and sophisticated computational and visualization tools. The “CDTree” software system interactively links displays of evolutionary sequence trees, the taxonomic 'tree of life,' and ancient recombination history as inferred from protein domain architecture to facilitate assignment of protein domains into useful subgroups. Other computerized procedures update structure-based alignments and hierarchies of conserved domains by automatically

scanning the PubMed database of biomedical journal literature and identifying new structures, sequences, and citations. 3,904 domain families have been curated.

Additional development of these software tools not only improved the efficiency and quality of the data curation by NLM's National Center for Biotechnology Information (NCBI) staff but also provided researchers with powerful discovery tools. Distribution of these tools facilitates the submission of outside research results to NCBI, thus further enriching the classification resource. Using NCBI-developed software for structure-based alignments and molecular evolutionary classification, outside experts are able to make contributions, based on their own research, in identifying homologous sites and in adding site-specific functional annotation.

Additional refinements in classification increased the utility of the database in carrying out research in such areas as targeted drug design. Better identification of the conserved regions of viruses, for example, can lead to more effective antiviral drugs. Standard operating procedures were developed to identify conserved domain subgroups of biomedical importance, including proteins from pathogens and human proteins that are potential drug targets. The database was expanded to include structure-based sequence alignments for these domains.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Develop software for making comparative alignments of protein domains according to structure and molecular evolutionary classification, and which provides functions for domain family updates.	(FY02) 256 domain families curated; software to align domains by structure and class unavailable	◆					
FY03	*Actual Performance:* (MET) Software was released which improved structure-based alignments of proteins and classification of protein domain families based on molecular evolution; software was used to annotate over 500 protein domain families.						
Obtain annotation for a total of 1,500 protein domain families in the conserved domain database using two advanced classification methods: (1) structure-based alignment and (2) molecular evolutionary classification. Cover 35% of sequences in PubMed (the National Library of Medicine's database of biomedical research literature), extended to 70% by adding first-generation alignments.	(FY03) 800 domain families curated; 25% coverage of PubMed sequences		◆				
FY04	*Actual Performance:* (MET) 1,674 domain families curated through enhancing software for molecular evolutionary classification and by bringing Conserved Domain Curator team to full strength.						
Obtain annotation for total of 2,500 protein domain families annotated by structure-based alignment and molecular evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.	(FY04) 1,500 protein domain families curated; 35% coverage of PubMed sequences			◆			
FY05	*Actual Performance:* (MET) 2,814 expertly curated protein domain families curated by further developing the software and increasing the size of the Conserved Domain Curator team. 45% of PubMed sequences covered and, with first generation alignments, an estimated 75% covered.						
Complete goal of developing methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	(FY05) 2,800 protein domain families curated; 45% coverage of PubMed sequences				◆		
FY06	*Actual Performance:* (MET) By the end of FY 2005, 75% of proteins from sequenced genomes according to evolutionary origin and biological structure had been classified and the goal had been met. In FY 2006, several enhancements were implemented beyond the goal of classifying 75% of proteins which enabled the team to produce a total of 3,904 expertly curated protein domain family models.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and the goal has been ACHIEVED. By the end of FY 2005, 75% of proteins from sequenced genomes according to evolutionary origin and biological structure had been classified and the goal had been met. In FY 2006, several enhancements were implemented beyond the goal of classifying 75% of proteins: (1) The "CDTree" software system for molecule evolutionary classification was further developed to implement all original design goals. (2) The Conserved Domain Database curator team was maintained at a strength of 16 biologists, with intensive training for newly appointed team members. Together, these efforts enabled the team to produce a total of 3,904 expertly curated protein domain family models, which is 1,090 (39%) more models than in FY05, when the goal of classifying 75% of known genome sequences was reached. The classification of proteins by conserved regions is of key importance to researchers studying protein function since conserved regions are the fundamental biological unit within sequences. For example, knowing the location of these short stretches of sequence allows the investigator to concentrate on just these locations to design better drug targets.

Implementation Strategy Advances or Other Highlights

The "CDTree" software system assists curators/users in identification of domain subfamilies with distinct biological function. The software calculates hierarchical clustering trees based on molecular sequence similarity and couples their display to taxonomic information, so curators may identify clusters corresponding to evolutionarily ancient, conserved, functions; additional useful information such as the domain architecture and search-model performance of clusters is also displayed. The software furthermore functions as an efficient data manager, allowing curators to automatically declare and record new subfamilies and/or to modify the underlying sequence/structure alignments using the "Cn3D" structure-based editing software.

While software can make their work efficient, the goals of the Conserved Domain Database project can only be met by a team of trained and expert biologists/curators. The curator team is above all responsible for identifying and citing scientific publications that describe the biological function of domain family members. By interpreting protein 3-dimensional structure, the curator team can furthermore annotate features such as enzyme active sites. Occasionally, curators must exercise judgment in interpretation of molecular data, for example in identification of possible horizontal gene transfer events or conformational flexibility. Training of the curator team by cross-checking and frequent discussion has thus been an essential component of the project.

Efficiency

During the course of FY 2006 CDD has identified and implemented software features that make domain family curation more efficient and the team produced 1,090 (39%) additional expertly curated protein domain family models beyond what was produced by the end of FY 2005 when the goal of classifying 75% of known genome sequences was reached. Updates to the CDD can now be done interactively, and optionally focused on portions of the family hierarchy selected by the curator, allowing them to concentrate on new and/or modified subfamilies. Another feature the team has incorporated into the "Cn3D" software is an

algorithm for automated refinement of sequence/structure alignments. NIH has found that this procedure improves alignments, in some cases significantly. Now that 3,904 domains have been curated, it has also become apparent that earlier classification projects seriously underestimated the number of subfamilies with distinct function. In identifying these subfamilies by molecular evolutionary methods CDD thus achieves a greater "depth" of detailed functional annotation and thereby narrows the search space to a smaller, more functionally related set of proteins instead of having groupings of hundreds of distantly related proteins. A narrowed search space reduces time spent on scanning much larger pools of proteins in studies focused on potential drug targets. This detailed functional annotation is accomplished efficiently only by means of the "CDTree" and "Cn3D" software tools, which largely automate the tasks of ancient subfamily identification and alignment.

SRO-2.2	By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.

BACKGROUND

Prevalence/Incidence

The number of overweight and obese Americans has risen dramatically in the past two decades and is now at epidemic levels.

- Approximately 66 percent of U.S. adults are overweight or obese; more than 32 percent of U.S. adults are obese.
- About 17.1 percent of children and teenagers ages 2 through 19 are overweight, with ominous implications for our Nation's future health.
- Racial and ethnic minority populations are disproportionately affected by obesity, particularly African American, Hispanic American, and American Indian women and children.

Disease Burden

Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, stroke, osteoarthritis, gallstones, breathing problems, and certain cancers. Type 2 diabetes, formerly viewed as a disease of older adults, has been increasingly reported among children. This alarming trend is thought to be a consequence of increased obesity along with decreased physical activity. In addition to the negative impact on quality of life and the increased risk of premature death, overweight and obesity exact enormous economic costs. In 2000 costs associated with obesity were estimated to be $117 billion.

Rationale

Overweight and obesity develop when energy intake (food calories) exceeds energy expenditure. Although genetic factors may contribute substantially to the predisposition for obesity, the recent dramatic increase in obesity prevalence is clearly fueled by environmental and behavioral changes interacting with genetic susceptibility. Results from the NIH-funded Diabetes Prevention Program (DPP) clinical trial demonstrated a substantially reduced incidence of type 2 diabetes in a high-risk population using an intervention that combined moderate weight loss and exercise; however, these modest lifestyle changes required intensive individual behavioral intervention. In addition, the efficacies of different types of diets for weight loss and maintenance have not been compared in adequately powered trials of sufficient duration. Thus, the goal of obesity prevention may benefit greatly from new approaches to modify factors pervasive in the environment that promote over consumption of food and sedentary lifestyles, complemented by additional research on strategies to help individuals achieve and maintain behavior changes. For people who are extremely obese, expected weight loss from behavior change alone may not be sufficient to have a major impact on health. Bariatric surgical procedures, which restrict stomach size and/or lead to decreased absorption of nutrients, are being increasingly performed to treat severe obesity. These procedures can have dramatic benefits but also carry substantial risks. Coordinated clinical research on this surgery will enhance patient evaluation, selection, and follow-up

care and may also lead to improved understanding of factors underlying the development of obesity, leading to new strategies for prevention and treatment. Finally, the continued elucidation of the molecular factors and pathways responsible for appetite regulation, metabolism, and energy storage offers rich prospects for the development of new drugs that will promote safe and effective long-term weight loss. A major goal of NIH-funded research is to develop and evaluate strategies to prevent obesity and promote sustained weight loss among individuals who are overweight or obese. In addition to mechanisms falling within the three broad approaches to weight regulation just described, evaluation of other as yet unknown strategies may also be necessary to achieve success in meeting the goal. If successful, the approaches would decrease the risk of life-threatening diseases that accompany excess weight and also would reduce the social and economic costs of obesity.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Because of the complexity of factors associated with weight gain and obesity and the high risk of a goal of evaluating novel approaches to prevent weight gain and/or treat obesity, NIH is pursuing multiple strategies toward achieving this goal. Several of these are relevant to lifestyle modification; others are related to pharmacologic and other medical interventions.

NIH will explore five or more lifestyle-based approaches to obesity prevention, including behavioral or environmental interventions, in settings such as schools, communities, and homes; in addition, at least two studies will evaluate the effects on weight control of worksite interventions that include environmental components; and at least three studies will evaluate the effects of interventions delivered in primary care settings to treat and/or prevent obesity in children. Because maintenance of weight loss is a critical yet particularly difficult element of obesity treatment and prevention, NIH will investigate novel ways to help individuals who have intentionally lost weight to keep the weight off for at least 2 years. Specifically, the Weight Loss Maintenance Trial will compare three different strategies for maintaining weight loss among persons who are successful in losing a targeted amount of weight over the short term. Complementing these areas of investigation relevant to lifestyle interventions will be research to evaluate the efficacy of different types of diets and physical activities. Specifically, a study is being conducted to compare the Atkins diet with a conventional weight loss diet as to long-term effects on weight and other health parameters.

Research on the effects of bariatric surgical procedures designed to restrict food intake in adults and adolescents, who are seriously obese may increase the understanding of appetite and metabolism and thus inform the development of new prevention or treatment strategies for obesity. With respect to currently available medications, NIH will investigate the effects of at least one pharmacologic agent, either alone or in combination with behavior modification, on the treatment of obesity among children or adolescents. Finally, genetic and other studies in humans and animal models should reveal at least two new potential targets for drug discovery efforts; such targets could include signaling molecules or pathways that influence appetite or energy expenditure.

More broadly, the NIH is implementing the multidimensional research agenda of its Strategic Plan for NIH Obesity Research. Developed by the NIH Obesity Research Task Force with crucial input from external scientists and the public, the Strategic Plan, published in August 2004, serves as a guide for coordinating obesity research activities across the NIH and for enhancing the development of new research efforts. The NIH is supporting a spectrum of initiatives consistent with the recommendations of the Strategic Plan; these initiatives complement the NIH's strong portfolio of investigator-initiated obesity research. Additionally, the NIH continues to work with the external community on efforts to advance obesity research progress.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	(FY02) No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	◆e					
FY03	*Actual Performance:* (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.						
Develop and launch at least two studies to test the effects of worksite interventions on weight control.	(FY03) No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective		◆e				
FY04	*Actual Performance:* (MET) More than two studies to test the effects of worksite interventions on weight control were developed and launched.						
Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children 6 to 12 years.	(FY03) No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia			◆e			
FY05	*Actual Performance:* (MET) NIH scientists succeeded in enrolling 73 children in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.						
Enroll and randomize 240 predominantly minority pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain.	(FY04) Few effective community-based interventions are available to prevent weight gain in at risk children				◆		
FY06	*Actual Performance:* (MET) Two hundred forty ethnically-diverse pre-adolescent girls were enrolled and randomized to test the efficacy of an after school dance program in reducing weight gain.						
Develop and launch at least three new clinical trials to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children.	(FY05) Few obesity intervention programs targeting children have been designed and tested to establish their effectiveness outside of small clinical settings.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Complete delivery of the 2-year interventions being tested in the preventing obesity using novel dietary strategies (POUNDS Lost) clinical trial, which is comparing four diets of different macronutrient composition for their effects on weight loss and weight loss maintenance in overweight and obese adults.	(FY06) Few trials have adequately tested the effects of diets differing in macronutrient composition.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. NIH-supported scientists successfully enrolled and randomized 240 ethnically-diverse pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain. Girls, randomized to both a control or dance program group, will be followed to determine whether the dance intervention treatment group significantly reduces its weight gain over a 2-year study period. The study recruited girls between the ages of 7.00 and 10.99 years from 6 ethically and socioeconomically diverse public elementary schools. There were no minimum BMI or race-specific eligibility criteria for enrollment. The dance program is offered five days a week (Monday-Friday) and continues straight through the summer. To date, the overall daily attendance rates for the dance program range from 38% to 59% across the 6 schools. With many competing alternatives for after school activities (homework pressures, changing family dynamics and mobility), this participation rate is evidence of the motivating nature of the dance program as an after-school activity.

Implementation Strategy Advances or Other Highlights

As a result of support, in part by NIH, a new solution-oriented research paradigm has been proposed and is available in American Journal of Preventive Medicine 28 194-201 2005. Enrolled 90 subjects in a trial studying the efficacy of metformin for weight control in severely overweight children with hyperinsulinmeia. Results on the effects of two different intervention approaches to prevent obesity in African-American girls (the GEMS project) were reported at the GEMS Data and Safety Monitoring Board meeting on September 25, 2006.

SRO-2.3.2	By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.

BACKGROUND

In the 1940s, the widespread availability of newly discovered antibiotics led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms are remarkably resilient and have developed mechanisms of resistance that thwart or block the action of antimicrobial drugs. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. In addition, new, serious, and unforeseen infectious disease threats have emerged, including those posed by agents of bioterrorism. Because the existing repertoire of antimicrobial therapeutics may not in the future provide an effective defense against newly emerging and resistant organisms and bioterrorism agents, there is a need to develop new treatments that may be effective against a range of pathogens. Development of a "universal antibiotic," a drug effective against a wide spectrum of infectious diseases, would help address these challenges.

Rationale

From a strategic perspective, a broad spectrum antimicrobial therapeutic could be used either alone, or in combination with currently available antimicrobials, to protect individuals exposed or potentially exposed to pathogens of unknown identity. This would provide a valuable countermeasure in the case of an outbreak or bioterrorism attack. In addition, there is increasing concern about both naturally evolving drug resistant pathogens and the potential to engineer drug resistance into microbes to create bioterrorism agents. A new broad spectrum antimicrobial could be used to treat or to increase the effectiveness of current drugs against drug-resistant infections. Better understanding of intracellular pathogens, and the components of the immune response they may commonly activate during infection, could identify new pathways to target for the development of universal/broad spectrum antimicrobials with efficacy across multiple classes of pathogens. In addition, genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that the NIH is using to understand the microbes that cause disease and to devise strategies to overcome infection.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of developing one universal antibiotic/antimicrobial/antiinfective that is effective against multiple classes of biological pathogens, NIH will expand its capacity for medicinal and combinatorial chemistry, library and database resources, and screening assays for use in identifying novel antimicrobial drugs. New methodologies, chemical libraries, and software tools will expand the pool of compounds that can be screened for antimicrobial properties. Expansion of NIH genomic, proteomic, and bioinformatic resources will accelerate basic and applied research on microorganisms responsible for emerging and reemerging infectious diseases, including those considered potential agents of bioterrorism, as well as identification of gene products critical to

bacterial growth and pathogenicity that may serve as targets for broad-based antimicrobials. In addition, NIH is supporting research under several initiatives of the NIH Roadmap Program to develop a small molecule repository and PubChem database, a Molecular Screening Centers Network, and to support the development of screening tools and new assays for high-throughput screening. NIH will continue to support interagency and public-private collaborative research projects to develop new antimicrobial strategies.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	(FY02) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	◆					
FY03	*Actual Performance:* (MET) Two different molecules with a common role in different classes of microbes were identified.						
Identify one molecule or mechanism that is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	(FY03) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes.		◆				
FY04	*Actual Performance:* (MET) A drug/metabolite transporter molecule from the malarial parasite Plasmodium falciparum, that is similar to transporter molecules in other protozoa, may serve as a target for drugs to increase responsiveness to drug therapies.						
Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections. *Previous Target:* Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development.	(FY04) NIH does not have a complete set of screening tools that can be used to test compounds for activity against both bacterial and viral pathogens.			◆			
FY05	*Actual Performance:* (MET) A complete set of in vitro screening tools that can be used to test compounds for activity against bacterial and viral pathogens has been developed.						
Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases.	(FY04) Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed.				◆		
FY06	*Actual Performance:* (MET) Screening tools were used to evaluate compounds for potential activity against multiple classes of organisms of infectious disease.						
Through medicinal and/or combinatorial chemistry, optimize several compounds for antimicrobial activity.	(FY05) Resources provided to the scientific community for development of medicinal and combinatorial chemistry capacity and assay optimization.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Begin determining safety and pharmacology profiles (e.g. bioavailability) of at least 1 candidate compound that has shown broad spectrum activity in vitro.	(FY07) NIH has not yet begun safety and pharmacology profile determinations for candidate compounds that have demonstrated broad spectrum activity in vitro.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

NIH MET the FY 2006 target of using a set of screening tools to evaluate potential compounds or classes of compounds for activity against pathogens. Antimicrobial screening tools developed to meet the FY 2005 target were used in FY 2006 to conduct in vitro screens

for compounds showing antimicrobial activity against several different organisms, including organisms from NIAID's Category A, B and C Priority Pathogens list. Examples include gram positive bacteria Bacillus anthracis and Staphylococcus aureus and gram negative bacteria Brucella abortus, Francisella tularensis, Yersinia pestis, Burkholderia mallei, Burkholderia pseudomallei, Coxiella burnetii, and Escherichia coli. Drug resistant strains of non-select agent bacteria were also included. For example, in one study, 255 compounds were screened for activity against a subset of Category A and B organisms using a broth microdilution method to determine minimum inhibitory concentration. Fourteen compounds display potential broad-spectrum activity, defined as activity against four or more different organisms.

Other types of assays/screening tools developed for use in screening compounds to identify those with potential broad-spectrum activity include: a high throughput liquid transfer system to test minimum inhibitory concentrations of candidate compounds, a colorimetric drug screening assay, and a real-time polymerase chain reaction (PCR) assay for antibiotic susceptibility.

Development and use of screening tools that target broad-spectrum activity will allow the identification of compounds with antimicrobial activity against multiple pathogens, which is a critical step in development of novel broad-spectrum antimicrobials.

Implementation Strategy Advances or Other Highlights

In FY 2006, NIH supported the evaluation of 3,150 compounds for activity against NIAID biodefense category A–C viruses; 1,400 compounds were screened for anti-pox virus activity with a focus on identifying drugs with a different mechanism of action than cidofovir. New targets for pox inhibitor screens were identified using bioinformatics.

In FY 2006, NIH released two Broad Agency Announcements (BAAs) to solicit proposals for therapeutics development: "Development of Therapeutic Agents for Selected Viral Diseases" and "Development of Therapeutic Agents for Selected Bacterial Diseases." The viral therapeutics BAA specifically states that proposals addressing product candidates with broad spectrum activity against multiple viral classes is highly desirable. The bacterial therapeutics BAA solicits proposals to advance the development of candidate therapeutics with: a) demonstrated activity against one or more of the selected NIAID Category A and B biothreat bacterial pathogens; or b) broad spectrum activity against any of the Category C antimicrobial resistant pathogens and one more of the selected Category A and B bacterial pathogens.

NIH awarded nine grants in FY 2006 in response to an RFA, "Innate Immunity to Category B Protozoa" that solicited applications to elucidate mechanisms by which the innate immune system recognizes, responds to, and neutralizes the complex defense systems of protozoan pathogens. This area of basic science may provide the scientific foundation for future target identification for broad spectrum immunotherapeutics.

In addition, in FY 2006, NIH made awards for broad spectrum antimicrobial research through several other programs, including the Cooperative Research Partnerships for Biodefense, Small Business grant programs and the Biodefense and Emerging infectious

Diseases Research Program. Awards included a contract to advance the development of a broad spectrum RNA-interference-based anti-viral therapeutic against hemorrhagic fever viruses and grants for immunotherapeutics for biodefense.

On April 18, 2006, NIH hosted a workshop, 'Development of Broad Spectrum Therapeutics,' to provide a forum for discussion of the regulatory requirements for licensure of broad spectrum drugs. Participants included scientists from academia, industry, NIH, DHHS, DoD and FDA. The speakers and the panel discussions identified unique challenges faced by academia, and large and small pharmaceutical companies that are pursuing development of drugs for multiple pathogen indications.

SRO-2.3.4 By 2010, develop an HIV/AIDS vaccine.

BACKGROUND

Prevalence/Incidence

The human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic has killed more than 25 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. In 2005, an estimated 40.3 million of the world's population, including 2.3 million children younger than 15 years of age, were living with HIV/AIDS. In addition, over 3 million people died from AIDS in 2005, and approximately 5 million people were newly infected with HIV, of which 700,000 were children. The number of people living with HIV/AIDS has seen the steepest increases in East Asia, Eastern Europe and Central Asia. Although in the United States new infections have remained relatively stable at approximately 40,000 per year, the proportion of new HIV infections that occur among women and racial and ethnic minorities continues to rise.

Disease Burden

The impact of AIDS on developing nations is profound. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown and creating a generation of orphans.

Rationale

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on AIDS vaccines. As promising candidates move further in the vaccine pipeline, expanded clinical trials will become increasingly important.

NIH is designing and testing new vaccine candidates based on research findings on the structural components of HIV and on studies of immune responses in small animals and nonhuman primates (NHPs). Vaccine candidates also are being constructed based on isolates from many regions of the world, and several research groups are exploring mixtures of viral components from different isolates and clades. NIH is testing new vaccine strategies using different adjuvants, immune modulators, and delivery components to optimize the immune responses that result. NIH will fund additional basic research to better understand why some individuals exposed to HIV resist infection or are able to control disease progression.

In striving to meet the broader goal, a significant investment of NIH resources has been made in new and improved product designs to ensure that there is a vibrant pipeline to support HIV vaccine development efforts. NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on candidate vaccine products. As promising candidates move further in the vaccine pipeline, expanded trials with populations

at increased risk for HIV infection will become increasingly important.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has expanded and will continue to expand breeding of specific pathogen-free macaques at several primate centers to ensure adequate animal resources for the preclinical testing of vaccine candidates. In addition, NIH has produced and tested both simian immunodeficiency virus (SIV) and simian-human immunodeficiency virus (SHIV) virus stocks for challenge of vaccinated animals. Additional virus stocks that more closely match HIV are being developed and will be expanded and tested as they become available.

In addition, all HIV/AIDS clinical trials research networks funded by the NIH are being restructured; awards for the new Leadership of the HIV/AIDS Clinical Trials Networks and Clinical Trials Units were made in FY 2006 and the HIV/AIDS Clinical Trials Units will be made in FY 2007. The new structure is designed to improve the coordination, collaboration, efficiency and flexibility of the research networks to address continuing research challenges worldwide across therapeutic, vaccine and prevention research.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Design and develop new or improved vaccine strategies and delivery/production technologies.	(FY02) Existing DNA and viral-vector vaccines strategies require further evaluation	◆					
FY03	*Actual Performance:* (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.						
Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	(FY03) HIV Vaccine Trials Network currently supports clinical trials at 12 international sites		◆				
FY04	*Actual Performance:* (MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.						
Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	(FY04) NIH has conducted 68 phase I and phase II HIV vaccine trials to date			◆			
FY05	*Actual Performance:* (MET) NIH initiated five phase I trials for new products and six phase I and one phase II trials to further assess existing products. NIH expanded clinical trial capacity into 8 new international settings.						
Initiate 1 new phase IIb trial to determine if a third generation vaccine candidate has efficacy.	(FY04) NIH is conducting a phase III trial of a second generation vaccine (canarypox) in Thailand				◆		
FY06	*Actual Performance:* (MET) NIH initiated a Phase IIb study (test of concept) to evaluate the safety and efficacy of Merck's Adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in high-risk adults.						
Initiate another Phase II/IIb trial(s) of the most promising third generation vaccine candidate.	(FY05) NIH is conducting Phase I trials of a second third generation candidate (6 plasmid DNA plus Adv boost).					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Initiate a Phase IIb trial of a promising vaccine candidate that may protect across viral clades (or subtypes).	(FY06) NIH is conducting 3 phase I/II trials (HVTN 502, HVTN 050, HVTN 204) of products that might be further tested for protection across viral clades (or subtypes).						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. During FY 2006, NIH initiated a Phase Ilb, "test of concept" efficacy study to evaluate the safety and efficacy of a three-dose regimen of Merck's Adenovirus serotype 5 HIV-1 gage/pol/nef vaccine in high-risk adults. This study, which is being conducted by NIH's HIV Vaccine Trials Network (HVTN), was amended to expand enrollment to eligible HIV high-risk adults irrespective of pre-existing Ad5 antibody. In addition to assessing safety, the trial will test whether the vaccine will reduce the proportion of volunteers who acquire HIV infection and/or results in a decrease in HIV-1 viral load set-point in volunteers who acquire HIV infection, relative to placebo recipients. This trial is being conducted in countries where clade B HIV infection is prevalent; trials sites include Puerto Rico, Peru, Haiti, Dominican Republic, Jamaica and the United States. The study will also be opening at a site in Brazil. Additional sites are located in Canada (Toronto, Montreal, and Vancouver) and Australia (Sydney).

Implementation Strategy Advances or Other Highlights

During FY 2006, NIH, in collaboration with the US Military HIV Research Program (USMHRP) and the International AIDS Vaccine Initiative (IAVI), initiated six Phase I or Phase I/II HIV vaccine trials to assess new vaccine products; vaccines will be evaluated through the NIH Vaccine Research Center (VRC) or through the NIH-funded HIV Vaccine Trials Network. These trials, which evaluate safety and immunogenecity, support the identification and further assessment of candidate HIV vaccines. They include:

• A Phase I/II study (RV 172) of a VRC multiclade HIV-1 DNA plasmid vaccine boosted by a multiclade HIV-1 recombinant adenovirus-5 vector vaccine. The study is being conducted in East Africa through the USMHRP.
• A Phase I randomized, placebo-controlled, double-blind study (IAVI 001) of a multiclade HIV-1 DNA plasmid vaccine boosted by a multiclade HIV-1 recombinant adenovirus-5 vector vaccine using the same products being used in RV 172. This trial is being harmonized with RV 172 and another ongoing HVTN trial (HVTN 204) because all three studies involve the same multigene, multiclade HIV vaccine. All of these studies are on the critical path to an efficacy study of these VRC vaccine products and mark an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as the majority of clades causing the global HIV epidemic.
• A Phase I study (HVTN 064) of two vaccines, a multi-epitope protein vaccine and an HIV multi-epitope DNA plasmid vaccine, in uninfected adults.
• A Phase I study (HVTN 065) of an HIV clade B multigene DNA vaccine prime followed by a recombinant modified vaccinia Ankara vaccine (MVA) HIV 62 boost in uninfected adults.
• A Phase I study (HVTN 068) evaluating immune response kinetics of two prime boost regimens using VRC's 4-plasmid DNA vaccine in combination with the VRC multiclade HIV-1 recombinant adenoviral vectors.
• A Phase I study (VRC 011) testing the safety, tolerability, and immune response when different administration routes, intramuscular, subcutaneous and intradermal, are used for the priming vaccinations in a prime boost schedule.

In addition, during FY 2006, NIH provided funding for and scientific input into four ongoing trials being conducted by the USMHRP as part of an Interagency Agreement. This includes the Phase III HIV vaccine trial in uninfected adults in Thailand (RV 144) and three cohort development studies (RV 142, RV 143, RV 173) in Kenya, Tanzania, and Uganda. The cohort studies will characterize risk factors associated with infection and compare recruitment efficiency and follow-up rates between distinct cohort recruitment strategies.

During this period, NIH also supported 11 ongoing HIV vaccine trials conducted through the HVTN. Volunteer visits were completed in three studies conducted by the HVTN , one study conducted by the USMHRP and three in the VRC .

In addition a number of new international sites were added in FY 2006. This includes HVTN sites in Lima, Peru; Santo Domingo, Dominican Republic; KOSH (Klerksdorp, Orkney, Stilfontein, and Hartbeesfontein), South Africa; Cape Town, South Africa; and the USMHRP site in Kericho, Kenya.

In order to determine whether or not a candidate vaccine will move into clinical trials, HIV vaccine testing is conducted in animal models. Three new contracts for Simian Vaccine Evaluation Units (SVEU) were awarded in FY 2006 that together have the capacity to house 600 non-human primates for vaccine and related studies. Currently, there 12 active studies involving approximately 220 macaques. Six studies were completed in the past year that evaluated the efficacy of vaccines based on: recombinant alphavirus, recombinant rabies virus, recombinant pox virus, and recombinant replication-competent adenovirus. Studies were also conducted to test methodologies designed to enhance responses to DNA vaccines. Several of the recombinant vector vaccines, as well as the DNA vaccines that were designed to generate cellular immune responses are able to enhance the control of virus replication in the immunized animals without blocking infection. While this is important, as it is hoped that the reduction in viral load will contribute to reduction in HIV transmission in humans, studies in the non-human primates will continue to try to identify vaccine approaches that can prevent infection.

NIH has several contract mechanisms that provide a comprehensive range of support needed for small-scale research and Good Manufacturing Practice (GMP) production of experimental AIDS vaccines and preclinical testing, including laboratories capable of safety and toxicity testing, and producing documentation leading to investigational new drug (IND) submission for Phase I clinical testing in humans. Vaccine production projects supported through these contracts in FY 2006, included projects with University of Pennsylvania (3 DNAs), EuroVacc (Poxvirus), and a consortium with the University of Capetown and the South African AIDS Vaccine Initiative (SAAVI) (DNA plasmids and Poxvirus vector). NIH has additional contract resources for small-scale GMP production through the HIV Design and Development Teams (HVDDT) program. Contractors receiving funding in FY 2006 to advance their vaccine candidates toward GMP production include Wyeth (VSV vector), Progenics Phamaceuticals (recombinant protein), AlphaVax (VEE vector), Epimmune (DNA and poxvirus vector), Children's Research Institute (AAV vector), and Chiron/Novartis (alphavirus vector). One new contract award was made in FY 2006 under the HVDDT program to Berna Biotech (recombinant measles).

A number of other important awards were made in FY 2006 that will support various aspects of HIV vaccine research. A total of 14 awards were made under the vaccine Innovation Grant Program in areas such as, virus and bacterial vector design, T-cell and mucosal immunology, gene expression profilings and improving FACS analyses, non-human primate models, molecular adjuvant development, mechanisms of "elite" control and antibody enhancement, and improving envelope-based vaccines to induce broadly reactive neutralizing antibodies. In addition, a Program Project grant was awarded under the HIV Research and Design (HIVRAD) Program for research on HIV envelope immunogens to induce broadly reactive neutralizing antibodies.

Building on last year's award to establish the Center for HIV/AIDS Vaccine Immunology (CHAVI), the group has begun formulating several key questions in the areas of: viral/host interaction characteristics, host genetics in response to HIV, and HIV envelope structural characteristics. Among CHAVI's many accomplishments in the past year are the: establishment of 8 clinical trials sites (including 6 in Africa), development of 7 clinical trial protocols, initiation of a study comparing existing samples from individuals with acute HIV infection to samples from individuals exposed to HIV, but who are uninfected, organization of the EuroCHAVI Genetics Consortium, development of a single genome amplification method to characterize transmitted HIV, and the establishment of the HIV Transmitted Virus Sequence Database.

The NIH is supporting the Adolescent Trials Network for HIV/AIDS Interventions (ATN) to enable future vaccine trial research infrastructure for adolescents at domestic U.S. sites. Building on a community-based primary prevention protocol, the ATN has conducted a baseline assessment of behavioral data, including HIV risk behaviors, social networking patterns, and HIV prevalence among 12-24 year olds in community venues (ATN 016b). These data were used to inform the implementation of ATN 040, a community mobilization intervention to effect structural change and reduce HIV incidence among youth. As part of this process, ATN/Connect-2-Protect site staff and their community partners chose one of two CDC programs (Mpowerment and PROMISE) to implement as a targeted community level prevention intervention (ATN 041). Changes in HIV-related risk will be measured by comparisons of the baseline data obtained in ATN 016b to that of serosurveys conducted in the final year of ATN 040. The ATN continues to provide central coordination and evaluation of community partnerships and mobilization strategies and is working with the HVTN and the IMPAACT clinical trials networks to include adolescents in HIV vaccine trials, where appropriate.

PART

This goal was included in the FY 2005 PART of the HIV/AIDS Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-2.4	**By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.**

BACKGROUND

Across a wide range of acute and chronic disease and treatments, symptoms such as pain, fatigue, and psychological distress may arise and have an impact on the health outcome of the patient. Symptoms may impact patients in several ways: (1) symptoms may cause patients to reduce or abandon treatment, (2) symptoms may cause psychological distress, and (3) symptoms may contribute to the overall disease burden while decreasing both the functional status and the quality of life for the patient. These effects of disease- and treatment-related symptoms play an important role in health outcomes.

Disease- and treatment-related symptoms such as pain, fatigue, and psychological distress are common for diseases/conditions including cancer, acquired immune deficiency syndrome (AIDS), graft versus host disease and others. For example, persons undergoing certain chemotherapy or allogeneic bone marrow transplantation may develop stomatitis, an inflammation of the lining of the throat and mouth that may lead to ulcerations, mouth and throat pain, and decreased quality of life. Behavioral factors related to symptom burden also affect functional status and quality of life. Examples of behavioral factors include interventions used by patients and families to treat and manage physical and/or other issues resulting from symptoms. The investigation of biological mediating factors, as well as behavioral factors, need to be elucidated to provide the rationale for testing interventions targeted at increasing functional status and quality of life.

Newly established research programs addressing potential interventions of disease- and treatment-related symptoms are underway by NIH-supported scientists. Research efforts include studies of cancer treatment-related complications and associated pain, as well as symptom distress/quality of life. Through research of symptoms, NIH-sponsored scientists are identifying additional strategies to improve health outcomes.

Rationale

Elucidating interrelationships among the components of symptom experience, symptom management strategies, and symptom outcomes related to acute and chronic diseases/conditions and associated treatments is critical to providing appropriate preventative and treatment-related health care. The symptoms patients experience are often the first indicator of treatable disease, may signal disease progression, and/or may prevent optimal treatment. Understanding the biological basis or mechanisms of symptoms is a critical first step to developing and testing scientifically sound interventions that address the cause of the symptoms. NIH-supported scientists are capable of performing research investigations, including clinical trials, to develop interventional or therapeutic strategies targeted at improving the patient's health status and quality of life.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH-supported scientists are addressing disease- and treatment-related symptoms that are common for diseases/conditions. The following implementation strategies or steps have been identified to provide the basis for achieving the goal: (1) forming at least one collaboration that addresses either the biological mechanisms of pain, fatigue, or psychological distress or related potential therapeutic intervention(s); (2) identifying results from at least one study of symptom distress/quality of life; (3) identifying results of clinical trials addressing cancer treatment-induced oral complications and associated oral pain; and (4) evaluating two interventions for reducing pain, fatigue, or psychological distress in patients undergoing treatment for cancer or other illness/chronic disease. As both time and science advance, other implementation strategies or steps may be identified and employed to achieve the goal.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Integrate multidisciplinary approaches to investigate: 1) biological mechanisms of pain, fatigue, or psychological distress or 2) related potential therapeutic intervention(s) by establishing at least one intramural collaboration.	(FY05) Identification of potential intramural collaborations.			◆			
FY05 *Actual Performance:* (MET) One intramural collaboration was established.							
Contribute to the identification of potential interventions for symptom/illness burden by identifying results from one study of symptom distress/quality of life.	(FY05) One study of symptom distress/quality of life completed.				◆		
FY06 *Actual Performance:* (MET) Results from one study of symptom distress/quality of life were identified.							
Contribute to the identification of potential interventions for treatment-related oral complications and associated pain by analyzing the results of two (2) clinical research protocols relevant to cancer treatment.	(FY04) Two (2) IRB approved clinical research protocols addressing cancer treatment-related oral complications and associated pain are open to accrual.					◇	
FY07 *Actual Performance:* Performance results will be reported in February 2008.							
Evaluate two interventions for reducing pain, fatigue, psychological distress, or other symptoms in patients undergoing treatment for cancer or other illness/chronic disease.	(FY06) Potential strategies for reducing symptom burden of patients with a chronic disease/illness identified.						◇
FY08 *Actual Performance:* Performance results will be reported in February 2009.							

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET because results from one clinical study of symptom distress/quality of life were identified. The study addressed the complexity of the relationship between multiple genetic factors and individual pain responses. Researchers identified the associations between certain genetic factors and clinical pain ratings of patients undergoing oral surgery: two genetic factors were associated with the maximum post-operative pain rating, and one genetic factor was associated with the onset time of post-operative pain. Along with additional studies, these research efforts may provide the rationale for future studies of potential interventions.

Implementation Strategy Advances or Other Highlights

In 2006, clinical trials addressing cancer-related oral complications remain open for patient

enrollment. Strategies that reduce symptom or illness burden may be identified through these studies.

SRO-3.1	By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).

BACKGROUND

Prevalence/Incidence

Alzheimer's disease (AD) is a progressive, at present irreversible brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks of daily living.

- Approximately 4.5 million Americans currently have AD.
- The prevalence of the disease doubles with each 5-year increment in age in persons older than 65.
- Demographic studies suggest that if current trends hold, the annual number of incident cases of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will be over age 65.
- By the year 2050, the number of Americans with AD could rise to some 13.2 million, an almost three-fold increase.

Disease Burden

The cost of AD care varies by stage of the disease. In 1996 annual costs of caring for patients with mild, moderate, and severe AD were estimated as $18,408, $30,096, and $36,132, respectively. The national cost of caring for people with AD is now estimated to be about $100 billion every year. Also significant is the physical and emotional toll AD exacts on family, caregivers, and friends. The changes in a loved one's personality and mental abilities; the need to provide constant attention for years on end; and the demands of bathing, dressing, and other caregiving duties can cause tremendous stress to the caregiver, often impacting his or her health and well-being. Not surprisingly, caregivers of people with dementia spend significantly more time on caregiving tasks than do caregivers of people with other types of illnesses.

Rationale

The few agents that are currently approved by the Food and Drug Administration for treatment of Alzheimer’s disease have demonstrated only modest effects in modifying the clinical symptoms for relatively short periods. Likewise, the first and, to date, only agent shown to delay clinical diagnosis of AD in people with mild cognitive impairment (donepezil [Aricept®]) appears to forestall the transition from MCI to full-blown AD for only a brief period of time. However, a number of promising findings are now emerging to provide directions for potential interventions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH has a comprehensive plan to achieve, by 2013, the important goal of discovery and validation of an intervention that will delay the progression, delay the onset, or prevent the onset of Alzheimer’s disease. Achievement of this goal will require progress on a number of fronts, and the NIH is working to facilitate discovery in each of the following areas:

Neuroimaging and other Biological Markers. The ability to identify individuals at risk for developing Alzheimer's disease is increasingly important, as therapies are developed for testing and as we learn more about how those at risk can take steps to reduce the possibility of developing Alzheimer's. In late 2004, the NIH, in conjunction with several other Federal agencies, private companies, and organizations, launched the Alzheimer's Disease Neuroimaging Initiative (ADNI) to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The study could help researchers and clinicians develop new treatments and monitor their effectiveness as well as lessen the time and cost of clinical trials. The project is the most comprehensive effort to date to find neuroimaging and other biomarkers for the cognitive changes associated with MCI and AD.

Genetics. To date, only one risk factor gene for late-onset AD has been identified, despite the intense interest in determining a genetic basis for this disease. The AD Genetics Initiative was started to develop much-needed resources for geneticists to find the additional key late onset genes; finding and recruiting about 1000 families will be necessary to establish a data base for these studies. Thanks to an unprecedented alliance of AD Centers, researchers, and outreach personnel, aided by the Alzheimer's Association, nearly 1000 such families have been identified.

Basic Research. NIH is working to accelerate discovery of new risk and protective factors and how they interact with different genetic factors such as apolipoprotein E-4 in order to identify promising targets for treating and preventing disease through basic research. Basic research studies are identifying new pathways involved in the brain mechanisms that lead to AD, and the identification of these pathways, in turn, is then indicating new targets for the development of therapeutic agents for AD, MCI, and age-related cognitive decline.

Pre-Clinical and Translational Research. NIH also plans to speed drug discovery and movement of promising new treatments and prevention strategies into clinical trials. The launch of a major new translational research effort to expand the range of novel compounds to be tested for cognitive decline, mild cognitive impairment, and AD, and to more quickly move research from the laboratory to clinical trials in humans, will further support our efforts in this regard. Four key steps are needed in the preclinical development of new agents prior to clinical testing: Chemical optimization; proof of efficacy in an animal model relevant to the disease; pharmacokinetic profiling; and early toxicology screening. As new agents are identified, these steps will need to be taken in all of them.

Clinical Trials. In 2003, the NIH launched the Cholesterol-Lowering Agent to Slow Progression of Alzheimer's Disease (CLASP) study, which is investigating the safety and effectiveness of the drug simvastatin to slow the progression of AD. Recruitment for this study is complete, and results are expected in early 2008. Other clinical trials are ongoing; the NIH also plans to use the knowledge gained through the basic and mechanistic studies described above to select the most promising imaging and biological markers, as well as

improved clinical and neuropsychological evaluation methods, to perform less expensive, shorter, and more efficient drug trials.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	(FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	◆					
FY03	*Actual Performance:* (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.						
Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	(FY03) Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed		◆				
FY04	*Actual Performance:* (MET) NIH continued a preclinical toxicology program and expanded a program for pre-clinical drug discovery and development.						
Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	(FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression			◆			
FY05	*Actual Performance:* (MET) The NIH launched the Alzheimer's Disease Neuroimaging Initiative in late 2004.						
Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	(FY04) The genetics initiative has identified 259 families, too few for researchers to identify the remaining risk factor genes.				◆		
FY06	*Actual Performance:* (MET) Nearly 1000 new late-onset AD families have been identified and recruited to the AD Genetics Initiative.						
Identify and characterize molecular events that may prove to be targets for treating or preventing Alzheimer's disease through initiatives and projects focused on mechanistic and basic studies.	(FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
For at least one promising drug candidate for the treatment of AD, complete at least one of the four preclinical steps necessary for regulatory approval: chemical optimization; proof of efficacy in an animal model relevant to the disease; pharmacokinetic profiling; and/or early toxicology screening.	(FY06) It is anticipated that 1-3 promising drug candidates will emerge from NIH's research programs by FY 2008; these have not completed the preclinical steps necessary for regulatory approval.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was MET. The NIH has identified 'around 1000' new late-onset Alzheimer's disease families. As of June 2006, the most recent date for which published data exist, 922 such families had been identified and recruited to the Alzheimer's Disease Genetics Initiative. By September 2006, researchers had reviewed 982 pedigrees and had accepted 935 families into the study.

The goal of the Genetics Initiative is to develop the resources necessary for identifying the remaining late-onset AD (LOAD) risk factor genes, associated environmental or lifestyle factors, and their potential interactions. To date, only four of the approximately 30,000 genes in the human genome have been conclusively shown to affect the development of AD pathology. Three of these are linked to the early-onset form of familial AD, which accounts for only a small percentage of all AD cases. A fourth gene which occurs in about one-fourth of the population has been found to be a risk factor gene for late-onset AD (LOAD) and is present in about half of the AD patients who have been tested for the gene. Geneticists have suggested that additional and as yet unidentified genes may be risk factors for LOAD. Finding new risk factor genes will help to identify potential targets for treatment and prevention of AD.

This successful recruitment effort was made possible through an unprecedented alliance of AD Centers, researchers, and outreach personnel, aided by the Alzheimer's Association.

Implementation Strategy Advances or Other Highlights

In 2006, the NIA also established a National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) at Washington University as a national genetics data repository in order to facilitate access by qualified investigators to genotypic data for the study of the genetics of late-onset Alzheimer's disease. NIA's policy is that all Genetic Data derived from NIA-funded studies for the genetics of late-onset AD be deposited at NIAGADS or another NIA-approved site or both whenever possible. Investigators have already begun submitting appropriate data to NIAGADS and requesting additional data for genetic studies.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-3.2.1	By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.

BACKGROUND

Prevalence/Incidence

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys the insulin-producing islets of the pancreas. Approximately 120,000 people with type 1 diabetes are younger than 20 years of age, making this one of the most common chronic diseases of childhood. Approximately 30,000 new cases occur each year, the majority with onset in early childhood and the teenage years; approximately 1 in 300 cases of diabetes with onset in adulthood is autoimmune in origin.

Disease Burden

Type 1 diabetes is a chronic, lifelong disease characterized by elevations in blood sugar that, over time, lead to severe and life-threatening complications, including heart disease, blindness, peripheral neuropathy, foot ulcers, and kidney failure. Treatment requires insulin administration through multiple daily insulin injections or use of an insulin pump and careful attention to diet and activity; blood sugar levels must be measured several times a day. However, even with careful attention to insulin dosing, the most medically compliant patients are rarely able to maintain "tight" or physiologic control of their blood sugar. As a result, existing treatments can delay and diminish, but not prevent, many of the complications of diabetes. Even with careful attention to control of blood sugar, type 1 diabetes results in a reduction in quality of life and leads to premature death.

Rationale

Whole-pancreas and pancreatic islet transplants offer individuals with type 1 diabetes the potential for physiologic control of blood sugar as an alternative to insulin therapy. Whole-pancreas transplantation is associated with significant morbidity and even death around the time of the operation; whereas, islet transplantation is associated with considerably less morbidity and has not been associated with death in the peri-procedure period. In islet transplantation, clusters of cells from the pancreas called islets are isolated from a donor pancreas and injected into a large blood vessel that drains into the liver. The transplanted islets lodge in the liver where they produce insulin. Until recently, the intermediate and long-term success of this procedure has been disappointing: of the more than 300 islet transplants performed over a decade, fewer than 10 percent of patients remained insulin independent one year after the procedure. However, recent advances in pancreatic islet cell preparation and improvements in immunosuppressive regimens that are required to prevent transplant rejection have dramatically improved the prospect for islet transplantation. If these results are confirmed in larger, multi-site studies, approximately 40 to 50 percent of type 1 diabetics can be expected to remain insulin independent two years following islet transplantation. Despite these advances, there is a progressive diminution in function of the transplanted islets with current approaches, and patients must remain on potent immunosuppressive drugs to prevent immune-mediated rejection of the transplanted islets. Immunosuppressive agents increase the risk of serious infection, kidney damage, hypertension, and cardiovascular disease.

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders such as type 1 diabetes. If successful, tolerance induction would enable life-long maintenance of islets in the absence of the drugs currently used to prevent rejection of the transplanted cells by the host immune system, many of which have deleterious side effects and associated toxicities.

Clinical and basic research conducted over the last several years through the NIH-funded Immune Tolerance Network (ITN) and elsewhere has increased our understanding of the mechanisms of immune tolerance, and some initial "proof of concept" trials in highly selected patient populations have been successful. Nevertheless, subsequent trials of tolerance-inducing agents in people with autoimmune diseases other than type 1 diabetes indicate that the agents used are unlikely to induce total tolerance in patients with type 1 diabetes who received islet cell transplantation.

The scope of research relevant to this goal as originally written has been expanded to include multiple avenues of immune modulation research. The goal of immune modulation research is the selective modulation of the immune system through the inhibition of harmful immune responses while keeping protective ones intact. For example, in transplantation, donor-specific immune modulation — a selective blockade of immune responses directed against the graft — could enable long-term graft survival without or with less toxic systemic immunosuppressive therapy. In asthma and allergic diseases, the goal of immune modulation research is the development of methods to inhibit immune responses to allergens. In autoimmune diseases, the goal of immune modulation research is the inhibition of the immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Tolerance induction is one of the multiple immune modulation strategies that could potentially improve the safety and long-term success of islet cell transplantation in people with type 1 diabetes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of evaluating the feasibility of islet transplantation in combination with immune modulating therapies for the treatment of type 1 diabetes in human clinical studies, NIH will initiate, several Phase 2 and 3 trials to evaluate the impact of a variety of interventions on the success of clinical islet transplantation. Interventions to be tested will be incorporated into the islet manufacturing process and/or administered to the recipients of the transplants. Each trial will include detailed metabolic studies, immunologic studies, and formal quality of life assessments and is anticipated to take 7 to 10 years from the development of a clinical protocol to the publication of the trial results, thus the end date from this goal was shifted from 2013 to 2015. These trials will be conducted through the Clinical Islet Consortium (CIT), which consists of five clinical centers in the United States, Canada, and Sweden.

One of the challenges facing islet transplantation researchers is the scarcity of islets suitable for transplantation. In order to improve procedures for the preparation of islets and ensure consistency and quality across multiple CIT clinical trial sites, current manufacturing, validation, and characterization processes have been developed. It is expected that these

processes will also be useful in the production of islets for use in clinical protocols conducted outside of the CIT Consortium.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY02) First trial of anti-CD52 to promote tolerance.	→	×				
FY03	*Actual Performance:* (NOT MET) Anti-CD52 was determined to be unsafe by a non-NIH supported trial of the agent in the target population. Therefore, the opening of the NIH-supported trial was cancelled.						
Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY03) First trial of anti-CD3 to promote tolerance.		→	×			
FY04	*Actual Performance:* (NOT MET) The Phase I trial of the anti-CD3 antibody in patients who had undergone islet cell transplantation was cancelled because the amount of anti-CD3 antibody needed for the trial could not be obtained because the pharmaceutical company that owns the agent decided to use it for other clinical trials.						
Submit response to FDA addressing safety concerns about anti-CD3 antibody. *Previous Target:* Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	First trial of anti-CD3 to promote tolerance.			◆			
FY05	*Actual Performance:* (MET) NIH submitted a response to the FDA addressing safety concerns about anti-CD3 antibody. The FDA removed the clinical hold on April 29, 2005.						
Establish uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs. *Previous Target*: Analyze data from phase I trial(s); initiate development of efficacy trial(s); if appropriate.	CIT established.				◆		
FY06	*Actual Performance:* (MET) Uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers was developed.						
Develop 2 clinical protocols. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	Clinical protocols under development.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Initiate enrollment of individuals who have type 1 diabetes and who have severe hypoglycemic episodes and hypoglycemia unawareness into two Phase III clinical trials to evaluate the effectiveness of islet transplantation.	(FY07) Clinical trials under development.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A common manufacturing process for the production of human islets for transplantation has been developed by consensus among the six manufacturing sites in the CIT consortium, and it has been submitted in a Drug Master File

to the FDA. Analysis of the outcomes of previous human clinical trials evaluating transplantation of human islets cells has been hampered by the variability of islet cell preparations between sites. All islet processing facilities follow the same manufacturing process as described in the common Master Production Batch Record, Certificate of Analysis, and product specifications.

The two clinical protocols that are in development in FY07 will use this newly developed common manufacturing process to enable evaluation of islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes.

Implementation Strategy Advances or Other Highlights

A recent paper by Shapiro et al. described the results of the first international, multicenter trial to explore the feasibility and reproducibility of islet transplantation with the use of a single common protocol. The primary end point was defined as insulin independence with adequate glycemic control 1 year after the final transplantation. Sixteen (44 percent) of the 36 subjects met the primary end point, 10 (28 percent) had partial function, and 10 (28 percent had complete graft loss 1 year after the final transplantation. A total of 21 subjects (58 percent) attained insulin independence with good glycemic control at any point throughout the trial. Of these subjects, 16 (76 percent) required insulin again at 2 years; 5 of the 16 subjects who reached the primary end point (31 percent) remained insulin-independent at 2 years.

The study demonstrated the feasibility of conducting a multi-center trial of islet transplantation using the same well standardized method of islet preparation at multiple sites.

SRO-3.3	By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.

BACKGROUND

For many serious health conditions, early detection offers the best hope for cure. However, many individuals obtain a correct diagnosis only after they experience symptoms—and then it may be too late. The composition of saliva and other oral fluids reflects serum levels of substances that may be useful for diagnostic applications—such as therapeutic and recreational drugs, hormones, immunoglobulins, and toxic molecules. Oral fluids also can be used as a source of host or pathogen DNA. Thus, oral fluids could potentially be used to assess and monitor systemic health and disease as well as determine exposure to environmental and occupational hazards. Real-time monitoring of oral fluids may also have a role in biodefense by facilitating early detection of agents used in bioterrorism.

Rationale

Saliva is easy to collect and poses none of the risks, fears, or "invasiveness" concerns occasioned by blood tests. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, making sample collection unnecessary. However, because oral levels of most analytes are lower than blood levels, sensitive analytical techniques are required. (An analyte is any substance or chemical constituent of a body fluid that is analyzed.) To overcome this challenge and demonstrate the feasibility of salivary diagnostic tools, NIH is taking steps to accelerate the technology needed to analyze oral fluids. These efforts will require highly sensitive and accurate methods for the rapid detection of informative analytes in saliva, thus indicating the early stages of emerging disease. In addition, NIH will create a catalog of all proteins in human saliva as a starting point in distinguishing between health and disease states. The goal is to determine the efficacy of salivary diagnostics to monitor health and diagnose at least one systemic disease by 2013. If successful, this line of research could yield improved detection for a number of diseases as well as dramatically reduce the cost and risk associated with blood test-based diagnostics. This could catalyze a shift in the current system of disease detection to one of health surveillance within the community and the home.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH plans to implement research projects that will integrate technologies to efficiently and simultaneously analyze key components of salivary secretions. Conventional and emerging technologies will be used to analyze salivary secretions from the parotid, submandibular, and sublingual glands. Bioinformatics and biocomputational tools will catalogue and annotate salivary components, resulting in a fully developed salivary proteome knowledge base. It is anticipated that a multidisciplinary team will ultimately produce a "periodic table" of salivary secretory proteins. From the research done to date, investigators have detected many exciting new molecules with diagnostic potential. Moreover, it was discovered that saliva contains a vast array of low-molecular-weight peptides, many of them produced from larger precursor proteins such as histatins, proline-rich proteins and the

secretory component of the polyIg receptor. Mapping these fragments back to the parent molecules revealed a complex system that governs salivary protein processing. Using peptide signatures, scientists will be able to detect, characterize, and monitor proteinase activity in saliva and other biological samples. Furthermore, NIH plans to develop integrated microsystems to detect disease-associated biomarkers in human saliva. The NIH's ongoing projects to catalogue the human salivary proteome has already created a strong foundation on salivary biomarker discovery.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	(FY02) No integrated technologies to quickly and efficiently measure multiple substances in saliva	◆					
FY03	*Actual Performance:* (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.						
Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	(FY03) Technology available to help identify salivary proteomes		◆				
FY04	*Actual Performance:* (MET) Three research projects implemented to identify and catalog salivary proteomes.						
Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	(FY03) Systems to quantify C-reactive protein in saliva have not yet been developed.			◆			
FY05	*Actual Performance:* (MET) Integrated microfluidic assay systems have been developed to measure C-reactive protein in saliva.						
Finalize the fabrication of a portable handheld diagnostic device that can detect C-reactive protein and other analytes associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization.	(FY04) Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation				◆		
FY06	*Actual Performance:* (MET) A portable handheld diagnostic device has been fabricated.						
Establish a common proteome database that will include data from 2 subject groups that cover over 80 percent of the salivary proteome.	(FY05) Three groups of researchers are currently working to catalog the salivary proteome.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Complete the design of bioinformatics management systems for storing, searching, and disseminating salivary proteomics data.	(FY06) Scientists have begun efforts to design bioinformatics systems to store salivary proteomics data.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A portable handheld diagnostic device has been developed to detect multiple analytes associated with both oral and systemic diseases. Through new partnerships among universities, industry, and NIH, the development of the new system will be advanced until a fully integrated device is ready for an FDA clinical trial and subsequent commercialization. This device can make it easier to monitor C-reactive protein, an important biomarker for cardiovascular disease. Furthermore, the device can be adapted to include other key diagnostic analytes, potentially reducing the cost and invasiveness associated with blood tests.

Implementation Strategy Advances or Other Highlights

In the past several years, advanced engineering technologies have met up with new developments in medical diagnosis. Swift scientific progress has demonstrated that rapid, cost-effective, and non-invasive diagnostic tools are feasible. Through the Salivary-Based Diagnostics Technologies program, NIH is building towards a powerful and efficient system to simultaneously analyze multiple substances found in human saliva. The development of fully integrated, handheld devices for collecting and analyzing saliva will not only facilitate the detection of known biomarkers, but will also catalyze research efforts to identify new biomarkers for a wider range of oral and systemic diseases and conditions.

Research efforts are underway to bring this new technology to the consumer, but also to expand the number of people who will benefit from these exciting developments. A growing number of proof-of-principle examples have been established for using saliva to monitor systemic diseases and conditions. For example, one group of researchers reported recently that a combination of 4 salivary RNA proteins could discriminate between saliva of oral cancer patients and saliva of matched controls with a high degree of both sensitivity and specificity. Other investigators have established techniques to measure key biomarkers, such as C-reactive protein, in only a few drops of human saliva. Researchers are also looking to apply these techniques to pulmonary diseases, including asthma, pediatric cystic fibrosis, and COPD (commonly referred to as emphysema).

A complementary effort to the Salivary-Based Diagnostic Program is an effort to identify and catalog the salivary proteome. NIH-funded projects are designed to help identify all protein components in human saliva, as well as their natural variants and complexes. This research will develop a 'molecular tool box' for the functional characterization of salivary proteins and establish tools for dissemination of these data to the scientific community. With these baseline data in place, scientists will be able to detect changes in the composition of saliva among people with or at risk for various diseases and conditions. Already, a preliminary catalog of over 1000 proteins found in saliva, along with their functional categories, has been established.

SRO-3.5	By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies.

BACKGROUND

Many studies have indicated that genetic components contribute to the risk of substance use disorders and comorbid psychiatric disorders. Identifying susceptibility genes and understanding how they might contribute to these disorders have been major foci of research. This effort has been limited due to difficulties inherent to the genetic study of complex disorders. However, advances in the development of new technologies such as single nucleotides polymorphisms (SNPs) and haplotype genotyping have led to the identification of genes such as GABRA2 (chromosome 4) associated with alcohol and drug dependence and CHRM2 (chromosome 7) associated with alcohol dependence and major depressive disorder. In addition, a polymorphism of catechol-O-methyltransferase (COMT) gene has also been linked to several psychiatric disorders such as alcoholism, schizophrenia, and anxiety.

Identifying more genes that influence the risk for substance use disorders and comorbid psychiatric disorders has important implications for furthering the understanding of the etiology of these disorders and for developing effective pharmacotherapeutic and behavioral interventions for these diseases.

Prevalence/Incidence

In 2002, the World Health Organization cited alcohol as the third leading risk factor for preventable, premature death in developed countries, after tobacco and hypertension. In the United States, alcohol is the third leading root cause of death not attributable strictly to genetic factors, after tobacco and diet/activity patterns. Almost 16 million American adults are alcoholic (physically dependent on alcohol) or alcohol abusers (dysfunctional, but not dependent). Children also are at risk. Almost 30 percent of 9th to 12th graders report having five or more drinks, in a row, at least one day of the previous month.

According to the National Survey on Drug Use and Health, in 2003 an estimated 19.5 million Americans aged 12 or older were current users of an illicit drug, and an estimated 70.8 million Americans reported current use of a tobacco product. Moreover, an estimated 21.6 million persons aged 12 or older can be classified with substance abuse or addiction. In addition, according to the National Survey on Drug Use and Health, among the 15.9 million heavy drinkers aged 12 or older, 32.6 percent were current illicit drug users.

Co-occurring diagnoses of substance abuse and mental illness are highly prevalent, with some estimates of as many as 7 to 10 million Americans suffering from both. Up to 66% of substance abusers are likely to be diagnosed with a psychiatric disorder during their lifetimes. Persons with diagnoses of severe mental illness are far more likely to have co-occurring substance abuse disorders. 25% of individuals diagnosed with major depression also abuse drugs and/or alcohol. Women with bipolar disorder are seven times more likely to be

alcoholics than women without psychiatric diagnoses.

Disease Burden

Alcohol use disorders cost U.S. society almost $185 billion each year through injury, lost wages, property damage, death, and other factors. Unlike other drugs of abuse, alcohol can have toxic effects on any organ in the body. Heavy alcohol use can cause brain damage, contributes to cardiovascular disease, and is a leading cause of liver cirrhosis and pancreatitis. Alcohol use also is linked to some kinds of cancer.

Rationale

Clinical assessments show that many individuals diagnosed with substance use disorders are also affected with other psychiatric disorders. This suggests the possibility of common pathways in the etiology of these disorders. Recent evidence suggests that there are common genetic influences on the risk for substance abuse and psychiatric disorders. To date we do not know the specific genes associated with this shared genetic risk. Genome-wide linkage/association studies have identified many chromosomal regions containing candidate genes that contribute to the susceptibility of alcohol dependence and other comorbid disorders. Use of rapid genomic technologies such as SNP genotyping and haplotype map analysis have advanced the discovery of genes from previously identified chromosome regions. Identification of gene/allelic variations associated with alcohol and other substance dependence and mental disorders will advance the understanding of the genetics of alcohol dependence and comorbid disorders, provide important clues to the underlying etiology of these disorders, and ultimately, facilitate the development of new prevention strategies and therapeutic interventions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH plans to identify genetic variations underlying addiction vulnerability. This will be accomplished through positional cloning using whole genome scanning and a candidate gene association approach in samples that have been previously collected. How variation in the identified genes translate into addiction vulnerability will be examined through the use of knockout and transgenic mice, as well as through human pharmacogenetic studies that is examining differences in response to these drugs in individuals with different genotypes.

In the first three years, newly identified genes will be cross-validated by independent studies with different populations and sample sources. In the next three years, additional genes and variants contributing to these disorders will be identified. Finally, in the last three years of the goal, these identified genes will be studied and characterized for function.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Validate or replicate previously identified chromosome regions in different sample sources by one or more groups to identify genes.	(FY04) Regions have been previously mapped on chromosomes 1,4,7, and 15 by one or more independent groups.				◆		
FY06	*Actual Performance:* (MET) Replicated the genetic associations of GABRA2, ADH4, and CHRM2 to alcohol dependence in different sample sources in multiple groups.						
Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek potential functional differences coming from these haplotypes.	(FY06) Susceptibility genes located on identified chromosomal regions have been mapped.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Identify potential functional differences from fine mapping studies of specific haplotypes.	(FY06) Susceptibility genes located on identified chromosomal regions have been mapped.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. Research performed through the Collaborative Study on the Genetics of Alcoholism (COGA), a large family-based study, initially identified genes associated with an elevated risk for alcohol dependence. To date, research studies have replicated a subset of the COGA findings showing that variations in the GABRA2 (chromosome 4), ADH4 (chromosome 4) and CHRM2 (chromosome 7) genes are associated with an increased vulnerability for the development of alcohol dependence. The genetic associations of other chromosome regions, including those mapped to chromosomes 1 and 15, are yet to be replicated. The genetic association of GABRA2 to increased vulnerability to alcohol dependence was identified in European-American, Russian male, German, Irish, Plains Indian, and Finnish Caucasian male sample populations; the genetic association of CHRM2 was identified in European-American and African-American sample populations; and the genetic association of ADH4 was identified in European-American, European-Brazilian, and African-Brazilian sample populations. These results do not necessarily suggest these sample populations are at increased risk for alcoholism but rather individuals possessing variants of these genes may be more vulnerable to developing alcohol dependence.

Implementation Strategy Advances or Other Highlights

Recent studies replicated the initial findings demonstrating an association of increased risk for drug dependence with GABRA2, ADH4, and CHRM2. Studies to validate other genes associated with alcohol risk as demonstrated by the COGA study will continue.

SRO-3.6	By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.

BACKGROUND

Disease Burden

Although cardiovascular disease (CVD) death rates have declined over the past few decades, CVD (including coronary heart disease (CHD), heart failure, and peripheral artery disease) remains the leading cause of death and disability in the United States. According to the 2002 National Health and Nutrition Examination Survey, an estimated 13 million Americans have CHD and 7.1 million have experienced a heart attack. CHD accounted for over 2 million hospitalizations, at an estimated cost of $142 billion, and approximately one half million deaths during that year. The aging of the U.S. population and the growing epidemic of obesity will likely increase the prevalence and cost burden of CVD in the U.S. in coming years. Aggressive approaches to revascularization and advances in medical management have improved the lives of many patients with CVD. Nonetheless, continued disability for many patients and escalating attendant societal costs, mandate searches for improved treatments.

Rationale

Based on remarkable successes achieved in animal models of ischemia, cell-based treatments using stem and progenitor cells from a variety of tissues have begun to be tested in humans. Results from relatively small numbers of patients have suggested benefit from cell-based approaches, but methods to determine the localization and phenotypic fate of administered cells would provide insight into the mechanism(s) of benefit, enable development of other therapeutic approaches to accomplish similar end-points (e.g., using cells as a 'drug delivery devices'), and facilitate detection of possible toxic effects (e.g., accumulation of cells in nascent neoplasms). Conventional techniques for tracking exogenously administered cells in animal models require fluorescent or genetic marking with identification of cells in histological sections. Imaging modalities are needed to track cells in intact animals and, ultimately, in humans. Ultra-small supermagnetic iron oxide particles have been tested for cell imaging in studies using magnetic resonance imaging (MRI). Because they are incorporated into cells by endocytosis and concentrated in endosomes, resulting in magnification effects on the signals that are used to generate images (Hinds et al. Blood 2003; Arbab et al. Transplantation 2003), they may permit imaging of small numbers of cells over several weeks. Moreover, they appear to be biocompatible and non-toxic, with some preparations already approved by the FDA for non-stem cell applications. Initial work at NIH has used serial MRI of mesenchymal stem cells (MSCs) labeled with iron fluorescent particles in a pig infarct model (Hill et al. Circulation 2003; Dick et al. Circulation 2003) to show that labeled MSCs injected into the myocardium are readily visible up to 21 days post-infarction in the region of the infarct and that injection sites containing as few as 105 MSCs can be detected by MRI.

Scientific understanding of stem cell-based therapy has progressed considerably since the goal was initiated. Results reported in the literature from several pre-clinical and clinical

studies using stem cells to treat cardiovascular disease show promise for reducing the progression of disease but have not for reversing damage to the myocardium or generating new blood vessels. Other studies suggest that cytokines, proteins produced and secreted by stem cells, may play an important role in the repair of damaged tissues. The unexpected results have shifted thinking in the field. Scientists are now devoting considerable effort to understanding the role of cytokine production by stem cells rather than focusing solely on assessing their differentiation state and location *in vivo*.

Despite the new focus on cytokine production, the importance of understanding stem cell differentiation remains a basic, important problem in regenerative medicine. A promising new approach for assessing differentiation has recently been reported in the literature (Tallini et al., 2006). Scientists have inserted a reporter of calcium transients into stem cells. The reporter allows scientists to determine whether stem cells are coupled productively to the normal heart during the regeneration process. Researchers have begun using the new approach to control the differentiation of cells introduced into animal models. Control of differentiation will be critical for the eventual success of cardiovascular cell-based therapy. Imaging methods to detect and monitor the differentiation process are now the focus of efforts in numerous laboratories.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A multimodality imaging effort is being undertaken to develop tools to track cardiovascular stem cells *in vivo*, and ultimately in patients. Efforts in the intramural program entail:

- Development and testing of MRI agents for *ex-vivo* labeling and *in vivo* tracking of cardiovascular stem and progenitor cells. Cell labeling for MRI stem cell tracking has been conducted successfully with various iron preparations. The NIH has already demonstrated *in vivo* cell tracking of mesenchymal stromal cells (Hill et al. Circulation 2003). NIH investigators also have tracked hematopoeietic stem cells accumulating in injured rat hearts using clinical-grade reagents (EJ Read, JA Frank, submitted 2004).

- Development of a PET/MRI/CT system in which an animal model or patient can be imaged with no motion between the two modalities. Single-modality PET is employed for investigational and clinical applications. Compared with MRI or CT, PET radionuclides may enable detection of cells with higher sensitivity. However, PET suffers from low spatial and temporal resolution. In comparison, MRI or CT can provide superior spatial and temporal resolution, anatomic localization of cells to tissue injury, and generation of functional data. MRI provides local measures of cardiac function that would allow quantification of the recovery of function in areas where labeled cells are administered.

- Investigation of PET agents that can be used both in the acute phase to label stem and progenitor cells, and in subsequent generations, with agents that bind uniquely to daughter cells. An additional challenge in stem and progenitor cell imaging is to determine the phenotypic fate of administered cells; that is, do the administered progenitor cells differentiate and divide with the potential of regenerating injured muscle or vascular tissue, or do cells release cytokines and growth factors with local effects on adjacent tissue, which then in turn regenerate tissue?

- Identification of markers of differentiated cells from originally introduced stem cells. Cell labeling

and tracking using optical methods have been hampered by blood (hemoglobin) and tissue (myoglobin) attenuation of transmission and emission. Non-invasive optical imaging and spectroscopy of various contrast agents have been demonstrated in small mammals; comparable myocardial imaging has been demonstrated in open-chest animals and patients. Apposing illuminator/detector systems to tissue enables high resolution *in vivo* tissue imaging. For example, catheter-based optical-coherence-tomography devices have been developed, using near-infrared energy, for investigational coronary artery wall imaging in a blood-free field.

- Development and testing of catheter-based optical systems for *in vivo* imaging of cardiovascular stem and progenitor cell preparations within the myocardium. Catheter-based devices could be developed to appose optical systems to myocardium from the endocardial surface from a transvenous or transarterial approach, from within the coronary arteries or veins, or within the epicardial space. By using an optical spectral window in the near-to-far infrared, absorbance by hemoglobin or myoglobin could be avoided that should permit detection of labeled cardiovascular stem cells resident in nearby myocardium. Successful development of labeling and imaging devices could enable high-resolution detection and tracking of administered cells.

The development of a novel imaging technique to track stem cell mobility through cardiovascular tissues will capitalize on the current aspects of conventional imaging and labeling methodology:
- basic imaging modalities of optics, MRI, and PET
- the promise of studies using particle uptake as a labeling strategy
- the results of using initial genetic modification for fluorescence protein labels

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Initiate stem cell labeling strategy.	(FY04) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.			◆			
FY05	*Actual Performance:* (MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.						
Complete optical imaging probe development.	(FY05) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.				◆		
FY06	*Actual Performance:* (MET) Researchers in the NIH intramural program have developed probes that are compatible with optical microscopy techniques developed by intramural scientists.						
Initiate validation and toxicity studies.	(FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Initiate preclinical studies on the nature of stem cell migration in adult tissue.	(FY06) Studies of the distribution of exogenously applied stem cells within a living organism are needed.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was MET. Researchers in the NIH intramural program have developed probes that are compatible with optical microscopy techniques also developed by intramural scientists. The probes have different advantages and disadvantages for labeling stem cells

and monitoring their distribution in vivo. Examples include nuclear stains and genetically-expressed, fluorescently-labeled proteins such as red fluorescent protein (RFP). Using RFP as a probe, the NIH intramural program recently demonstrated that exogenously applied stem cells can be monitored in vivo in the chorioallantoic membrane of the chick embryo. Achievement of the FY06 target means that researchers now have the tools and protocols needed to follow stem cell migration and monitor stem cell location in a variety of tissues and in several different animal models. Thus, the imaging approaches needed to undertake the pre-clinical stage, the development of imaging modalities to track cells in intact animals, are now available.

Implementation Strategy Advances or Other Highlights

New probes developed by extramural scientists, including fluorescently-labeled microspheres, complement the advances being made in the intramural program. When appropriate, intramural researchers will use probes produced by the extramural community to continue progress on the goal.

PART

This goal was included in the FY 2007 PART of the Intramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-4.5.1	**By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.**

BACKGROUND

Prevalence/Incidence

The human immunodeficiency virus/acquired immune deficiency syndrome HIV/AIDS epidemic has killed more than 25 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. In 2005, an estimated 40.3 million of the world's population, including 2.3 million children younger than 15 years of age were living with HIV/AIDS. In addition, over 3 million people died from AIDS in 2005, and approximately 5 million people were newly infected with HIV, of which 700,000 were children. The number of people living with HIV/AIDS has seen the steepest increases in East Asia, Eastern Europe and Central Asia. Although in the United States new infections have remained relatively stable at approximately 40,000 per year, the proportion of new HIV infections that occur among women and racial and ethnic minorities continues to rise.

Disease Burden

The impact of the AIDS pandemic on developing nations is profound. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. The AIDS pandemic is affecting the military capabilities of some countries, as well as international peacekeeping forces. In Africa, the epicenter of the pandemic, AIDS is sabotaging economic development, leading to famine and massive social breakdown, and creating a generation of orphans.

Rationale

NIH supports a comprehensive therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its associated illnesses. Basic research on HIV continues to provide a strong foundation for the identification of new viral and cellular targets, as well as the design and development of better antiretroviral drugs and treatment regimens. Groundbreaking NIH-sponsored structural biology research has provided important insight into key viral proteins and enzymes and has been translated into the design of lead compounds with specific anti-HIV activity.

Building on the successful demonstration in 1996 that highly active antiretroviral therapy (HAART), including a protease inhibitor (PI) and two other antiretroviral (ARV) drugs, results in significantly decreased viral load and increased CD4+ cell numbers, as an indicator of intact immune function, NIH-supported studies have continued to define treatment regimens that slow disease progression. These powerful drug combinations have resulted in a decline in the incidence of new AIDS cases and HIV-related death rates. Since 1996, several new classes of ARVs, including fusion inhibitors, PIs, and nucleotide analogs, have been developed and shown to be safe and efficacious. Although these multiple drug combinations can successfully reduce viral load and restore immune responses in many HIV-infected individuals, metabolic and morphologic complications associated with these treatment

regimens present significant morbidity and mortality, thus warranting additional investigation.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH-supported clinical trial networks, with over 100 United States and international sites at major medical centers, academic institutions, and community-based clinics, conduct Phase I, II, and III clinical studies designed to evaluate the safety and efficacy of drug regimens to treat and control HIV disease among adults, adolescents, and children as well as to prevent mother-to-child transmission (MTCT) of HIV. The standards of care for the treatment of HIV infection and its associated illnesses in the United States and Western Europe are based on important clinical findings from NIH-sponsored clinical trials.

HIV therapeutics research entails the development of drugs and drug regimens to target HIV infection; prevent MTCT; and prevent and treat the various opportunistic infections, co-infections, cancers, and other clinical manifestations associated with HIV disease. In the area of anti-HIV drugs, NIH will continue to participate in the development of a minimum of three new anti-HIV compounds from existing and new classes of antiretrovirals, including agents that interfere with the viral life cycle or host-cell responses to viral infection.

All HIV/AIDS clinical trials research networks funded by the National Institutes of Health are being restructured; awards for the new Leadership for HIV/AIDS Clinical Trials Networks were made in FY 2006 and the awards for Clinical Trials Units will be made in FY 2007. The new structure is designed to improve the coordination, collaboration, efficiency, and flexibility of the research networks in order to address continuing research challenges worldwide across therapeutic, vaccine, and prevention research. Newly established networks will continue to pursue research of anti-HIV therapies (including studies of therapeutic vaccines) and/or anti-HIV multidrug regimens to identify treatment modalities with increased efficacy, diminished toxicity and side effects, improved bioavailability, minimal development of drug resistance, that thereby facilitate compliance. In addition, the NIH also funds a Pediatric and Maternal International and Domestic HIV Clinical Trials Network and an Adolescent HIV Trials Network that will continue to collaboratively develop and conduct studies with the NIH-funded Leadership and Networks as well as other international networks such as the Paediatric European Network for Treatment of AIDS. Research on HIV co-infections such as hepatitis C virus, hepatitis B virus, tuberculosis, cancers, neurological disorders, and organ-specific complications, will continue to be pursued, often in collaboration with other NIH partners and agencies.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Increase the ability of resource-poor countries to conduct clinical trials for the treatment and prevention of HIV disease by providing training and capacity building at 4 sites.	(FY02) 12 AACTG sites and 10 PACTG sites.	◆					
FY03	*Actual Performance:* (MET) Sites in resource-poor countries are better able to conduct HIV clinical trials as a result of training.						
Participate in the development of two agents for the prevention or treatment of HIV-associated manifestations, such as co-infections, opportunistic infections, cancers, neurological disorders, or organ-specific complications.	(FY03) 23 approved antiretroviral drugs exist for HIV infection treatment.		◆[e]				
FY04	*Actual Performance:* (MET) NIH has supported studies to develop treatments for three HIV-associated manifestations, hepatitis C virus (HCV), Cryptococcal meningitis (CM) and central nervous system (CNS)-associated neurological disease in individuals with HIV.						
Initiate clinical trials of new anti-HIV drugs and/or anti-HIV multidrug regimens in U.S. and international clinical trial sites.	(FY03) Clinical trials for the next generation of fusion inhibitors and lead compounds representing integrase inhibitors are being completed			◆			
FY05	*Actual Performance:* (MET) NIH initiated 1 clinical trial of a new anti-HIV drug and 4 trials of anti-HIV drug regimens.						
Evaluate interventions to reduce mother to child transmission (MTCT) of HIV and assess the impact of these interventions on future treatment options for women and children.	(FY04) Antiretroviral therapy has dramatically reduced MTCT in the developed world; many developing countries are implementing preventive MTCT programs using nevirapine and other antiretroviral regimens.				◆		
FY06	*Actual Performance:* (MET) NIH completed 1 study of viral resistance in infants, 2 studies to determine antiretroviral dosing levels in pregnant women and 1 perinatal intervention study.						
Achieve goal of evaluating the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.	FY 2003 to FY 2006 results					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. In FY 2006, NIH completed one study of viral resistance, two studies of antiretroviral dosing regimens in pregnant women and one perinatal intervention study through the Pediatric AIDS Clinical Trials Group (PACTG) and International and Domestic Pediatric and Maternal HIV Clinical Trials Network. Additionally in FY 2006, NIH initiated three studies that examined treatment options for women and children after exposure to antiretroviral agents through the NIH-sponsored Adult AIDS Clinical Trials Group (AACTG) and PACTG.

The four studies completed in FY 2006 include:

• A study (PACTG 1030) that examined the extent to which NNRTI drug resistant HIV variants become permanently archived in long-lived viral reservoirs in infants. (The infants received the NNRTI drug resistant HIV variants from their mothers via vertical transmission or developed them during nevirapine prophylaxis to prevent MTCT.) These findings suggest that mutations resistant to NNRTIs may remain archived and retrievable for prolonged periods of time in infants despite viral suppression resulting from their own treatment with

non-NNRTI containing regimens.
• Two studies (PACTG 394, PACTG 1026s) examined antiretroviral dosing in pregnant women. One study examined Tenofovir disoproxil fumarate (TDF) levels and the other examined levels of LPV/r in pregnant women. The data from the studies support increasing the dose of antiretrovirals such as: TDF, administered in single-dose to pregnant women in labor and LPV/r administered in a continuous regimen twice daily in pregnant women from the third trimester through labor. The increased dose of both drugs resulted in a favorable safety profile and concentrations in cord blood showed antiretroviral activity. However, because the dose of TDF used resulted in suboptimal drug exposure in pregnant women in labor; even higher doses of TDF should be studied.
• An investigator-initiated perinatal intervention study conducted in Botswana, the Mashi Trial, was completed and published in FY 2006. This study demonstrated that when antenatal short course zidovudine (ZDV) is given to the mother and the infant and infants receive single-dose NVP at birth, the maternal single-dose NVP may not be required; omission of the maternal dose would remove the risk of development of NVP resistance in the mother following single-dose NVP. Additionally, the study demonstrated that breastfeeding with infant ZDV prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but was associated with a lower mortality rate at seven months. Both strategies had comparable HIV-free survival at 18 months; these results demonstrate the risk of formula feeding to infants in sub-Saharan Africa, and the need for studies of alternative strategies.

Implementation Strategy Advances or Other Highlights
NIH supports the HIV/Opportunistic Infections (OI) Therapeutics Database of 135,000 compounds and testing data for potential inhibitors of: HIV, HIV-associated OIs, and several other viruses of medical importance. It also sponsors the Cell/HIV Protein Interaction Database, which catalogues host-cellular proteins known to interact with HIV proteins during viral gene expression and replication. During the past year, 1,571 new entries were added to the database. The database now has over 2,868 unique HIV-1-to-human host protein interactions that can be used to elucidate molecular mechanisms of HIV infection and virus-host interactions relevant to the discovery of antiretroviral drugs and the development of HIV vaccine candidates.

The two regulatory proteins of HIV, Rev and Tat, and their mechanisms of action, represent targets of high priority for the development of new therapeutic drugs to treat HIV infection and AIDS. During the past year, 440 compounds from governmental sources and 4,808 from private sector sources were screened for activity against Rev and its interaction with Rev Response Element (RRE), a component of viral RNA that binds to Rev and is essential for RNA transport, or Tat and its interaction with TAR, a component of viral RNA, that along with Tat is essential for HIV transcription. Twelve compounds exhibited the ability to inhibit Tat/TAR interactions, while 13 were capable of blocking Rev/RRE interactions. These lead compounds are undergoing additional testing.

In addition, NIH is continuing to evaluate a new drug candidate that appears effective against both actively-dividing and slow-growing Mycobacterium tuberculosis (M.Tb) and may help shorten the time needed to treat tuberculosis. Tuberculosis is a major co-infection with HIV. Approximately, 24 additional clinical studies are underway to evaluate treatments for HIV-related conditions, metabolic complications of HIV disease, and co-infection with hepatitis C

virus.

During FY 2006, the NIH also funded the leadership group awards for the six newly formed AIDS clinical trials networks. The clinical trials units and clinical research sites that will carry out the proposed research of each network will be funded in the first quarter of FY 2007. The networks that will address adult, adolescent and pediatric therapeutic HIV research priorities include: the AIDS Clinical Trials Group (ACTG), which will focus primarily on translational research and treatment optimization; the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network focusing on prevention of mother to child transmission (MTCT), translational research and optimization of treatment for children and adolescents; and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), which will focus on strategies to optimize HIV treatment.

The International and Domestic Pediatric and Maternal HIV Clinical Trials Network continues to collaborate in pediatric and women-specific clinical trials with the IMPAACT and ACTG, and it will be recompeted in FY 2007. The Adolescent Trials Network for HIV/AIDS Interventions (ATN) was funded by NIH for its second five-year project period in FY 2006. The research agenda of the ATN falls into three primary areas: therapeutics, behavior, and community prevention. The primary mission of the ATN is to conduct research to explore promising behavioral, microbicidal, prophylactic, therapeutic and vaccine modalities in HIV-infected and at –risk adolescents. ATN research is conducted independently and in collaboration with the existing research networks such as IMPAACT. The ATN also has started joint development of a microbicide study in adolescents with the newly-funded Microbicide Trials Network.

PART

This goal was included in the FY 2005 PART of the HIV/AIDS Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-4.5.4	**By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.**

BACKGROUND

Disease Burden

Diseases of the nervous system—stroke, trauma, drug addiction, alcoholism, autism, unipolar major depression, epilepsy, Parkinson's disease (PD), schizophrenia, multiple sclerosis, chronic pain, and hundreds more—collectively constitute one of the largest disease burdens in terms of disability, economic costs, personal tragedy, and death.

Rationale

This goal addresses the shortage of new drugs emanating from the private sector that target the nervous system, including those for low-prevalence 'orphan' diseases, many of which are neurological. Translation of basic research discoveries into new therapeutics is not occurring at the rate expected by the public or the private sector. This goal aims to speed this translation by expanding the role of the public sector in therapeutics development and engaging the public sector in the early stages of drug discovery.

Recent advances in understanding the nervous system and the completion of the Human Genome Project have provided an enormous cache of new biology to be studied and potential new drug targets to be investigated. Carefully designed small molecules can be powerful modulators of gene function; this principle underlies their use as basic research tools and as pharmaceuticals. The objectives of this goal are to (1) identify research tools and candidate therapeutics among currently available small molecules and (2) make new small molecules available to the public sector to further stimulate basic research and drug discovery.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH created a publicly available physical repository of select bioactive compounds to facilitate access and evaluation for therapeutic potential, diagnostic use, or use as research tools in neurobiological and other research. The number of compounds is sufficient to yield multiple hits in most assays (tests), yet is small enough to be utilized without robotic equipment, making the collection broadly and immediately useful to investigators in both academia and industry. This project involved identifying candidate compounds; evaluating the quality of the existing data for candidate compounds; creating a database of the chemical, pharmacological, and toxicological properties of selected existing compounds; and creating physical repositories of selected compounds and drugs for use in neurobiological and other research.

Utilizing High-Throughput Screening (HTS) approaches, NIH is identifying potential research tools and drug leads for neurological disorders. Activities include screening at least three neurodegenerative disease assays per year with a set of 100,000 compounds at the HTS Facility for Neurodegenerative Disease; developing a cost-effective, high-throughput behavioral screen to identify molecules with promise for treating alcohol abuse and

dependence; and completing the screening of four novel chemical libraries with a total of more than 80,000 compounds for activity at D1 dopamine receptors to develop a selective D1-dopamine receptor agonist as a potential treatment for cocaine addiction.

Through the Anticonvulsant Screening Project (ASP), a public-private partnership, small molecules are identified that can be used for potential anticonvulsant treatments, including drug-resistant epilepsy and epileptogenesis. This program will need to enroll new industrial and/or academic suppliers of small molecules with potential anticonvulsant activity and test additional compounds to identify potential drug development leads.

A contract-based approach has been explored as a new paradigm for accelerated funding and milestone-driven management for therapy development in rare diseases. A project focused on spinal muscular atrophy (SMA) was initiated in FY 2003, and calls for research proposals to be issued in accordance with a 4-year research plan that addresses all preclinical aspects of therapeutics development. FY 2004 Request for Proposals were issued to establish three centralized facilities: one focuses on compound development, the second tests compounds in cell-based models, and the third tests promising compounds that emerged from cell-based assays in mouse models of SMA. Compounds that prove to be safe and effective in models of SMA eventually may be tested in SMA patients in controlled clinical trials.

Tremendous opportunities exist for the application of positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in studies of the pathophysiology and treatment of brain disorders, but relatively few radioligands are currently available for functional imaging of target molecules implicated in normal brain function and aging and in brain and behavioral disorders. NIH is stimulating collaborations with industry and academia to create novel radioligands for PET and SPECT imaging in the human brain. This initiative is intended to facilitate the development of (1) PET and SPECT probes for molecular targets that are of broad interest to the neuroscience research community, and (2) new technologies for radiotracer development.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	(FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	◆					
FY03	*Actual Performance:* (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.						
Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	(FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened		◆				
FY04	*Actual Performance:* (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.						
Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	(FY03) Known bioactive compounds require further evaluation of activity and improved availability			◆			
FY05	*Actual Performance:* (MET) Compounds selected based on evaluation of properties; collection assembled for public use.						
Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	(FY04) SMA program established; 3 promising compounds identified in screens; SMA mouse models available				◆		
FY06	*Actual Performance:* (MET) Three promising compounds, trichostatin A and two indoprofen analogs, were tested in SMA mouse models.						
Complete goal of identifying 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	(FY06) Compounds identified in screens and advanced to various stages of preclinical development					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. In FY 2006, two NIH-supported research teams tested whether small molecules identified in cell-based screens for SMA drugs had therapeutic effects in mouse models. Researchers in the NIH intramural program showed promising results for the HDAC inhibitor trichostatin A (TSA). Repeated doses of TSA increased the amount of protein and RNA produced by the SMN gene, the gene affected in SMA. In addition, the drug extended survival of the SMA mice significantly and improved their body weight and motor functions. The researchers will go on to explore the relationship between the molecular and physiological effects and test whether other compounds from the HDAC family may be even more effective. In a separate effort, SMA Project investigators tested two other compounds, both indoprofen analogs, in SMA mouse models. These drugs did not increase survival of the mice, but recent insights into indoprofen's mechanism of action suggest that these mice may not be suitable models for assessing the physiological effects of indoprofen-based drugs. Studies are now underway to determine whether these drugs may nevertheless have positive effects in the mice at a molecular level, increasing the levels of SMN protein and RNA. The SMA Project has also begun optimizing the HDAC inhibitor phenylbutyrate and plans to test improved analogs of that molecule in animal models.

The NIH is on track to meet the overall goal by the end of FY 2007. Three potential drugs have completed preclinical testing and are undergoing evaluation in clinical trials: ceftriaxone (to treat amyotrophic lateral sclerosis or ALS), ICA-69673 (to treat seizures), and YPK3089 (to treat anxiety). Two imaging agents for visualizing amyloid plaques, a characteristic feature of Alzheimer's disease, have also entered clinical stages of development. Dozens of compounds have met various preclinical milestones, including demonstration of efficacy in animal models, toxicity testing, and chemical optimization. Examples are provided in the following section.

Implementation Strategy Advances or Other Highlights

Progress has been made in small molecule screening. Researchers have identified several new molecules that interact with various neurotransmitter systems and are developing a subset into new PET and/or SPECT imaging agents. The Psychoactive Drug Screening Program and Treatment Units for Research on Neurocognition and Schizophrenia continue to identify many novel ligands. The Small Molecule Repository has built a collection of 100,000 small molecules for screening against a variety of targets to identify novel chemical probes.

NIH-supported investigators published several notable studies this year demonstrating the effectiveness of small molecule drugs in animal models of nervous system disorders. Researchers showed that eight compounds that target neuronal signaling receptors affected alcohol consumption, seeking, or tolerance in rodent models of alcohol drinking and dependence. The drug 7-OH-DPAT stimulated the development of new neurons and improved motor functions in a rat model of Parkinson’s disease. A new class of nicotine analogs decreased the rewarding effects of dopamine release and may aid smoking cessation programs in humans. Galantamine, a drug already FDA-approved for treatment of Alzheimer’s disease, protected guinea pigs from lethal doses of nerve agents and insecticides. Middle-aged rats treated with ampakine drugs showed changes in brain chemistry associated with the reversal of age-related memory loss. A previously developed cannabinoid receptor antagonist may be useful in human obesity research and treatment. These “proof-of-principle” studies are a crucial step toward the development of treatments for patients.

NIH programs continue to provide preclinical drug development support to advance small molecules toward clinical testing. In 2006, the Anticonvulsant Screening Program (ASP) attracted eleven new compound suppliers. The ASP screened several hundred molecules in assays for epilepsy and related disorders. Three molecules advanced through the ASP full screens and two will enter industry toxicology studies. The NIH also expanded ASP to address chemically-induced seizures as part of a larger NIH effort to develop medical countermeasures for chemicals that could be used in a terrorist attack. The Toxicological Evaluation of Novel Ligands Program and Chemical Synthesis and Drug Supply Program advanced a number of new compounds toward clinical testing.

SRO-4.5.5	By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings.

BACKGROUND

Prevalence/Incidence

Drug abuse and addiction, including alcoholism are complex public health problems that impact society at multiple levels. In 2005, approximately 68 million Americans were current users of an illicit drug or cigarettes. (Substance Abuse and Mental Health Services Administration [2006]. Results from the 2005 National Survey on Drug Use and Health: National Findings [Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194]. Rockville, MD.) Recent epidemiologic studies have shown that between 30 and 60 percent of drug abusers have concurrent mental health disorders, in addition to comorbid alcohol abuse. Despite the extensive prevalence of drug abuse and addiction, the lack of effective treatment for certain types of addictions or population groups, and the lack of utilization of those treatments known to be effective, continue to be substantial barriers to reducing the prevalence and impact of this major health problem.

Disease Burden

The estimated total cost of illicit drug abuse and nicotine addiction to our Nation is almost $524 billion a year, including health care expenditures, lost earnings, and costs associated with crime and accidents.(a) The health consequences of smoking: a report of the Surgeon General. [Atlanta, GA.]:Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Washington, D.C.:For sale by the Supt. of Docs., U.S. G.P.O., 2004. (b) Office of National Drug Control Policy (ONDCP). The President's National Drug Control Strategy 2004. Available at: http://www.whitehousedrugpolicy.gov/publications/policy/ndcs04/index.html. (c) Harwood H. Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Update Methods, and Data. Report prepared by The Lewin Group for the National Institute on Alcohol Abuse and Alcoholism, 2001. Based on estimates, analyses, and data reported in Harwood H, Fountain D, and Livermore G. The Economic Costs of Alcohol and Drug Abuse in the United States, 1992. Report prepared for the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Department of Health and Human Services, NIH Publication No. 98-4327, Rockville, MD, National Institutes of Health, 1998. Drug addiction is a biologically-based illness that is influenced by genetic and environmental factors, and it is a chronic disease similar to Type II diabetes, cancer, and, cardiovascular disease. Furthermore, drug abuse is a major vector in the spread of infectious diseases such as HIV/AIDS, tuberculosis, and hepatitis C. Given all of these factors, one can begin to see the devastation that drugs can inflict on individuals, families, and communities.

Rationale

Although research has demonstrated that drug abuse treatment can be effective in reducing drug use and addiction, including alcoholism, few science-based interventions have been developed and tested widely within the health care field. The reasons for this are, in part,

related to cultural, financial, and institutional barriers. In an effort to narrow the drug abuse treatment gap, recent drug abuse treatment studies have focused on deploying interventions in the community. To move research forward in this arena, new drug abuse treatment approaches will be tested within community-based settings.

One important tool to treat substance abuse is behavioral treatment, which has been documented to be effective in improving drug abuse and drug addiction outcomes. Recent promising findings have been achieved by interventions that target specialized populations: minorities, adolescents, families, and women diagnosed with Post-Traumatic Stress Disorder (PTSD). Brief Strategic Family Therapy (BSFT) is a family-based intervention aimed at preventing and treating child and adolescent behavior problems, including substance abuse, in inner city, minority families. Seeking Safety is a cognitive-behavioral substance abuse intervention for women with a DSM-IV diagnosis of PTSD. This treatment intervention is tailored to concurrently address the co-morbidity issues associated with substance abuse and trauma. Another behavioral approach, known as Motivational Enhancement Treatment (MET), which is based on the principles of motivational psychology, has been shown to be effective in improving treatment engagement, retention, and outcome for many substance abusers. Incorporating MET into the standard entry process for drug abuse treatment will likely enhance treatment participation.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In order for NIH to be successful in achieving this goal, a series of ambitious steps were planned. These steps included building the treatment research infrastructure necessary followed by recruitment of 1000 patients from specialized populations to participate in these research and community-based treatment approaches.

In FY 2004, NIH used the Clinical Trials Network to adapt and test drug abuse treatment approaches in an effort to more rapidly bring research-based treatments to communities. These drug abuse treatment interventions, BSFT and Seeking Safety, are designed to reach specialized populations that are frequently under-represented in drug and alcohol abuse research and are often underserved in drug and alcohol abuse treatment centers. Several other research-based treatments for alcoholism are being adapted and tested in community settings. Potentially these will contribute to treatments available to the community.

In FY 2005, drug and alcohol treatment providers were trained to deliver standardized behavioral treatment interventions of BSFT, Seeking Safety, and MET to patients within the framework of the clinical trials research design. Treatment providers were trained to maintain data on patient's symptoms, behavior, and drug use to determine clinical and research outcomes. To ensure treatment protocol adherence, treatment providers were videotaped, supervised, and monitored. Also during FY 2005, outcome data for patients were collected at regular intervals on substance abuse, risk behaviors, and comorbid psychiatric symptoms to determine the overall treatment effects of the evidence-based interventions.

During FY 2006, recruitment of more than 1000 patients was completed for participation in BSFT, Seeking Safety, or MET treatment protocols.

During FY 2007 the investigators from MET and Seeking Safety will submit the results of their studies for publication in peer-reviewed scientific journals. In collaboration with others within the Clinical Trials Network, investigators and clinicians will conduct lectures, materials and training sessions to share the results of the trials, and to discuss ways to best implement successful treatments in a variety of settings. The BSFT trial is expected to finish patient enrollment in early 2007, and a year-long follow-up of patients will be conducted.

During FY 2008, the investigators from MET and Seeking Safety will work with the Clinical Trials Network and NIH to determine if more specialized materials should be prepared for wider distribution. The investigator/clinical team working on BSFT will analyze their data, present results to the Clinical Trials Network, and submit their findings for publication in peer-reviewed scientific journals. Depending on the results of the trial, they will work with colleagues to prepare dissemination materials for the wider Clinical Trials Network.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	(FY03) No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations		◆e				
FY04	*Actual Performance:* (MET) Three treatments have been adapted for community-based settings.						
Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	(FY03) Fewer than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings			◆e			
FY05	*Actual Performance:* (MET) The Clinical Trials Network has trained 184 providers (94 more than planned) in BSFT, MET, or Seeking Safety, which are being tested in community settings.						
Recruitment will be completed of approximately 1000 patients from specialized populations to test the efficacy of community-based treatments.	(FY04) Enrollment of subjects for Seeking Safety, BSFT, and MET was initiated.				◆e		
FY06	*Actual Performance:* (MET) The Clinical Trials Network has enrolled more than 1,200 patients in BSFT, MET, and Seeking Safety interventions which are being tested in community settings. Treatments are being delivered to diverse communities that are 20%, 34%, and 41% African American, respectively, and 43%, 7%, and 14% Hispanic, respectively.						
Analyze data from completed behavioral protocols and report initial findings from data analysis.	(FY05) Providers trained, subjects being recruited for intervention.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Complete development and testing of two new evidence-based treatment approaches for drug abuse in community settings.	To be determined by FY07 results.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A total of 1,274 (274 more than the target of approximately 1,000) patients were recruited into protocols testing community-based treatments. Specifically, the Seeking Safety protocol recruited 353 patients and the MET protocol

recruited 496 patients. Patient recruitment for these protocols is complete. The BSFT protocol has recruited 425 patients, and recruitment will be completed by Spring 2007. The populations served include adolescents at high risk for drug addiction and their families, abused women, as well as members of minority groups. The patients involved in the three protocols may be described as follows:

Female 46%
Abused Women 28%
African American 32%
Multi-race 8%
Hispanic 22%
Under Age 18 33%

Efficiency

A total of 1,274 patients - 274 more than planned - were recruited into protocols testing community-based treatments. This efficiency was achieved due to extensive efforts by the study teams to closely monitor recruitment and assist the Community Treatment Programs with strategies to reach out to potential patients in specialized populations that can be difficult to recruit. Strategies included advertising, speaking with individual practitioners, and educating staff at the community practices about the studies and the goals of the research. Brochures that described the research and answered basic questions were produced and kept at each site. The study teams and the community practitioners held weekly calls to discuss the study and brain-storm ideas on how best to enroll subjects. Each study team shared experiences among its sites to ensure that best practices for one site could be implemented if a site was having difficulties.

SRO-5.2	By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).

BACKGROUND

Disease Burden

Lupus is a disorder of the immune system known as an autoimmune disease. In autoimmune diseases, the body harms its own healthy cells and tissues, leading to inflammation and damage to various body tissues. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have many different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

Lupus is a complex disease whose cause is unknown. It is likely that there is no single cause but rather a combination of genetic, environmental, and possibly hormonal factors that works together to cause the disease. Scientists are making progress in understanding the processes leading to lupus. Lupus is three times more common among African American women than among Caucasian American women and is also more common in women of Hispanic, Asian, and Native American descent. Age at disease onset is a predictor of outcome, and children often have severe end organ disease. At present, there is no cure for lupus. Lupus is the focus of intense research as scientists try to determine what causes the disease and how it can best be treated.

Rationale

Atherosclerosis is a thickening of the inside walls of arteries that is caused by the gradual buildup of fatty substances in arteries. This thickening narrows the space through which blood can flow and can result in heart attacks or strokes. Atherosclerosis usually occurs when a person has high levels of cholesterol (a fat-like substance), which can build up on the walls of arteries. Women and children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis. The data on cardiovascular and lipid abnormalities in children with lupus implicate atherosclerosis as an important potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease (CVD). Statins not only decrease mortality and morbidity from coronary artery disease in adults, but also have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A five-year study, known as the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythymatosus) trial, plans to test children diagnosed with systemic lupus erythematosus (SLE, or lupus). The double-blind, placebo-controlled trial randomizes patients to receive either statins or a placebo for 36 months. Atherosclerosis is measured at baseline and at six-month intervals using ultrasound imaging.

This is a unique study designed to investigate a clinically challenging disease: the occurrence of atherosclerosis in children with lupus. The study is designed to test the efficacy of statins (cholesterol-lowering agents) in delaying the progression of atherosclerotic arterial thickening in children with lupus. Not only do statins decrease mortality and morbidity from coronary artery disease in adults, but they also have intrinsic anti-inflammatory properties, which may be especially beneficial in lupus.

This is a multi-center, prospective, randomized, double-blind intervention study for children with lupus, and involves 20 centers from the Childhood Arthritis and Rheumatology Research Alliance (formerly the Pediatric Rheumatology Research Network). Initial plans included enrollment of a total of 280 children with recent-onset lupus, thereby establishing the largest cohort of pediatric lupus patients ever prospectively studied in the United States. There is limited information regarding the overall compliance with study medication in children and adolescents in clinical trials of long duration for chronic diseases. Compliance with study medication is important to sustain low levels of blood lipid profiles and to diminish the likely inflammation associated with the progression of arterial wall thickening in atherosclerosis. The development of strategies to better track compliance will provide valuable insights into this and other clinical trial designs.

When a new clinical trial is initiated, a number of steps must be completed in launching the study. A key dimension is training staff members who will be involved in the conduct of the study in the sophisticated techniques that will be used. For APPLE, this included (1) complete training and full certification of sonographers who are involved in establishing the degree of atherosclerosis in the children participating in the study, and (2) training for the Interactive Voice Response System that is used for trial randomization and drug kit assignment, which takes advantage of novel and efficient technologies that improve trial conduct and cost-effectiveness.

Conducting additional related studies increases the value of a clinical trial, and the design of this trial includes the development of ancillary, mechanistic substudies to explore the processes that contribute to disease progression. These additional studies leverage the value of the investment made by NIH in terms of scientific knowledge, as well as improve the integration of translational research from this clinical trial. Baseline data analysis on enrolled patients were completed, including any adverse events. Data on monitoring study progress and adverse events are routinely provided from the clinical sites to NIH.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	(FY02) Standard operating procedures are being completed but training not yet done	◆					
FY03	*Actual Performance:* (MET) Training of all appointed sonographers has been completed.						
Launch patient enrollment in at least 10 of the 20 planned sites.	(FY03) Protocol for patient enrollment established		◆				
FY04	*Actual Performance:* (MET) There are currently 16 sites actively recruiting patients into the study.						
Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	(FY03) One ancillary study approved to assess the effect of statins on blood cells			◆			
FY05	*Actual Performance:* (MET) The ancillary studies are underway. One example is a study that explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus in pediatric patients.						
Complete baseline data analysis on the enrolled patients, including any adverse events.	(FY04) 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events				◆[e]		
FY06	*Actual Performance:* (MET) Baseline characteristics of the study population as of August 2006 have been analyzed and the results were shared with the Study Data and Safety Monitoring Board.						
All clinical sites will be actively enrolling/following pediatric lupus patients, to result in an overall average recruitment rate of 3 new patients per month.	(FY06) Number of Clinical Sites: 20					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Implement two strategies to attain study medication compliance rate of at least 80 percent.	(FY06) Previous research suggests that compliance among pediatric patients receiving treatment for chronic illness can be as high as 70% due in part to factors such as family support and severity of symptoms						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. Results of baseline measurements of cardiovascular health (e.g., arterial wall thickness, blood chemistry analysis including blood lipid profiles) have been analyzed for participants who were enrolled as of August 2006. The analysis--which also included the number, distribution, and severity of adverse events (e.g., medical complications leading to hospitalization, such as worsening of lupus nephritis, acute abdominal pain, severe headaches, or fever)--was shared with the Study Data and Safety Monitoring Board (DSMB) in September 2006. Distribution between treatment groups is on target, and safety monitoring has continued as planned. A procedure to re-certify sonographers has been implemented and is ongoing in all sites according to a specified schedule.

Implementation Strategy Advances or Other Highlights

Ancillary studies are underway to leverage the investment of the APPLE trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus. One ancillary study explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus. Specifically, researchers are investigating plasma nitric oxide metabolite levels and expression of nitric oxide 2 and 3 (NOS2 and

NOS3) in endothelial cells. Nitric oxide is an important molecule that mediates many vascular and inflammatory processes that participate in tissue damage in lupus. Institutional Review Board approval for the ancillary studies has been obtained or is in progress in 15 participating sites. Sample collection is underway at six sites.

Efficiency

Retention rates have been excellent, with only three percent of patients permanently discontinued from the study. Interim analysis of the data revealed that repeated measurements of fat buildup in the blood vessels varied less than researchers had expected (when they initially estimated the number of participants that would be needed to obtain a statistically meaningful result). Because this greater precision leads to a smaller standard error for statistical analyses, the investigators were able to decrease the sample size from 280 to 220 and complete recruitment ahead of schedule.

SRO-5.3	**By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.**

BACKGROUND

Rationale

The Nation is facing a pressing need for new drugs. Many existing medicines are becoming ineffective due to antibiotic resistance. In other cases, the side effects of existing drugs are as severe as the diseases they are designed to treat. Most drugs are discovered by randomly screening thousands of chemical compounds for desired biological effects. To speed the discovery of new medicines, scientists need to have access to larger collections of chemicals to test. One approach is to increase the efficiency of isolating and screening natural products. Another especially promising approach to invigorating and strengthening the new drug pipeline is by using a new and powerful chemical strategy called diversity-oriented synthesis. This method can quickly generate a large number of potential drug compounds (a 'chemical library'). Such a library could contain anywhere from a few chemical compounds to millions and can be designed to include either related versions of a single molecule or a wide variety of completely new chemical structures. This new technique offers unprecedented opportunities for the discovery of molecules that may be developed into lifesaving drugs more efficiently.

Since diversity-oriented synthesis is such a new and intellectually challenging endeavor, the number of methods for designing, making, and analyzing chemical libraries is still limited. This restricts the variety of structures that chemists can make. Although the pharmaceutical industry has embraced chemical library screening as a useful drug discovery strategy, it has not invested in the long-term research needed to improve the technique. Similarly, few academic scientists have made a special effort to develop chemical library-related methods. The investment will likely enrich the field of diversity-oriented synthesis and give pharmaceutical scientists important tools for discovery of molecules that show promise as future medicines.

NIH funding is leading to the discovery of new chemical library methods, which in turn will enhance the range and quality of chemical compounds available for drug discovery. Rapid and efficient biological screening of improved chemical libraries may speed the discovery of new medicines.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A total of four Centers of Excellence in Chemical Methodologies and Library Development have been established and five new multi-institutional "Groups" and seven planning grants were funded to develop natural products drug discovery programs under the International Cooperative Biodiversity Groups Program. In FY 2004 and beyond, these centers and "Groups," as well as new initiatives to be supported through the NIH Molecular Libraries

and Molecular Imaging Roadmap, will focus on (1) developing innovative methods of synthesis and library creation; (2) increasing the sharing of knowledge among researchers, (3) increasing access to research results by exploring and developing systematic means to inventory newly created chemical libraries and methods of synthesis, (4) biologically screening the libraries and inventorying the outcomes of these screening procedures as new libraries are created, and (5) coordinating and setting priorities for these initiatives through the use of scientific advisory groups.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	(FY02) Prior to FY 2003, only two centers existed.	◆					
FY03	*Actual Performance:* (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.						
Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.	(FY03) High throughput methods for making chemical libraries for drug development are limited.		◆[e]				
FY04	*Actual Performance:* (MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.						
Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	(FY03) CMLD centers are currently being established; screening of their libraries has not yet begun.			◆			
FY05	*Actual Performance:* (MET) Support for CMLD centers provides facilities to validate new methodologies used to synthesize chemical libraries. These new methods are being made available to the scientific community.						
Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	(FY03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs.				◆		
FY06	*Actual Performance:* (MET) Supported the development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).						
Begin development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds.	(FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Use chemical libraries in high-throughput biological screens.	(FY06) CMLD libraries under development.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. NIH supported the development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products). Until the latter part of the 20th century, nature generally was regarded as the most prolific source of bioactive small-molecules. Most of the 877 small-molecule new chemical

entities introduced as drugs worldwide during 1981–2002 can be traced to or were inspired by natural products. However, over the past 10-15 years, scientists have turned away from natural products chemistry. Instead, high-throughput chemical synthesis is now the predominant source of structurally diverse molecules. The reasons for this paradigm shift are largely economic. Natural products chemistry (i.e., isolation, purification, and structure elucidation) is labor-intensive and time-consuming and is not easily adapted to a high-throughput format. Also, bioactive natural products may not be readily available in substantial quantities (from natural sources or by chemical synthesis), as would be needed for drug manufacturing or even for investigational studies. The FY 2006 target for this GPRA goal was to stimulate the development of a new generation of methods for natural products chemistry, and in doing so, to reinvigorate the investigation of nature as a prolific source of small molecules with the potential to interact with all of the proteins that participate in cellular process in health and disease.

Implementation Strategy Advances or Other Highlights

In the early 1990s, pioneering advances were made in strategies and methods for diversity-oriented synthesis. Using these processes, sets of compounds ("chemical libraries") are generated simultaneously in a predictable fashion by using techniques that involve parallel chemical reactions. When subjected to high-throughput biological screening, chemical libraries offer unprecedented opportunities for more rapid identification of small molecules with significant and unique physiological effects that show promise as the foundation for future medicines. The strategy for reaching this GPRA goal is to support researchers who will develop platform technologies to help determine protein structure and that will be essential for high-throughput screening of chemical libraries.

As part of this implementation strategy for FY 2006, the Roadmap Small Molecule Repository became functional and began supplying the Roadmap Molecular Libraries Screening Centers with molecules to screen. In addition, new methodologies for isolation and identification of new, bioactive compounds from nature have begun. A total of seven International Cooperative Biodiversity Groups are creating both physical and virtual natural product chemical libraries of plants, marine invertebrates, marine and terrestrial microorganisms, and endophytic fungi. Isolated chemical compounds and extracts from these libraries are being screened in a wide range of bioassays representing multiple therapeutic areas. Novel bioactive compounds have been isolated, some of which are moving into animal testing. Groups are also experimenting with new methodologies in collection, pre-fractionation, and screening.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-5.6	**By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.**

BACKGROUND

Tobacco use in the United States is a major cause of death and disability. Approximately 440,000 deaths in the U.S. each year are attributed to cigarette smoking. (The Health Consequences of Smoking: A Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.) The high failure rate reported for smoking cessation efforts (75-90%) challenges health care professionals to explore innovative approaches to treating the highly addictive behavior of tobacco use.

The agent largely responsible for maintaining tobacco addiction is nicotine. In addition to animal studies that have shown the addictive properties of nicotine, studies in humans show that smokers adjust their smoking behavior to maintain a relatively stable concentration of nicotine and that the reinforcing effects of nicotine are blocked by pretreatment with the nicotinic receptor antagonist, mecamylamine. Nicotine addiction perpetuates itself by enhancing the release of multiple neurotransmitters to produce stimulation, pleasure, and reward. Tolerance to elevated nicotine levels develops over time, as does the dependence upon nicotine to maintain brain function. Withdrawal symptoms after abstinence result from a return to subnormal levels of some of these neurotransmitters. Withdrawal symptoms, such as depressed mood, anxiety, insomnia, irritability, difficulty concentrating, increased appetite, and decreased heart rate, usually peak at one week after abstinence and taper off over time.

Besides behavioral interventions, the Public Health Service Consensus Panel on Clinical Practices Guidelines has recommended two primary types of pharmacotherapies for treating tobacco use and addiction: nicotine replacement therapy (NRT) with nicotine gum, patch, inhaler, or nasal spray; and bupropion sustained release (SR). NRT works by supplying an alternate source of nicotine that has a much slower rate of absorption than the nicotine found in cigarette smoke, hence reducing the potential for its abuse. Cessation rates for NRTs have been examined by meta analysis and are in the range of 17 to 31%. Bupropion SR (Zyban), an inhibitor of norepinephrine and dopamine reuptake, also interacts with nicotinic receptors, and has been approved by the FDA for use in both smoking cessation and treatment of depression (under the trade name Wellbutrin). Clinical trials suggest that bupropion SR may be more effective than NRT for smoking cessation. In a study that compared nicotine patch, bupropion, or bupropion plus patch to placebo control, the 12-month cessation rates were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group, and 35.5 percent in the group given both bupropion and the nicotine patch. New medications and approaches are clearly needed to help the large percentage of tobacco-addicted individuals who do not respond to currently available treatments.

Prevalence/Incidence

Forty years after the Surgeon General's first report on smoking and health, tobacco use continues to pose an enormous public health threat to the United States and the world. In 2004, the median prevalence rate of current cigarette smoking by adults among the different states comprising the United States was 24.9%. (Results from the 2004 National Survey on Drug Use and Health: National Findings [Office of Applied Studies, NSDUH Series H-28, DHHS Publication No. SMA 05-4062.] Substance Abuse and mental Health Services Administration. Rockville, MD. [2005].) This prevalence rate is more than double the nation's year 2010 Healthy People goal of achieving a 12 percent prevalence rate. The prevalence rates among some adult minority population groups is nearly four times the desired rate, and prevalence rates for youth are also very high.

Disease Burden

Cigarette smoking causes approximately 440,000 deaths annually in the United States, or more than 1,000 deaths per day. The annual economic cost attributable to tobacco use in the United States is approximately $157 billion.

Rationale

Tobacco addiction is a preventable cause of disease and death. Therefore, it is crucial that more effective treatments for this condition be developed. Despite almost two decades of tobacco treatment research, treatment options for tobacco addiction remain limited and only moderately effective.

Modifying existing compounds to increase their selectivity is one promising strategy for the development of new medications for smoking cessation. As mentioned previously, the nicotinic receptor antagonist mecamylamine has been shown to block the reinforcing effects of nicotine. Its use as a smoking cessation agent, however, is hampered by its peripherally mediated side effects, possibly due to its nonselective action at multiple nicotinic receptor subtypes. Therefore, the development of nicotinic receptor subtype selective antagonists may prove useful for treating tobacco addiction.

Another promising avenue for the development of novel medications is the development of a nicotine vaccine. By developing nicotine-specific antibodies that cannot cross the blood-brain barrier, this treatment would prevent nicotine from reaching the brain. In pre-clinical trials, a nicotine vaccine has been shown to reduce nicotine uptake in the brain, and to attenuate its behavioral and cardiovascular effects. In humans, such a vaccine might be an effective aid in smoking cessation and in reducing the time to relapse. Clinical trials are needed to determine the safety and efficacy of this human vaccine as a treatment for tobacco addiction.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Crucial knowledge gaps hinder the ability to treat tobacco addiction optimally. Basic, pre-clinical, and applied research is currently being conducted to identify new and better treatment options, including:

Pre-clinical approaches: To identify new compounds for potential use as smoking

cessation medications, several studies are being supported that use medicinal chemistry to modify existing compounds to increase their selectivity for their targets (e.g. selective nicotinic receptor antagonists) and to evaluate these compounds in animal models of nicotine self-administration, withdrawal, and nicotine-induced reinstatement (relapse prevention).

Clinical studies of a Nicotine Vaccine (NicVAX): Based on the results of earlier pre-clinical and clinical research, this project was designed as a proof of concept study to assess the safety, immunogenicity, and clinical efficacy of NicVAX among smokers. The assumption is that vaccination will reduce the reinforcing effects of nicotine and result in smoking cessation.

The nicotine vaccine trial will enroll approximately 200 subjects at 3 sites over a 2 year period. The primary measure of outcome will be four weeks of continuous smoking cessation within the 26-week period of the study.

Clinical trial of a Glycine Antagonist: This clinical trial will compare a novel glycine antagonist to bupropion or placebo for effectiveness in smoking relapse prevention. It will start with an 8-week, open smoking cessation intervention in adult smokers with nicotine replacement therapy (NRT) and a behavioral intervention. Those participants who demonstrate 7-day point prevalence abstinence after 7 weeks open label treatment with NRT will be eligible to enter the 8-week, double-blind, placebo-controlled, relapse prevention trial. The primary outcome measure will be smoking abstinence.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify 1-2 promising compounds as candidate medications for tobacco addiction.	(FY05) Current medications inadequate to address tobacco addiction.			◆			
FY05	*Actual Performance:* (MET) Four candidate medications, instead of two, have been identified for tobacco addiction, and research is continuing on these candidates.						
Begin at least one clinical trial of a candidate medication for tobacco addiction.	(FY05) NicVAX shows promise in pre-clinical or early clinical trials.				◆		
FY06	*Actual Performance:* (MET) Three candidate medications are being tested in: Phase II clinical trials, multi-site trials, and human laboratory studies.						
Develop and test 1-2 potential new compounds for tobacco addiction in animal models.	(FY06) Preclinical work on compounds that target nicotinic or GABA receptors is continuing based on preliminary positive results.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Analyze results from the FY 2006 clinical trial (Phase II) to determine whether an additional clinical trial should be initiated.	To be determined by results in FY06 and FY07.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and exceeded. The Phase II trial of a nicotine vaccine was started in FY 2006. The trial of oral selegiline was completed. A trial of selegiline patch was

started, and a multi-site trial was planned. A human laboratory study on tiagabine was started after successful completion of a pilot study.

Tobacco addiction is a preventable cause of disease and death, and clinical trials of identified candidate medications for smoking cessation is critical for improving public health. The candidate medications noted above all have the potential to aid in smoking cessation: a vaccine that is safe and effective could prevent nicotine from reaching the brain; selegiline acts by inhibiting an enzyme that contributes to the reinforcing effects of nicotine; and modulation of GABA indirectly affects the dopamine system – important for the addictive properties of nicotine and other drugs of abuse (tiagabine).

Implementation Strategy Advances or Other Highlights

The Phase II trial of the nicotine vaccine is a multi-center, randomized, double-blind, placebo-controlled study to assess efficacy in smokers who want to quit. The purpose is to determine whether vaccination with the medication will result in a higher continuous abstinence rate than without it.

Efficiency

Clinical trials and human lab studies are being conducted on three candidate medications, instead of the two planned, for tobacco addiction. These three medications will enable treatment via different systems/approaches: antibodies that will block nicotine effects – currently in a Phase II clinical trial; an inhibitor (selegiline) of an enzyme (MAO-B) that contributes to the reinforcing effects of nicotine – currently being tested in a patch formulation for improved delivery; and a GABA agonist (tiagabine) that should reduce nicotine's effects on the pleasure pathway – currently being tested as a proof of concept. It was not originally expected that the tiagabine pilot study would support further human lab studies. Results were, however, promising; therefore, the lab study is now planned. Efficiency in medication development is often achieved by having the resources and flexibility to respond to promising results, whether expected or not. These studies are moving forward on a timely basis, and because three separate mechanisms are being explored in these advanced trials, the likelihood is high for the development of at least one new pharmacotherapeutic approach to the single largest addictive public health problem.

SRO-5.6.2	**By 2011, assess the efficacy of at least three new treatment strategies to reduce cardiovascular morbidity/mortality in patients with type 2 diabetes and/or chronic kidney disease.**

BACKGROUND

Prevalence/Incidence

Diabetes and kidney disease are both increasing in prevalence and both diseases markedly increase the risk for life-threatening cardiovascular disease (CVD).

- In 2005, the prevalence of diabetes in the United States was approximately 20.8 million people, or 7 percent of the population, with approximately 90-95 percent of this number having type 2 diabetes.
- CVD accounts for two-thirds of deaths among people with diabetes.
- Chronic kidney disease is estimated to affect as many as 10 to 20 million Americans and can lead to kidney failure. While this estimate is used by advocacy groups, there is substantial uncertainty in the numbers. Unpublished internal NIH analyses suggest lower estimates for chronic kidney disease.
- The number of patients with kidney failure or end-stage renal disease (ESRD) has doubled over the past decade and now stands at nearly 400,000.
- Heart disease and stroke are the leading causes of death in patients with ESRD.

Disease Burden

The Nation faces national epidemics of both type 2 diabetes and ESRD. In 2002, the economic cost of diabetes in the United States was estimated at $132 billion. Once considered a disease of adults, type 2 diabetes now increasingly strikes during childhood. Rates of type 2 diabetes are approximately twice as high among African Americans and Hispanic Americans as among Caucasian Americans and are even higher among American Indians. Among adults with diabetes, heart disease death rates are two to four times higher than in the general population. Diabetes also negates the protection gender affords non-diabetic women. Even among individuals with impaired glucose tolerance, in which glucose levels are higher than normal but do not yet indicate diabetes, CVD death rates are elevated 1.4 fold. Chronic kidney disease is also a significant health burden. In its most severe forms, it leads to ESRD, in which either dialysis or kidney transplantation is required to maintain life. About half of new cases of ESRD are as a consequence of diabetes. The number of patients with ESRD has doubled over the past decade, with the increasing disease burden most pronounced among minority populations, especially African Americans and American Indians. The markedly reduced life expectancy of patients with ESRD is due largely to death from heart disease and stroke; rates of CVD are tenfold to a hundredfold greater than in the general population. Even among chronic kidney disease patients with a mild to moderate reduction in kidney function, CVD rates are increased twofold to fourfold. The cost of caring for the ESRD population was estimated at $18.1 billion dollars in 2003 and consumed about 7 percent of the Medicare budget. According to new data released by the NIDDK-supported United States Renal System, rates for new cases of kidney failure have stabilized after 20

years of five to ten percent annual increases; however, racial disparities in the rates of ESRD persist.

Rationale

For both diabetes and kidney disease, premature CVD is the major cause of death. This goal addresses a significant public health problem by seeking to evaluate approaches for reducing CVD outcomes, such as heart attacks and strokes, in patients with type 2 diabetes and/or chronic kidney disease. Application of the results of the trials, if favorable, would extend the lifespan and improve the quality of life for persons with type 2 diabetes or kidney disease.

Goal SRO-5.6.2 also addresses a critical knowledge gap. While some clues and some promising therapies have emerged from previous epidemiologic and clinical trials, many unanswered questions remain. For example:

- Recent clinical trials established the benefit of the management of both blood pressure and low-density lipoprotein-cholesterol (LDL) in reducing CVD risk in type 2 diabetes and of glucose control in reducing CVD risk in type 1 diabetes, but a number of potential strategies to reduce CVD risk require further study.
- Although even moderate weight loss can dramatically reduce the development of type 2 diabetes among those at high risk, a benefit of intentional weight loss in preventing cardiovascular complications in people with diabetes has not yet been established.
- Even though improved blood glucose control dramatically reduces the eye, kidney, and nerve complications of diabetes, and has recently been shown to reduce CVD in type 1 diabetes, its benefits in reducing CVD in type 2 diabetes are not fully established, and it is not known whether insulin-providing or insulin-sensitizing strategies for glucose control is more effective in reducing CVD mortality.
- Lowering of LDL cholesterol has been shown to prevent CVD in general, but type 2 diabetes is associated with a distinct lipid profile, with low high-density lipoprotein (HDL) cholesterol and increased triglycerides. Research is needed to establish optimal management of lipids and blood pressure to reduce CVD in type 2 diabetes.
- Homocysteine, an amino acid produced in the body, is a known risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease, their effect on CVD risk remains to be determined.
- Kidney transplant recipients typically have reduced levels of kidney function, thus they serve as an excellent model for chronic kidney disease in patients.
- Once individuals with diabetes develop coronary artery disease, the optimal treatment approach is not clear; for example, it is not known whether bypass surgery or artery-opening with placement of a drug-eluting stent would provide a better outcome.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH has initiated a set of major, multicenter, randomized clinical trials, each of which has both long term objectives and milestones that provide performance targets/measures. The set of trials is unparalleled in scope and research intensity and, collectively, could not be replicated by other organizations.

Look AHEAD [Action for Health in Diabetes] Trial. This is the largest clinical trial to date to examine the long-term health effects of intentional weight loss in patients with type 2 diabetes: specifically assessing the benefits and risks of weight loss with respect to cardiovascular events. The study will also investigate the cost effectiveness of the intervention. Over 5,000 patients with type 2 diabetes, with or without CVD, who are overweight or obese at study entry (BMI of 25 or over) are enrolled.

Note: Although the Look AHEAD clinical trial will not be completed until 2013, it will generate intermediate outcomes that will contribute to realizing GPRA Goal SRO-5.6.2 by 2011. For example, the Goal SRO-5.6.2 target for FY 2006 is to provide outcome data on the success of the one-year intensive weight loss phase and the effect of the weight loss intervention on important clinical measures such as diabetes control, lipids, blood pressure, and fitness. Significant cost savings will accrue from not having to conduct similar studies in a separate trial.

ACCORD [Action to Control Cardiovascular Risk in Diabetes] Trial. The objective of this trial is to determine whether each of three treatment approaches reduces the incidence of cardiovascular complications of type 2 diabetes. The target patient recruitment is 10,000 patients with type 2 diabetes who either have CVD or are at high risk of developing CVD. The three treatment approaches are: (1) intensive control of blood glucose compared with standard control, (2) intensive control of blood pressure compared with standard control, and (3) treatment to raise HDL cholesterol (the "good" cholesterol) and lower blood triglycerides as well as lower LDL cholesterol (the "bad" cholesterol) compared with a treatment that only lowers LDL cholesterol.

BARI 2D [Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes] Trial. The primary long-term aim of the trial is to answer the following questions: (1) Does immediate elective revascularization reduce CVD morbidity and mortality over and above intensive medical management of the patients' coronary artery disease and risk factors? (2) Does blood glucose control that includes lowering insulin resistance reduce CVD morbidity and mortality more than comparable blood glucose control without medicines that lower insulin resistance? The target patient recruitment is 2,300 patients with type 2 diabetes and stable coronary artery disease who might be candidates for revascularization.

FAVORIT [Folic Acid for Vascular Outcome Reduction in Transplantation] Trial. This trial aims to determine whether reduction of level of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in a significant reduction in arteriosclerotic CVD (compared with a control group whose homocysteine levels are expected to remain the same over time). The target patient recruitment is 4,000 kidney transplant recipients).

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	(FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	◆					
FY03	*Actual Performance:* (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.						
Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	(FY03) Look AHEAD had recruited about half (2,500) of its patients		◆[e]				
FY04	*Actual Performance:* (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.						
Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	(FY03) ACCORD had recruited 1,184 participants in a Vanguard phase			◆			
FY05	*Actual Performance:* (MET) The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005.						
Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	(FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population				◆		
FY06	*Actual Performance:* (MET) Initial findings from Look AHEAD were presented at the annual Society of Behavioral Medicine meeting in March 2006. One-year results from Look AHEAD on reduction in weight and cardiovascular disease (CVD) risk factors in type 2 diabetes were presented at the annual American Diabetes Association meeting in June 2006.						
Complete at least 90% of the total enrollment for the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial which aims to determine whether reduction of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in atherosclerotic CVD.	(FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Review and evaluate collectively, indicators of Look AHEAD's progress to date (measures such as safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends) in order to determine whether the science is progressing appropriately--in accord with the clinical trial's protocol--and whether the trial will be continued.	(FY07) Human clinical trials require periodic review and evaluation to assess progress.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Initial findings from Look AHEAD on weight loss in type 2 diabetes were presented at the annual Society of Behavioral Medicine meeting in March 2006. One-year results from Look AHEAD on reduction in weight and cardiovascular disease (CVD) risk factors in type 2 diabetes were presented at the annual American Diabetes Association meeting in June 2006. Look AHEAD succeeded in achieving one year weight loss goals and in reducing cardiovascular disease risk factors at one year in the intervention group relative to the

control. A formal manuscript describing one year results has been submitted for publication.

Implementation Strategy Advances or Other Highlights

'The Look AHEAD Study: A Description of the Lifestyle Intervention and the Evidence Supporting It' has been published in the May 5, 2006 issue of Obesity. The Look AHEAD Research Group published a study "Correlates of health-related quality of life in overweight and obese adults with type 2 diabetes" in May issue of OBESITY. Manuscripts describing the design of the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial were published in June 2006. A Look AHEAD ancillary study "Decreased Expression of Adipogenic Genes in Obese Subjects with Type 2 Diabetes" was published in September 2006 issue of OBESITY. One-year results from the Look AHEAD trial were presented at the NIDDK Advisory Council meeting on September 20, 2006.

PART

This goal was included in the FY 2006 PART of the Extramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-5.7	By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy.

BACKGROUND

Lung cancer is one of the leading causes of death in the United States, with an estimated 160,000 deaths occurring annually and an estimated incidence of 173,000 newly-diagnosed cases each year. Only one-third of newly diagnosed cases are diagnosed at a stage early enough to allow for effective therapeutic intervention while more advanced stages of the disease are characterized by a median survival rate of less than one year. The development of new drug treatments for lung cancer has been slowed by difficulty in both early detection and measurement of early therapeutic drug response. Currently, standard anatomic CT imaging is the primary modality for measuring lung tumor response to therapy. Unfortunately, since this modality measures drug responses only in terms of significant tumor shrinkage, it is not an adequate method for evaluating drug responses that precede significant tumor shrinkage. The goal of this proposed research is therefore to evaluate, validate and compare varying functional imaging methods that could serve as more sensitive approaches to the measurement of early drug response than standard or conventional anatomic imaging techniques that are based on significant tumor shrinkage. The availability of such sensitive measurement methods or modalities could significantly streamline clinical trials and, hence, accelerate new drug approvals. The imaging methods to be evaluated are FDG-PET, FLT-PET and DCE-MRI.

Rationale

Clinical trials in non-small cell lung cancer (NSCLC) have demonstrated that F-18-labelled-fluorodeoxyglucose positron emission tomography (FDG-PET) images can provide an early indication of therapeutic response. Thus, FDG-PET has the potential to improve patient management by signaling the need for early therapeutic changes in non-responders, thereby avoiding the side effects and costs associated with ineffective treatments. Furthermore, as an early indicator of therapeutic response, the modality also has the potential to facilitate oncologic drug development by both shortening Phase II trials and detecting response to therapy at an earlier stage in Phase III investigations. Studies to further explore and validate these approaches can be conducted in parallel with those employing endpoints now used for oncologic drug approvals.

Uptake of F-18-labelled-fluoro-L-thymidine (FLT-PET) is an indicator of DNA synthesis. FLT-PET, therefore, has potential to be more accurate than FDG-PET in distinguishing lung malignancies from inflammation or non-proliferating cells. It is highly promising as a detector of early disease or as an early indicator of response to drug therapy as manifested by a decrease in cellular proliferation.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is sensitive to the development of new blood vessels (angiogenesis) required to support tumor growth. It is, therefore, a potentially sensitive measure of responses to antiangiogenic drug therapy. The evaluation of antiangiogenic agents could be very important to lung cancer therapy as

suggested by the recent promising increase in survival of advanced NSCLC patients treated with the anti-vascular endothelial growth factor (VEGF) drug bevacizumab (Avastin).

Validating imaging methods as potential biomarkers for tumor response to treatment requires demonstrating a high degree of test-retest reproducibility for the imaging method, and a strong correlation with the biologic parameter of interest. Therefore, test-retest reproducibility will be an element of all trials conducted for this goal.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Clinical Trials

To lay the foundation for accepting an imaging method as a potential biomarker for drug development, the proposed or putative imaging method should be tested in one or more clinical trials where patients receive therapy known to be effective for the disease under study. The method in question should not be initially evaluated in a trial studying novel therapies due to the high number of unknown variables inherent in such trials. Therefore, patients in clinical trial protocols will receive standard, accepted platinum-based chemotherapy for lung cancer and imaging measurements (FDG-PET, FLT-PET, or DCE-MRI) will be obtained before and after therapy to be subsequently correlated with patient outcome.

Test-Retest Reproducibility

In addition, because of the importance of ascertaining and documenting the degree of test-retest reproducibility, the clinical trial protocol will include provision for duplicate testing of individual patients to generate such data. Test-retest reproducibility is a measure of the variability of the test result when it is administered to the same patient at different times or under different conditions but during a period of time when the biologic process being measured is constant.

Electronic Infrastructure

Another necessary part of our implementation strategy is to create an electronic infrastructure so that all sites in a multi-site trial can submit images to a central archive. Centralizing the images is necessary for quality assurance evaluation, for analysis (data extraction or interpretation), to facilitate blinded reads, and for secure storage (archiving) to enable secondary analyses. The FDA requires such procedures to establish confidence in the validity and robustness of the data supporting a proposed biomarker and to permit audits of the data, if needed.

Consensus Standards

Finally, an essential part of this implementation strategy is the development of consensus standards for interpreting or extracting quantitative data from the imaging studies.

Therefore, the implementation strategy consists of several parts. In FY 2005 a clinical trial protocol was conducted to include serial FDG-PET scans in Stage III and IV lung cancer patients before and after therapy. Therapy will be standard, not experimental, therapy. Scans will be done on state-of-the-art combined PET-CT scanners. The trial was initiated during FY 2006 by the NIH-funded imaging cooperative group known as ACRIN

(www.ACRIN.org). Half of the patients will receive duplicate FDG-PET scans prior to treatment, and half will receive duplicate FDG-PET scans after treatment. The duplicate scans will allow us to assess test-retest reproducibility. At the conclusion of the trial, patient outcome will be compared to the change in FDG-PET uptake before and after therapy. FDG uptake will be measured by the Standardized Uptake Value (SUV). Most cancers display highly elevated glucose metabolism prior to treatment and therefore take up a lot of FDG. If cancer cells are responding to therapy, glucose metabolism falls rapidly and FDG uptake decreases. If therapy has no effect, FDG uptake will stay the same or increase. Preliminary published data suggest that patients whose SUV falls by at least 25% - 35% will subsequently show favorable response to therapy. This correlation with patient outcome needs to be confirmed, and meaningful changes in SUV values need to be determined.

A trial to evaluate FLT-PET for lung cancer was planned in FY 2006 and will be initiated in FY 2007.

In FY 2005, plans for the electronic infrastructure to capture all the images in a central archive were initiated. This infrastructure was implemented in FY 2006.

To develop consensus standards and quantitative tools for image assessment, workshops of relevant experts on PET and MRI scanning have been held. The resulting recommendations and the proposed clinical trial protocols will be reviewed with FDA staff.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Convene workshops of relevant experts on PET and MRI scanning to develop consensus standards and quantitative tools for image assessment.	(FY05) Workshop planned.			◆			
FY05	*Actual Performance:* (MET) FDG-PET and DCE-MRI workshops have been held. Consensus guidelines are on the Cancer Imaging Program web site: imaging.cancer.gov.						
Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial.	(FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.				→	→	
FY06	*Actual Performance:* (EXT) Launch of the public-private partnership responsible for conducting the lung cancer therapy trial was delayed, which led to delays in initiating the study and collecting test-retest repeatability data. Preliminary analysis of the test-retest repeatability data will be conducted in early 2007.						
Perform additional analysis of test-retest repeatability data from 1st year of trial. *Previous Target:* Complete accrual in lung cancer therapy trial and perform final analysis of test-retest reproducibility of functional imaging scans.	(FY05) Trial not complete.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Correlate patient outcome data from the lung cancer therapy trial with serial functional imaging scan results to determine the efficacy of this imaging technique.	(FY06) Performed preliminary analysis of test-retest repeatability data from 1st year of trial.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was EXTENDED. Launch of the NIH Biomarkers Consortium, a public-private partnership responsible for conducting the study, was delayed until October 5, 2006 due to protracted negotiations between NIH and pharmaceutical industry attorneys on intellectual property agreements, data sharing agreements, and anti-trust issues. The NIH Biomarkers Consortium chose the FDG-PET lung cancer trial as one of its first two projects. The FDG-PET protocol has been written and approved by the Cancer Evaluation Therapy Program (CTEP) (ACRIN protocol # 6678), thereby initiating the trial and collection of test-retest repeatability data. Preliminary analysis of the test-retest repeatability data will be conducted in early 2007. In addition to NIH support, several pharmaceutical companies contributed funding to this trial. This additional support has enabled a cost savings for NIH; thus, creating an efficiency.

Implementation Strategy Advances or Other Highlights

A protocol team has been established within ACRIN to implement the protocol for the FDG-PET lung trial. The ACRIN protocol team is finalizing the implementation details and case report forms. Within the next few weeks the protocol will be distributed to participating sites for submission to their IRBs. Accrual is expected to start in the first quarter of 2007.

A study of volumetric algorithms for lung cancer response is also included in ACRIN protocol # 6678. In September 2005, a public web site, which provides a central repository for images for development and evaluation of algorithms such as 3-D volumetric assessment, was made available. A large number of serial CT scans from patients with lung cancer have been added to that web site in 2006. In addition, an agreement was reached with a pharmaceutical company whereby it will send PET/CT scans and associated clinical data from their existing clinical trials of lung cancer treatment to the website.

A future component of this GPRA goal is a trial to evaluate FLT-PET as a biomarker of response in lung cancer therapy. A contract was awarded in 2006 to investigators to write a protocol to evaluate FLT in lung cancer. Also in 2006 NIH awarded a competitive contract to a company to provide individual injectable doses of the radiopharmaceutical FLT for use in these clinical trials.

Efficiency

The FDG-PET lung trial was projected to cost a total of $1.8 million ($600,000K for 3 years). NIH was able to establish an industry collaboration reducing the cost to $1.5 million ($500,000K for 3 years).

SRO-5.8	**By 2011, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies.**

BACKGROUND

Vasomotor symptoms, including hot flashes and night sweats, are symptoms frequently reported by menopausal women as well as breast cancer survivors and men undergoing androgen deprivation therapy. Until recently, estrogen and other forms of hormone therapy were used to treat vasomotor symptoms among menopausal women. However, the findings of the NIH-funded Women's Health Initiative, released in 2004, indicated that the benefits of hormone-based therapies for hot flashes are outweighed by the risks of heart disease, stroke, and pulmonary embolism. Furthermore, hormone therapy is not an appropriate treatment for hot flashes in individuals with a history of hormone-dependent tumors.

People are now turning to other means to manage hot flashes, including complementary and alternative medicine (CAM) therapies. There is a long history of using CAM therapies for this purpose, but the empirical base to assess their safety and efficacy is neither extensive nor very strong. Moreover, the FDA now recommends when hormones are used for the treatment of hot flashes, they be used at the lowest effective dose and for the shortest possible period of time. However, little is known about risks and benefits for smaller doses, shorter treatment times, and different routes of administration. Thus, it is likely that researchers will be investigating both hormone and CAM treatments to reduce hot flashes in the years ahead.

In January 2004, NIH convened a meeting to assess current approaches to measuring hot flashes. A limited number of studies conducted in research laboratories and ambulatory settings have used sternal skin conductance monitors for these measurements. The meeting participants determined that (1) sternal skin conductance devices were limited in the amount of data that can be collected and for use under ambulatory conditions; and (2) improved devices were needed to assess new therapeutic approaches including complementary and alternative medicine (CAM). The criteria for an improved device include accuracy in measuring sternal skin conductance with increased device data storage capacity. Usability under ambulatory conditions is another important criterion, as some devices are too bulky or heavy and interfere with daily activities and sleep. Once device development is complete, clinical studies will be undertaken to assess both CAM and conventional therapies for the treatment of hot flash symptoms.

Rationale

In light of the aging U.S. population and the findings of the Women's Health Initiative, further clinical trials of interventions for hot flashes will undoubtedly need to be conducted. Some treatments are likely to be relatively weak when compared with estrogen, but many women may find partial relief acceptable if the benefits of treatment outweigh the risks. Given the large placebo effects that have been reported in many studies, the instability of self-reported measures of hot flashes, and modest treatment effects; important choices in the conduct of future trials must be made. Investigators can either conduct very large studies to accommodate the limitations of subjective self-reported measures, or they can develop more

sensitive and reliable objective measures for use in smaller studies, which could provide substantial economies in time and resources. For these reasons, the scientists convened by NIH to consider issues surrounding the measurement of hot flashes recommended improvements in sternal skin conductance monitors.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To ensure that investigators will have effective tools for measuring the effects of hot flash therapies in clinical trials, NIH requested applications from small businesses to conduct research to improve sternal skin conductance monitors in September 2004. NIH made the first awards for this research and development in FY 2005. Following the development of improved devices, clinical validation testing in FYs 2006 and 2007, and announcing the availability of these improved measurement tools to the scientific community in FY 2007, NIH expects to call for proposals to test the new device(s) in one or more clinical studies of a CAM therapy for hot flashes and related symptoms beginning in FY 2008.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Initiate at least 3 research projects to improve objective measures of hot flash frequency.	(FY04) Currently available monitors are not suitable for multiple day ambulatory studies.			◆			
FY05	*Actual Performance:* (MET) NIH initiated seven research projects.						
Develop and validate improved devices to measure hot flash frequency.	(FY05) Improved devices not yet available.				◆		
FY06	*Actual Performance:* (MET) NIH funded three projects to further validate new sternal skin conductance monitors.						
Continue validation of at least 2 devices to measure hot flash frequency.	(FY06) Prototype device from FY05 target should be available for additional validation testing.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Initiate 1 clinical study that includes a treatment for hot flashes in which the investigators would use a sternal skin conductance monitor to measure hot flash frequency.	(FY06) No clinical studies of hot flashes using user-friendly sternal skin conductance monitors exist.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. In FY 2006, NIH issued an RFA to further validate new sternal skin conductance monitors against self reported measures of hot flash frequency to be collected using portable electronic devices, which will also allow investigators to collect data on other menopausal symptoms. Of the four applications submitted by investigators funded to improve sternal skin conductance monitors in FY 2005, three received scores that resulted in funding in FY 2006. This new series of research projects should provide validated objective measures (sternal skin data) and subjective measures (self reported data) on hot flashes. The new awards will program hand held electronic devices with a validated questionnaire on menopausal symptoms. Subjects will wear a sternal skin conductance monitor and will record symptom data on the new devices. This combination of systems for

collecting data on menopausal symptoms is needed for future clinical studies of therapies for hot flashes and other menopausal symptoms.

SRO-5.9	By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.

BACKGROUND

The goal is to establish the role of genetic factors in three major diseases for which health disparities are noted. The element of unplanned discovery in research makes it virtually impossible to predict accurately when significant scientific advances will be made in the genetics of any specific disease. Thus, the focus will be on programs that seek to determine genetic factors across the genome and specifically on research in disease areas that are likely candidates for genetic advances in the next few years.

Comparable to a drug discovery in which many compounds are screened and tested to yield a small subset to pursue, to identify genetic factors in three major diseases NIH is pursuing many more than three areas of disease research. Since it is unrealistic to include all areas of research in one goal, NIH has chosen three areas of research in which it is likely that important genetic factors related to disease will emerge by 2010.

Building on the foundation of the Human Genome Project (HGP), NIH, as part of the International HapMap Consortium, has developed a way to scan large regions of chromosomes for variants (called SNPs, or single nucleotides polymorphisms) associated with an increased risk of disease. Researchers can use the HapMap to find genes and variants that contribute to many diseases; it is also a powerful resource for studying the genetic factors contributing to variation in individual response to disease, drugs, and vaccines. Understanding the role of genetics in major diseases that have been noted for disparities, and thus achieving this goal, will rely on such tools.

Prevalence/Incidence

Virtually all diseases have a genetic component, even though the vast majority of human genetic information is the same for all people. Indeed, any two individuals share 99.9% of their DNA sequence. However, this translates to approximately 10 million DNA sites where people commonly differ, many of which may be medically important. Some of these variations affect an individual's risk for disease; others influence how an individual may respond to drugs. Most genetic variations, including those that are medically important, are shared by all racial, ethnic, and cultural groups. Thus, much of human genetics research applies broadly to all groups of people, regardless of which individuals are studied.

A disease may be said to be 'common' if its incidence is high and it is seen in many populations, although not necessarily at similar frequencies in each population. Many diseases that have a genetic component affect populations in different ways. For example, diabetes is a debilitating disease that affects an estimated 18.2 million people in the United States and is the sixth leading cause of death. Type 2 diabetes (noninsulin-dependent diabetes mellitus, or NIDDM) is the most common form and occurs more frequently among minority groups. Overall, Hispanic/Latino and African Americans are nearly twice as likely, and American Indians are 2.6 times more likely to develop type 2 diabetes than are whites.

- Diabetes is the sixth leading cause of death in the U.S. affecting an estimated 18.2 million people. Type 2 diabetes is the most common form and occurs more frequently among minority groups. Hispanic/Latino and African Americans are nearly twice as likely, and American Indians are 2.6 times more likely to develop type 2 diabetes than are whites.
- Deaths due to cerebrovascular diseases are highest among African Americans and lowest among American Indians and Alaska Natives, with whites at an intermediate risk.
- Over 60 million Americans, or approximately 20% of the population, have hypertension. Many minorities have higher rates of hypertension, tend to develop hypertension at an earlier age, and are less likely to undergo treatment to control their blood pressure than whites.
- Within the U.S., racial and ethnic disparities in risks of developing and dying from a number of different cancers have been recognized for decades. Whites have the highest rates of breast cancers, Asian Americans have the highest rates of liver and stomach cancers, and Native Americans have the highest rates of gall bladder cancers. African Americans are at the highest risk of a number of different cancers, including those of the esophagus, lung, colon, pancreas and prostate. Prostate cancer is the most common non-skin cancer and the second leading cause of cancer-related death in U.S. men. Thus, the 60% higher rate of development of prostate cancer and a two-fold higher risk of death from it among African American men is a major health problem.

Rationale

Understanding how genetic variations contribute to various diseases will hopefully lead to a better understanding of why individuals are at particularly high risk of developing health problems. Genetic variations associated with a disease are identified through analyses of large study groups; only these offer the statistical power needed to identify and confirm genetic and environmental contributors to complex diseases.

Although many of the large population studies such as Framingham and the U.S. Physicians Health Study have had a major impact on the health of all U.S. population groups, they do not have appropriate minority representation across the U.S. population.

- For serious but less common diseases such as cancer, these studies may not be able to uncover specific genetic reasons for the differences in disease rates for minority populations. Because of this, the NIH has developed specialized study populations to collect large amounts of data on minority populations to combine with the data from other large cohorts. The Black Women's Health Study is providing insight into causes and prevention of breast and other cancers. The Multiethnic/Minority Cohort Study explores the relationship of diet and other lifestyle factors to cancer in African American, Japanese, Latinos, Native Hawaiian, and white. The Southern Community Cohort focuses on the gene-environment risk of cancers in the southern U.S. All of these minority cohorts along with the established general population cohorts are engaged in the Consortium of Cohorts at NIH.
- A series of coordinated projects funded by NIH will use the Consortium along with

new technologies in candidate gene approaches, whole genome scans, and the HapMap to identify and validate genes that influence the development and progression of prostate cancer and to assess their contribution to racial and ethnic disparities for this malignancy.

- The adult Pima Indian population, half of whom have type 2 diabetes, has over 20 times the rate of new cases of kidney failure as the general U.S. population, with diabetes as the cause in over 90% of cases. Researchers have been collecting DNA from Pima tribe members since 1983 and have studied over 90% of the individuals on reservations. This study group is a tremendous resource for investigating the complex genetics of type 2 diabetes.
- The Finland-United States investigation of type 2 diabetes (FUSION) involves the phenotyping and DNA analysis of 10,000 controls and individuals with diabetes living in Finland. The Finnish population provides an ideal basis for studies of complex genetic diseases such as type 2 diabetes due to its relative genetic and environmental homogeneity, excellent data sources, and a population strongly supportive of biomedical research.
- The Family Blood Pressure Program (FBPP) is a large, multi-center, collaborative study of genetics and blood pressure initiated by NIH to locate and characterize genes that contribute to hypertension and related conditions in multiple racial and ethnic groups.

These studies will provide great insights into the genetic factors in diseases for which health disparities are noted, but it is currently unknown which studies will bear specific results. It is expected that this goal will yield knowledge about the genetic factors in diseases such as hypertension, prostate cancer, and diabetes, but over the life of this goal, research into other diseases may develop additional results.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Genomic research is rapidly producing new opportunities for understanding disease biology, and promises to enhance health care and health outcomes significantly through improved strategies for prediction and prevention, targeted drug treatment, and innovative molecular-based therapies. A major concern in the era of genomic health care is to insure that all racial, ethnic, and cultural groups can benefit fully from genomic technology.

Researchers at NIH have been engaged in FUSION, a large collaborative study of 10,000 controls and individuals with diabetes from Finland, using careful detailing of diabetes and diabetes associated traits, and genome-wide genetic linkage and association. The majority of the samples have already been subjected to a genome scan using microsatellite markers, and several regions of interest have been identified. Those samples are now being genotyped in order to map these areas finely, in an effort to identify the specific genetic variants that contribute to risk for this common illness.

The Family Blood Pressure Program (FBPP, see above) is a multidisciplinary project, with a goal of locating and characterizing genes that contribute to hypertension and related conditions in multiple racial and ethnic groups (non-Hispanic whites, African Americans, Hispanics, and Asians). Investigators involved in the FBPP have recently identified many

hypertension susceptibility genes and regions of the genome that are likely to contain them. Pooled data generated by the FBPP have been made available to the scientific community, and data training workshops will be held to facilitate research in this area. The goal of the FBPP is to enable improvements in hypertension prevention and treatment.

To help meet the challenge of eliminating suffering and death from cancer, it is important to capitalize on the extraordinary momentum generated by advances in human genetic research. Currently, a comprehensive study of hormone related gene variants is planned, utilizing a coalition of investigators involved in population follow-up studies (Consortium of Cohorts). In addition, a new study entitled the Cancer Genetic Markers of Susceptibility (C-GEMS) will use the latest genomic technologies to perform dense whole genome scans to identify and validate susceptibility genes in the induction and progression of prostate cancer and clarify gene-gene and gene-environment interactions. This work will provide new insights into mechanisms of carcinogenesis and point the way to novel strategies for accelerating the prevention, early detection, and treatment of prostate cancer.

The first phase of the HapMap Project, a comprehensive catalog of human genetic variation, was completed in 2005 and identified 1 million SNPs, markers of genetic variation, in four population groups. The second phase of the project will provide researchers with a denser map to narrow gene discovery more precisely to specific regions of the genome. In the third phase of HapMap, ten carefully chosen regions will be genotyped in additional populations to assess how well the HapMap and its tag SNPs work in other groups. This will aid in exploiting the utility of HapMap across the range of populations in the US.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Collect a cumulative total of 5.8 million genotypes from the FUSION study.	(FY04) 3 million genotypes collected in the FUSION study.			◆[e]			
FY05	*Actual Performance:* (MET) The FUSION study collected 3.0 million genotypes, making a cumulative total of 6.0 million genotypes collected for this study of genetic variants that predispose to common type 2 diabetes. The cumulative total exceeded the projected target by 200,000 genotypes.						
Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community.	(FY05) No FBPP data publicly available to the scientific community.				→	→	
FY06	*Actual Performance:* (EXT) The pooled data with documentation and web utility were made publicly available in September 2006. Public data training is scheduled for March 2007.						
Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study.	(FY06) Scientific infrastructure established and RFP for initial scan released.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
HapMap III: Analyze data from samples from additional populations to assess how well the genome-wide HapMap applies to additional populations, as well as to figure out how to choose HapMap SNPs to make them most useful for additional populations.	(FY07) HapMap III not started						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was EXTENDED. The target was primarily met because the pooled data with documentation and web utility were made publicly available on Friday, September 21, 2006. Delays in release of the public data set occurred as a result of delays in receiving all IRB approvals necessary for data release. In turn, this has caused a delay in scheduling the public training program. Public data training is scheduled for March 2007, at which time the target will be completed.

Implementation Strategy Advances or Other Highlights

Building on the success of the International HapMap Project which completed its first two phases in 2005, the genotyping of several additional populations was undertaken to assess how well the HapMap works for populations across the world. The original plan was to collect five populations in addition to the four originally involved in the HapMap: Nigeria (Yoruba), Japan, China and the United States (Utah residents with ancestry from northern and western Europe). In 2006, the HapMap exceeded its goal by collecting samples from six populations: (1) a Metropolitan Chinese community in Denver Colorado, (2) the Luhya from Webuye, Kenya, (3) people of Mexican origin in Los Angeles, California, (4) people with African ancestry in the Southwestern United States, (5) Tuscans in Italy and (6) Gujarati (from India) in Houston, Texas.

PART

This goal was included in the FY2007 PART of the Intramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-6.1	By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.

BACKGROUND

Prevalence/Incidence

Age-related macular degeneration (AMD) is a sight-threatening degenerative eye disease that affects the part of the retina known as the macula and leads to varying degrees of vision loss depending on the form and severity of the disease. Of the nearly 60 million people in the United States age 55 or older in the year 2000, an estimated 7.3 million are at risk of developing advanced, sight-threatening AMD in one or both eyes and 1.75 million citizens currently have AMD. This number is expected to increase to nearly 3 million by the year 2020. Glaucoma is a group of eye disorders that shares a distinct type of optic nerve damage that can lead to blindness. Approximately 2.2 million Americans have glaucoma currently, and this number will increase to over 3.3 million by the year 2020 due to the aging of the U.S. population. As many as 120,000 people are blinded from this disease.

Disease Burden

AMD is the leading cause of irreversible vision loss in the United States among persons older than 65 years of age, the fastest growing segment of the U.S. population. AMD threatens the eyesight and independence of the growing U.S. population of older Americans. People older than 60 are at greatest risk for AMD. Glaucoma is a major public health problem and is the number one cause of blindness among African Americans. It is often described as a "silent thief" of sight, because there may be no symptoms in the early stages of the disease process until the loss of side or peripheral vision becomes noticeable. As the disease progresses, the field of vision narrows until blindness results. African Americans older than age 40, everyone older than age 60, and people with a family history of glaucoma are at increased risk for glaucoma.

Rationale

The development of effective treatments for AMD has been limited by the complicated nature of the disease and the fact that the pathophysiology of the disease is poorly understood. The genes for other forms of macular degeneration, including Stargardt disease and Best macular dystrophy, have been identified and are being studied to learn whether similar disease mechanisms are involved in AMD. These genes have also been considered as candidate genes for AMD, but the results suggest a complex underlying genetic predisposition or susceptibility to biological and environmental factors in the pathogenesis of this complex disorder. Additional investigation of the genes that control this predisposition or susceptibility may improve understanding of the disease process and ultimately lead to improved treatments or the means to prevent this disease. Glaucoma is not a single disease but rather a group of diseases characterized by a particular type of retinal ganglion cell death that is usually, but not always, associated with an increase in intraocular pressure. Current treatments, whether surgical or pharmacologic, are aimed at reducing intraocular pressure and are often inadequate in preventing vision loss. A variety of mutations have been identified that may play a role in the development of primary open-angle glaucoma. The multiple genetic loci and gene associations linked to various forms of glaucoma are other

indications of the complex nature of this disease and underscore the need for additional research to clarify the roles of environmental and genetic risk factors in the pathology of this heterogeneous disease.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH began to implement strategies for achieving this long-term goal by increasing the scope and availability of the genomic resources to researchers via NEIBank, an Internet-accessible database of genes and proteins expressed in the eye and visual system, and via several related trans-NIH activities. Expanding the available genomic resources (e.g., information on DNA sequences from human and other species, new and variant forms of genes, unique human eye- expressed genes) enables researchers to accelerate the identification of genes that control risk for AMD and glaucoma.

Another important implementation strategy was developing standards for AMD phenotyping and agreement on precise definitions of the diverse retinal phenotypes found in macular disease. Future work on AMD human genetics requires common disease descriptors and a systematic phenotyping system. This was accomplished through an existing network of reading/grading centers that review photographs of ocular pathology, both nationally and internationally. Currently, these centers have established in-house methodologies and phenotypic definitions that are specific to an individual reading center. Representatives from each of these centers helped set uniform standards, examined existing descriptors to find common elements, pooled data, and determined mechanisms for sharing data. Using a consensus approach, a descriptive manual with standards will be developed that will allow investigators around the world to have a 'common language' to describe different stages and forms of macular disease.

Also important in progress toward this goal is making genetic material and information from well-characterized patients available to investigators. Population-based resources of blood, transformed lymphocytes, and DNA from patients with well characterized AMD and glaucoma will be made available to investigators nationally. Because of the rigor and uniformity in characterizing the disease status of the participants, ongoing clinical trials will be used to collect specimens and create large databases of genetic information for additional analysis. It will also be necessary to accelerate the application of candidate gene and other genetic approaches to the study of AMD and glaucoma.

Complex diseases like AMD and glaucoma may require animal models exhibiting multiple genetic changes to produce the full range of pathologic conditions seen in these human diseases. These models can allow the further characterization of the genetic and biochemical abnormalities that lead to the disease process. After identification of potential genes related to these diseases, modifications of these genes can be introduced into animal models to determine whether they cause pathology in the animal similar to that found in humans. Ultimately, therapies that delay, prevent or reverse these genetic alterations in the animal can be tested. Several candidate genes for use in an animal model, including fibrillin-6 and Stargardt gene for AMD, and optineurin for glaucoma, have already been identified.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	(FY02) 31,000 human gene sequences; 12,000 unique human eye-expressed genes	◆					
FY03	*Actual Performance:* (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.						
Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	(FY03) No consensus descriptions on AMD phenotypes exist		◆				
FY04	*Actual Performance:* (MET) A consensus was reached on a manual of classification standards for use by fundus photograph and reading centers that will aide in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections.						
Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	(FY04) DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available			◆			
FY05	*Actual Performance:* (MET) Collected samples from over 4,000 well-characterized patients with either AMD or glaucoma. Created the National Eye Disease Genotyping Network (EyeGENE).						
Conduct studies in animal models to identify potential modifier genes.	(FY05) Modifier genes for AMD and glaucoma have not yet been identified.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Conduct haplotype analysis to identify common risk haplotype for genes associated with primary open-angle glaucoma (POAG) through single-nucleotide polymorphism (SNP) genotyping.	(FY06) A dozen genes associated with glaucoma have been mapped and half a dozen genes have been cloned.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SRO-6.3	By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.

BACKGROUND

Disease Burden

Chemicals in the environment (including arsenic, lead, mercury, polychlorinated biphenyls [PCBs]) and other air and water pollutants contribute to the burden of human disease. In addition, lifestyle exposures to alcohol and nicotine compound adverse environmental health outcomes. Public health is also adversely influenced, for example, by exposure to household chemicals such as pesticides and through abuse of common over-the-counter pharmaceuticals such as analgesics. The problems of identifying environmental factors involved in the etiology of human disease and performing safety and risk assessments of drugs and chemicals have long been formidable issues. The prediction of potential human health risks involves consideration of (1) the diverse structure and properties of thousands of chemicals and other stressors in the environment, (2) the time and dose parameters that define the relationship between exposure and disease, and (3) the genetic diversity of organisms used as surrogates to determine adverse chemical effects. Toxicogenomics is a new scientific field that examines how chemical exposures disrupt biological processes at the molecular level. The pattern of regulation of various genes is different for different chemicals, creating characteristic "signatures," which scientists hope will be useful in classifying chemicals and other stressors by their biological activity. These signature patterns provide a means of potentially predicting effects on human health from chemicals about which little is known. To enable this predictive capability, a toxicogenomics knowledge base must be established. The result will be the emergence of "systems toxicology" as an information science that will facilitate thorough analysis, iterative modeling, and discovery across biological species and chemical classes.

Rationale

The global techniques evolving from successful genomics efforts are providing exciting new tools with which to address the formerly intractable problems of environmental health and safety assessment. Identifying molecular events that serve as precursors of adverse health outcomes early in the development process would eliminate much of the expense (estimated in billions of dollars annually) associated with the development of new pharmaceutical products. Similar considerations apply to prevention of disease associated with common environmental exposures. To benefit from these new technological advances, environmental toxicology and safety assessment must develop into an information science in which experimental toxicogenomics data sets are compiled and where computational and bioinformatics tools are applied to systematically develop a new understanding of toxicant-related disease. NIH is creating a knowledge base on Chemical Effects in Biological Systems (CEBS). More than a database, the CEBS knowledge base will contain data on global gene expression, protein expression, metabolite profiles, and associated chemical/stressor-induced effects in multiple species. With such information, it will be possible to derive functional pathways and network information based on cross-species homology. The CEBS knowledge base will develop relational and descriptive compendia on toxicologically important genes,

groups of genes, polymorphisms, and mutants and their functional phenotypes that are relevant to human health and environmental disease. Designed initially as an interpretive tool for toxicogenomics, the CEBS knowledge base will ultimately become a knowledge base to support both discovery- and hypothesis-driven research.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Part of NIH's strategies to reach this goal is to capture and present quality control parameters, basic data preprocessing and normalization, basic visualization and statistical summary information, and basic annotation. This provides the set of tools needed for microarray data analysis.

NIH also implemented international standard file format for data exchange, extended the database object model to include toxicology/pathology fields, and created a data portal that loads National Toxicology Program (NTP) and commercial Xybion toxicology data. This creates the capability to import (and export) and link molecular expression data to animal effects data so as to evaluate global changes in gene and protein expression as a function of dose, time, and severity of toxic effect.

In addition, NIH has developed quality control indicators for submitted data sets and implement microarray cross-platform gene mapping, advanced data preprocessing and normalization, statistical comparisons, and automated gene annotation. This enables automated loading and quality checking of data and automated full-chip gene annotation.

To link the knowledge base's search outcomes to existing literature databases, NIH plans to (1)sequence anchor all probe sets from public sequence-defined microarray platforms to respective genomes within CEBS, demonstrating chromosome/gene alignment of probe sets within a genome browser; (2) create extensive study and subject search capability such that the correspondence of gene expression profiles to specific study designs, subjects, and experimental outcomes may be determined; and (3)enable a literature searching algorithm and user interface to identify and visualize relationships among known gene sets via query of PubMed.

NIH, international counterpart databases (e.g., European Bioinformatics Institute Tox-ArrayExpress), industry, and academia are collaborating to create a repository of high-quality toxicogenomics data sets on selected bioactive compounds to facilitate access and evaluation for discovery- and hypothesis-driven research.

This goal will be ending in 2008, four years earlier than planned. Several factors contribute to the early termination of this goal. Scientific advances in the fields of proteomics and metabolomics did not materialize, requiring NIH to revise its approach to the development of CEBS. Additionally, competing interests have prompted a shift in priorities and changes in resource allocation. Hence, this goal will cease further development after FY 2008, when it finishes the high-risk, long-term expectation of providing a knowledge base that integrates microarray data, toxicological data, and histopathological visualizations, the three components of toxicogenomics that are currently achievable. However, current database

content and robust object models, CEBS SysBio-OM and CEBS SysTox-OM, provide sufficient groundwork for alternative developments in the future.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	(FY02) Intramural databases and commercial software to build ProtoCEBS available	◆					
FY03	*Actual Performance:* (MET) ProtoCEBS launched, tested, and implemented.						
Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	(FY03) CEBS object model to capture molecular expression data (only) designed but not tested		◆				
FY04	*Actual Performance:* (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.						
Create and provide public access to a global molecular expression and toxicology/pathology database of both chemicals found in the environment and drugs that have an effect on biological systems (CEBS), featuring simple query download capability.	(FY03) CEBS version 1.0 launched in August 2003 contains only microarray data.			◆			
FY05	*Actual Performance:* (MET) CEBS versions 1.5 and 1.6 have been made available to the public. These programs provide simple query download capability of global molecular expression and toxicology/pathology data on a select number of studies of chemicals found in the environment and drugs that have an effect on biological systems.						
Enhance the CEBS to allow the capture and integration of transcriptomics, proteomics, and toxicologic data for the same compound.	(FY04) The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound				◆		
FY06	*Actual Performance:* (MET) CEBS has been enhanced. Version 2.0.7 is the first public repository designed to capture and fully integrate with 'omics data, toxicological, histopathological and other biological measures.						
Enhance electronic sharing of 'omics and biology endpoint data.	(FY06) Initial integration of microarray and toxicologic/histopathologic data achieved					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Complete goal of developing a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	(FY07) CEBS currently does not link outcomes of searches to existing literature databases.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. CEBS version 2.0.7 was released on September 6, 2006 and is the first public repository designed to capture and fully integrate with 'omics data, toxicological, histopathological and other biological measures. Thus, the target to enhance electronic sharing of 'omics and biology endpoint data was fully met, and the initial integration of microarray and toxicologic/histopathologic data was achieved.

The revolution in genomic techniques that arose from the Human Genome Project provides an opportunity to greatly improve the field of toxicology. This new "toxicogenomics" combines studies using "-omic" technologies for genetics, genomic-scale mRNA expression, and bioinformatics to understand how environmental toxicants interact with the genome to

cause normal cells and tissues to become diseased. This vastly improved understanding of molecular events that lead to environmentally associated illnesses can potentially (1) improve regulatory risk assessment, (2) identify toxic products earlier in development, and (3) identify mechanisms of toxic action that could be modified in product development.

Implementation Strategy Advances or Other Highlights

The CEBS Systems Toxicology object model (CEBS SysTox-OM) was completed (to replace the simpler CEBS ToxArm). CEBS SysTox-OM was designed and implemented to enable capture of information on the toxicogenomics study design and toxicology/pathology outcome datasets. The scope of data captured from toxicogenomics studies includes observations made of the subject throughout the study timeline, both before and after the specimen was taken for toxicological, histopathological or other biological analysis. CEBS also captures descriptions of the protocols used in the study, in-life observations of subjects, and all associated biochemical measurements and histopathological analyses. These protocols, temporal events, and analytical measurements are useful in integrating microarray or proteomics data with a defined patho-physiological phenotype. Acetaminophen is an example compound for which all mentioned datatypes have been integrated within CEBS.

PART

This goal was included in the FY2007 PART of the Intramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-6.4	**By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.**

BACKGROUND

Prevalence/Incidence

Asthma prevalence has increased significantly over the past 20 years so that by 2002 nearly 11 percent of U.S. adults had been diagnosed with asthma. In the adult population, the disease affects women and minorities disproportionately with prevalence rising to over 20 percent in some groups. Prevalence in children has reached 12 percent in the United States. Boys are more likely to be diagnosed with asthma than girls. Prevalence in boys begins to decrease around puberty at the same time that it begins to increase in girls, resulting in an overall increased prevalence in women. Minority and low socioeconomic status children are disproportionately affected and are more likely to have suffered an attack in the past twelve months.

Disease Burden

Asthma is a major cause of lost days from work and school, sleep disruption, restricted activities, physician and emergency department (ED) visits, and asthma-related mortality. By 2002, nearly 30 million people in the U.S. had received a diagnosis of asthma at some point in their lives, resulting in nearly 13 million physician visits and nearly 2 million ED visits. The annual cost of asthma to the U.S. economy is estimated at $20 billion. Hospitalizations and ED visits account for nearly 50 percent of the overall cost. Although only 20 percent of asthmatics have been admitted to an ED or hospital, they account for more than 80 percent of total direct costs and the average annual cost per patient who had an asthma attack is more than three times higher than the cost per patient who did not have an attack. Asthma exacerbations (AE) contribute significantly to loss of disease control and increased healthcare costs.

Rationale

The NIH supports a comprehensive asthma program to develop new approaches to prevent, treat, and control asthma. AE cause many of the negative effects of asthma and management of AE accounts for a large proportion of the estimated annual cost to the U.S. economy. In contrast to our understanding of the basic underlying inflammatory mechanisms of asthma pathogenesis, little is known about the pathophysiologic processes that occur during an exacerbation, how exacerbations are resolved, the effect of AE on future exacerbation severity and frequency, and the long term effects of AE on lung physiology, function, and disease progression. Research is needed to develop more effective treatments to control exacerbations and to maintain or improve lung function.

Molecular pathways, chains of sequential biochemical reactions that take place inside cells, are responsible for the characteristic responses that underlie physiological states and pathophysiological states, including asthma exacerbations. The many steps that comprise a pathway can offer numerous targets for intervention with drugs or immune modulators. Defining which pathways participate in the physiological processes observed in AE is an

essential prerequisite for the discovery of new therapeutic agents.

The potential relationship between exacerbations and progressive loss of lung function needs to be explored and defined. Since exacerbations often occur while a patient is receiving treatment, it is likely that the mechanisms responsible for AE are distinct from the processes in more stable asthma. Many patients with asthma experience AE that seem to resolve completely with periods of normal lung function in between each exacerbation. However, it is unclear whether changes in lung structure, function, and immune response remain following AE that lead to future episodes and ultimately contribute to disease chronicity and persistence.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Little is known about AE, one of the principal causes of asthma morbidity. In order to develop new interventions to prevent and/or help resolve AE, the NIH initiated a set of basic, clinical, and translational studies to determine the molecular, cellular, and genetic causes of AE. The long term goal is to identify and characterize two molecular pathways of potential clinical significance that may serve as a basis for discovering new medications for preventing and treating AE. The studies will address diverse areas including: the role of environmental triggers in enhancing airway hyperresponsiveness, the relationship of environmental factors to frequency and severity of AE, specific effects of initiating events on lung physiology and inflammation, genetic approaches to individual susceptibility for AE, and the role specific immune and lung cells play in the pathobiology of AE.

Glycans are molecules that may play a role in host defense, including defense against viral airway infection, one of the most common triggers for AE. An individual's 'secretor' status is defined by enzymatic activity involved in glycan biosynthesis (glycosyltransferases) and glycan degradation (glycosidases). The secretor status and frequency of viral airway infection in asthmatic patients hospitalized for management of acute asthma symptoms will be compared to asthmatic individuals without a history of exacerbation requiring hospitalization. The role of glycans and glycosidases during virus-induced AE will also be studied.

As the studies to determine the molecular, cellular, and genetic causes of AE progress, periodic review and analysis of data collected (prior to completion of the studies) is critical for determining future research direction. During the course of the studies, investigators will meet to share experiences, successes, and concerns, as well as to assess the state of the field.

Imaging modalities have not been used effectively to study the development of AE. Research directions beyond FY 2007 could include evaluating the use of new imaging techniques to assess obstruction in the lung as it relates to the thickness of the airway wall and inflammation and to visualize the ventilated airspaces under both dynamic and static conditions. The research will contribute to the understanding of lung physiology, in general, the relationship between inflammation and lung physiology, and alterations in lung physiology that occur during AE.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Initiate study of molecular, cellular, and genetic causes in AE.	(FY05) Little is known about the factors that predispose asthmatics for exacerbation.			◆			
FY05	*Actual Performance:* (MET) Developed and funded a program consisting of twelve studies which will examine the molecular, cellular, and genetic causes of AE.						
Initiate study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history.	(FY05) Little is known about the role glycosidase activity may play in modification of airway glycans and the promotion of virus-induced AE.				◆[e]		
FY06	*Actual Performance:* (MET) A study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history was initiated in July 2005.						
Analyze data from studies of molecular, cellular, and genetic causes in AE.	(FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Use advanced radiological and molecular imaging techniques to increase understanding of changes in pulmonary physiology associated with asthma exacerbations.	(FY06) Limits of imaging methods have made it difficult to understand how AEs affect pulmonary physiology.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history was initiated in July 2005. As of November 2006, recruitment has not been completed. In the fall, people begin to experience viral infections more frequently which can make it more difficult to recruit a healthy asthma patient. Thus, the Principal Investigator needs one more subject to complete enrollment for this study.

The study will provide information on the association between expression of specific blood group antigens in the airway and risk for asthma exacerbation due to viral infection. Potentially, the study could identify individuals at risk for exacerbation during an infection, allowing for prophylactic adjustment of asthma medication.

Efficiency

Because of unexpectedly rapid research progress, progress that could not have been anticipated when work toward the target began, the study was initiated sooner than originally anticipated.

SRO-7.2	**By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.**

BACKGROUND

Prevalence/Incidence

Cancer is the second leading cause of death in the United States. In 2004 an estimated 1,368,030 persons in the United States will be diagnosed with cancer, including 230,110 prostate cancers, 215,990 female breast cancers, 173,770 lung and bronchus cancers, and 146,940 cancers of the colon/rectum. These estimates do not include most skin cancers; new cases of skin cancer are estimated to exceed 1 million per year. Over two-thirds of all cases of cancer occur among people age 65 years and older.

Disease Burden

The Nation's past investments in cancer research are paying major dividends:

- Americans are increasingly adopting good health habits to reduce their cancer risk.
- Overall, cancer incidence and mortality rates are dropping, especially mortality rates for cancers that are diagnosed prior to metastatic spread.
- Overall, the more than 9 million cancer survivors in America are enjoying a higher quality of life than was possible just a few years ago.

However, in the face of these significant advances, cancer remains a major public health problem, and with the aging and changing demographics of America, expected increases in numbers of new cancer cases loom as a potential health care crisis.

Rationale

Recent advances in understanding the molecular basis of cancer and the associated development of novel molecular technologies in areas such as proteomics, portend a future where cancer can be detected early and preempted before it spreads, perhaps on an individual basis. For example, nanoscience offers unparalleled opportunities to measure and monitor changes within cells at the level of multiple atoms. Applications of nanotechnology have the potential to shift the paradigm of cancer toward earlier detection and prevention and provide a new platform for eventual high-throughput diagnostics and, ultimately, real-time monitoring of patients.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To accomplish the goal of integrating nanoscale components into a system capable of detecting cancer at its earliest stage, NIH established intramural and extramural collaborations to develop, characterize, standardize and test nanoscale devices that are 10-200x smaller than human cells. Concomitantly, a new National Nanotechnology Characterization Laboratory generated profiles of nanoparticles in biological systems; developed standards for nanodevices enabling researchers to develop cross-functional platforms; generated data to assist researchers in choosing a nanoscale device for a

particular clinical or research application; and developed data to support regulatory sciences for the translation of nanotechnology into clinical applications.

In addition, NIH has used a Request for Information (RFI), Broad Agency Announcements (BAAs), contracts and grants to identify critical technology platform needs and to develop technology programs that will create platforms for clinical application in cancer research.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	(FY02) Lack of relevant collaborations.	◆e					
FY03	*Actual Performance:* (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.						
Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	(FY03) No current core laboratory with needed capacity		◆e				
FY04	*Actual Performance:* (MET) The national Nanotechnology Characterization Laboratory (NCL) has been established and will enable development of essential data about the profiles of nanoparticles in biological systems.						
Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	(FY03) Existing nanosensors and nanoparticles not integrated into a common platform.			◆			
FY05	*Actual Performance:* (MET) Nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings.						
Complete goal of integrating nanotechnology-based components into a system capable of detecting specific biomarkers to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	(FY05) Nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings.				◆		
FY06	*Actual Performance:* (MET) Nanotechnology-based components have been integrated into systems capable of detecting specific biomarkers (molecular signatures), serving as proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. Goal completed.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target has been MET and the goal was ACHIEVED. Nanotechnology-based components have been integrated into systems capable of detecting specific biomarkers (molecular signatures), serving as proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. This achievement is demonstrated by a few representative examples drawn from a broad cross-section of technological advances: (1) The development of nanoparticle-based biobarcodes; (2) the development of a multifunctional polymeric micelles; (3) the demonstration of dendrimer-based nanoparticles delivering antisense oligodeoxynucleotides into breast cancer cells; and (4) the application of nanoparticles to computed tomography (CT) imaging.

Implementation Strategy Advances or Other Highlights

Researchers at one of the NIH-supported Center for Cancer Nanotechnology Excellence (CCNE) developed nanoparticle-based biobarcodes that can detect three different

protein tumor markers: prostate specific antigen (PSA); human chorionic gonadotrophin (HCG), a marker for testicular cancer; and α-fetoprotein (AFP), a liver cancer marker. Each protein is detected using a gold nanoparticle coated with an antibody that binds specifically to that protein. Each nanoparticle also contains an oligonucleotide "barcode" whose sequence is specific for each protein and a universal sequence common among all oligonucleotides. The assay also uses a set of three magnetic microparticles, each coated with an antibody that binds specifically to a different portion of the target protein.

Other NIH-supported researchers have developed multifunctional polymeric micelles with cancer-targeting capability, controlled drug delivery, and efficient magnetic resonance imaging (MRI) contrast characteristics. Doxorubicin and a cluster of superparamagnetic iron oxide (SPIO) nanoparticles were loaded successfully inside the micelle core. This integrated nanomedicine platform will open many exciting opportunities for the targeted delivery of therapeutic agents to cancerous tumors as well as the use of MRI as a noninvasive strategy to monitor tumor targeting efficiency to improve the therapeutic outcome of drug therapy.

Another team of NIH-supported researchers demonstrated that dendrimer-based nanoparticles can deliver antisense oligodeoxynucleotides into breast cancer cells. The researchers formed the nanoparticles using a biocompatible dendrimer made of poly (propyleneimine) (PPI). This particular type of dendrimer belongs to a family of what are known as amine-terminated polymers, a class of compounds that other investigators have found promote gene uptake by cells. These dendrimers are also relatively easy to modify chemically, affording the option of adding tumor-targeting agents or additional anticancer drugs to the nanoparticle.

Researchers have also demonstrated the application of nanoparticles to computed tomography (CT) imaging. The polymer-coated Bi2S3 nanoparticles demonstrates excellent stability at high concentrations, high X-ray absorption (fivefold better than iodine), very long circulation times in vivo and an efficacy/safety profile comparable to or better than iodinated imaging agents. These nanoparticles and their bioconjugates are expected to become an important adjunct to in vivo imaging of molecular targets and pathological conditions.

PART

This goal was included in the FY2006 PART of the Extramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

SRO-7.8.1	**By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.**

BACKGROUND

Genomics, the science of deciphering and drawing information from the genetic code of an organism, is a powerful tool that NIH is using to understand the microbes that cause disease and to design strategies to overcome infectious disease. With microbe-specific genome information, drugs can be targeted to specific genes, and the products of specific genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains. Recognizing the enormous potential of microbial genomics research, NIH has made a significant investment in the large-scale DNA sequencing of the genomes of human pathogens and invertebrate vectors of disease, including microorganisms considered to be potential agents of bioterrorism.

Rationale

Genomic information will aid in the identification of gene products critical to growth and pathogenicity of microbes and their vectors; these may serve as targets for new therapeutics, vaccines, and diagnostics. Significant progress in DNA sequencing technology has allowed genomic DNA to be sequenced more efficiently and cost-effectively. Critical companions to state-of-the-art DNA sequencing techniques are the bioinformatics, computational tools, and databases that provide the scientific community with the resources needed to query, analyze, and annotate the sequencing data and to assemble genomes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In FY 2006, NIH continued to support several activities to provide comprehensive genomic, bioinformatic, and proteomic resources to the research community for basic and applied research to rapidly address the Nation's biodefense needs. These activities include: (1) the Microbial Genome Sequencing Centers, (2) the Bioinformatics Resource Centers, (3) the Pathogen Functional Genomics Resource Center, and (4) the Proteomics Research Centers.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Complete the genomic sequences for at least five bacteria and two protozoa that cause infectious disease.	(FY02) Genome sequences for 32 bacterial pathogens, 1 protozoan parasite, and 1 insect completed.	◆[e]					
FY03	*Actual Performance:* (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.						
Complete the genomic sequences of at least five bacterial pathogens, two protozoa, and three fungal pathogens that cause infectious disease.	(FY03) Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed		◆[e]				
FY04	*Actual Performance:* (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.						
Complete the genomic sequences of at least five bacterial pathogens, four protozoa, two fungal pathogens that cause infectious disease.	(FY04) Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi and 1 insect completed			◆[e]			
FY05	*Actual Performance:* (MET) Genomic sequencing projects for 30 bacteria, 1 protozoan, 1 insect and 3 fungi were completed.						
Complete the genome sequence of at least six bacterial pathogens, two protozoan parasites, and one invertebrate vector of infectious diseases.	(FY05) Genome sequences for 88 bacterial pathogens, 9 protozoan parasites, 6 fungi, and 2 invertebrate vectors of infectious diseases completed				◆[e]		
FY06	*Actual Performance:* (MET) Genomic sequencing projects of 44 bacteria, 6 protozoa, 1 parasitic worm, 2 fungi, 1 invertebrate vectors of disease and 1 plant were completed in FY 2006. One additional invertebrate vector which was completed in FY2005 ahead of schedule also counts toward meeting/exceeding the FY06 target.						
Complete goal of determining the genome sequences of 45 human pathogens and 3 invertebrate vectors	(FY06) Genome sequences for 132 bacterial pathogens, 15 protozoan parasites, 8 fungi, 1 parasitic worm, 1 plant, and 3 invertebrate vectors of infectious diseases completed					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and exceeded by completing genome sequences for 53 pathogen genomes, including 44 bacterial pathogens, six protozoan parasites, two fungal pathogens and one plant.

Also completed in FY 2006 were sequencing projects for one parasitic worm and one insect vector of disease. In addition, one invertebrate more invertebrate vector of disease sequencing project that was completed by NIAID ahead of schedule in FY 2005 contributed to meeting this FY 2006 target. By the end of FY 2006, NIH had completed a total of 160 pathogen and invertebrate vectors of infectious diseases genome sequencing projects: 132 bacteria, 8 fungi, 15 parasitic protozoans, one parasitic worm, one plant and three invertebrate vectors of infectious diseases. This exceeds the FY 2006 annual target, but one more invertebrate vector needs to be completed in order to complete the goal because one of the three insect vectors completed thus far was part of the baseline.

Completion of some projects earlier than anticipated is largely due to advances in molecular biology that have led to remarkably fast and accurate methods for sequencing genomes. Briefly, 44 (rather than 6) bacterial pathogen sequencing projects were completed in FY 2006, including Burkholderia cenocepacia, Burkholderia dolosa, Burkholderia mallei (3 strains), Burkholderia pseudomallei, (3 strains), Camplyobacter (9 strains), Coxiella burnetii (2 strains), Escherichia coli (1 strain), Listeria monocytogenes (16) Mycobacterium tuberculosis (2 strains), Pseudomonas aeruginosa (3 strains), Rickettsiella grylli (1 strain),

Shigella dysenteriae (1 strain), Yersinia pestis (1 strain). In addition, DNA sequencing projects for six protozoan parasites (Entamoeba invadens, Entamoeba dispans, Plasmodium falciparium (2 strains), Toxoplasma gondii (1 strain), Trichomonas vaginalis (1 strain), one plant (Ricinus communis) and two fungi (Aspergillus clavatus and Aspergillus fischerianus) were completed. Also completed were full sequencing projects for Trichinella spiralis (a parasitic worm) and Pediculus humanus (body louse which is a vector for trench fever and epidemic typhy).

Implementation Strategy Advances or Other Highlights

In FY 2006, NIH supported 40 large scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites and invertebrate vectors including: Borrelia, Clostridium, E.coli, Salmonella, Streptococcus pneumonia, Ureaplasma, Coccidioides, Penicillium marneffei, Tararomyces stipitatus, Lacazia loboi, Histoplasma capsulatum, Blastomyces dermatitidis, Crytosporidium muris, Dengue viruses, avian influenza viruses and additional sequencing of Aedes aegypti. Sequencing of other genomes, including two invertebrate vectors of infectious disease, Ixodes scapularis and Culex pipiens, is ongoing.

Efficiency

Technological developments have resulted in a great increase in efficiency and drastic decrease in the cost to sequence DNA. The sequencing process has become faster and more accurate. The Institute for Genomic Research (TIGR), an international microbial sequencing center, reported that the price to sequence a piece of DNA approximately 650 nucleotides in length decreased from $7.70 in 1996 to $0.98 in 2004. In 2006, the cost of sequencing continued to decrease to $0.70 due to improvements in technology.

SRO-7.8.3	**By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.**

BACKGROUND

The Reference Sequence (RefSeq) Collection provides a unified view of the genetic knowledge of organisms. A single, high-quality collection of reference sequences for multiple species that is richly annotated and highly connected to other information sources makes it possible to undertake large-scale comparative analyses. The ability to make discoveries in one organism (such as mouse models of a human disease) and immediately apply them to another organism (such as humans) is one of the most powerful aspects of molecular biology. The academic and pharmaceutical research communities use reference sequences in this way to investigate basic molecular biological processes and medical problems, such as different disease susceptibilities for individuals or targeted individual drug treatment approaches. The availability of a RefSeq Collection means that time once spent identifying resources, gathering data, and reviewing its quality is freed for research.

Rationale

Hundreds of millions of dollars have been invested by Federal agencies, international governments, and charitable foundations to obtain genomic and transcript sequence data for organisms, from human to viruses. Although a wealth of sequence data is now available, these data exist in multiple formats, and locations and are not connected to other information; furthermore, the data produced by different groups are often redundant, inconsistent, or partially overlapping. Without a cohesive representation of the data, it is difficult to reap the full benefit of the massive public investment in obtaining the data. The RefSeq Collection serves as a foundation for genomic research by providing a centralized sequence set integrated with other information, including publications, phenotypes, and disease catalogs. This collection was built and maintained through both computational and expert analysis to integrate large quantities of disparate data while also providing a high-quality resource. Both the computational and expert tasks must be ongoing so that (1) the collection stays current as new data become available, (2) quality is ensured, and (3) new opportunities that add value are identified.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The RefSeq project expanded and enhanced its access to the general biomedical research community. RefSeq is intended as the most comprehensive and stringently reviewed collection of gene sequences publicly available with a broad domain of applications, from investigating the function of single genes to assisting in the conduct of large-scale comparative analyses of genes across multiple organisms. With the introduction of the Web-based Genes database, NIH is providing the 20,000 users who daily search for

sequence information with a highly interactive and powerful means of accessing a unified and richly annotated view of sequence and gene data.

To facilitate more sophisticated and specialized uses of RefSeq, the database is available for complete downloading to allow commercial or academic groups to generate value-added versions of the database to target specialized or species-specific audiences and allow them to perform exhaustive analyses across the entire data set. Through extended development of the suite of RefSeq analytic tools, NIH has increased by many times the number of scientists who are able to carry out computationally sophisticated analyses on the RefSeq Collection without the need for programming skills.

Finally, methods were developed to foster collaborations with outside groups to augment the public data. These collaborations include whole-genome annotation, functional annotation of multigene families, expert review of single genes, and annotation of single records from multiple sources. Related resources at NIH for functional gene information include the Comparative Toxicogenomics Database, the Encyclopedia of DNA Elements and Mammalian Gene Collection, the Cancer Genome Anatomy Project, and the database of eye-related genomic information.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	(FY02) At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	◆e					
FY03	*Actual Performance:* (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.						
Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	(FY03) RefSeq collection includes sequence data from 2124 species; only a limited database is available		◆e				
FY04	*Actual Performance:* (MET) The RefSeq collection is now fully available via the online resource Entrez Gene.						
Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	(FY04) About 40 collaborations in place for obtaining annotated RefSeq records and other functional data			◆e			
FY05	*Actual Performance:* (MET) The RefSeq project was expanded through the deployment of a database and web site that both tracks the submission of genome sequencing projects and supports the generation of RefSeq records from those submissions. Collaborations were established at multiple levels to support the expansion and curation of the project.						
Complete goal of building a publicly accessible RefSeq Collection to serve as the basis for medical, functional, and diversity studies	(FY05) Database and website deployed. Collaborations established at multiple levels.				◆		
FY06	*Actual Performance:* (MET) The goal was completed by building a publicly accessible RefSeq Collection to serve as the basis for medical, functional, and diversity studies.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and the goal was ACHIEVED. A publicly accessible

Collection of Reference Sequences was built to serve as the basis for medical, functional, and diversity studies. The RefSeq Collection serves as a foundation for genomic research by providing a centralized sequence set integrated with other information, including publications, phenotypes, and disease catalogs. The RefSeq Collection benefits scientists and researchers by substantially reducing the search space for identifying related gene sequences and thereby accelerating research into the functional properties of genes. The expansion and curation of the RefSeq collection is supported by numerous collaborations, the Genome Project database, targeted outreach activities, and staff curation.

Collaborations are supported by two complementary approaches that include database support for tracking and managing large-scale data as well as a curation team that engages in outreach, education, and data curation for targeted organisms. Collaborations are established at multiple levels including working with genome sequencing centers that submit assembled annotated genome sequence data to research groups that contribute information about specific subsets of data such as gene-families or features of proteins, or even single genes. All levels of collaboration have been well-received and welcomed by the sequencing and research communities.

The Genome Project Database tracks the status of whole genome sequencing projects as they progress from a funded proposal to submitted sequence data in GenBank and in the RefSeq collection. The International Nucleotide Sequence Database collaboration (INSD) between GenBank, EMBL, and DDBJ now requires a registered ID in the NIH Genome Project database for submissions of whole genome assemblies. The NIH provides a web service to support assignment of project IDs for the INSD. The Genome Project ID is used to track the association between the submitted sequence data, the project description, and the resulting records generated for the RefSeq collection. The availability of this type of tracking is significant as it helps ensure that expansions and updates to the RefSeq collection continue to be comprehensive and timely.

Implementation Strategy Advances or Other Highlights

The content of the RefSeq collection was increased using the databases and infrastructure that has been developed. Incremental changes to the infrastructure and databases are made over time, as needed, to accommodate additional sources of data and to maintain the process flow in updated computer platforms. Use of this infrastructure has successfully realized increased growth in the RefSeq collection and companion resources Entrez Gene and Genome Projects, and in active collaboration with the scientific community.

The tables below show the growth of RefSeq, Entrez Gene, and collaborations. Collaborations also resulted in an increased content for the Map Viewer resource which provides graphical displays of map data and annotated eukaryotic genomes. The number of organisms with data presented in the Map Viewer increased by 200% from 2003 to 2006 (16 and 48 species, respectively), with sequence annotation displays available for 37 organisms and 176 distinct non-sequence maps available (genetic, radiation hybrid, or cytogenetics maps).

RefSeq Growth:

Time Frame	Number of Species	Number of Records	Number of Proteins
As of October 2002	Not tracked	Not tracked	446,000
As of October 2003	2,214	1,097,404	831,287
As of October 2004	2,645	1,709,723	1,218,266
As of September 2005	3,060	3,400,773	1,899,454
As of September 2006	3,774	4,311,543	2,879,860

Entrez Gene Growth:

Time Frame	Number of Species	Number of Records
As of October 2003	Resource not available	Resource not available
As of December 2003	1,982	708,846
As of October 2004	2,491	1,071,343
As of September 2005	2,913	1,492,065
As of September 2006	3,547	2,042,476

Collaborations Growth:

Time Frame	Number of Collaborations
As of October 2003	Not available
As of December 2003	Not available
As of October 2004	20
As of November 2005	167
As of November 2006	469

Outreach activities to promote collaborations included conference calls, workshops, posters, and other activities such as Plant & Animal Genome Conference XIV, Yeast Genetics and Molecular Biology Meeting, Mouse Molecular Genetics Meeting, American Society of Human Genetics, Zebrafish workshop, Sea Urchin Meeting, and conference calls regarding Honey Bee, Bovine, Sea Urchin, and Human genome maintenance.

SRO-8.2	**By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.**

BACKGROUND

Skeletal health depends on the process of bone turnover, in which small regions of bone are broken down (resorbed) and replaced with new bone. The regulation of the balance between bone resorption and new bone formation, which can be affected by nutritional, endocrine, and pharmacological factors, is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis. Osteoblasts are the cells that form new bone during bone turnover. Osteoblasts that remain embedded in the bone become osteocytes. Recent work has shown that osteocyte survival is an important requirement for skeletal health.

Bone is composed of mineral crystals embedded in a matrix of many different proteins. Interactions between matrix proteins and proteins found at the cell surfaces of osteoblasts and osteocytes are thought to produce signals that are important for regulation of bone turnover and survival of osteocytes. However, the molecular details of cell-matrix interactions have been explored in only a few instances. If known, the mechanisms of these interactions could yield targets for new drugs that might act to stimulate bone formation or block bone resorption. Understanding how the number and activity of osteoblasts are controlled could lead to new therapies for restoring lost bone, either with drugs or by tissue-engineering approaches.

Rationale

It is clear from work to date that altering cell-matrix interactions can produce changes in bone remodeling activity and bone mass. Before these findings can be translated into therapeutic applications, however, it will be necessary to refine our understanding of known cell-matrix interactions and identify new interactions with important roles in the maintenance of skeletal health. Recent advances, particularly in the genetic manipulation of mice, make it possible to define the function of different matrix proteins and the cell surface proteins that interact with them. For example, mice can be produced either to lack a matrix protein or to produce abnormally large amounts of the protein. Cell surface proteins thought to interact with matrix proteins also can be tested in this way. It is important to conduct these experiments with intact, genetically modified mice, in addition to cell cultures, for two reasons. First, although osteoblasts can be induced to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal. For example, osteoblasts do not become osteocytes within the bone produced in culture. Second, the consequences of interfering with specific cell-matrix interactions can be assessed thoroughly by examining the bones of mice. This can even indicate the ultimate effect on the mechanical strength of the bones.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To date, nine relatively abundant proteins (in addition to collagen, the principal structural component of bone) have been identified in bone matrix. Two non-collagen proteins, thrombospondin-2 (TSP2) and osteonectin, were selected for initial study, based on evidence that they play important roles in the generation and survival of osteoblasts. Studies now also have been initiated on three additional matrix proteins: fibronectin, dentin matrix protein-1 (DMP-1), and connective tissue growth factor (CTGF). Genetically modified mouse strains lacking these proteins have been generated. Using cells isolated from the genetically modified mice, cell culture systems have been developed in which the effects of the matrix proteins on osteoblasts and their precursor cells can be determined. These mice and cell culture systems are valuable tools for the strategies outlined below.

NIH will use existing mouse strains and cell culture systems to (1) determine the effects of matrix proteins on the generation of osteoblasts from precursors and on the survival of the cells, (2) identify the biochemical pathways within cells that mediate the effects of the proteins, (3) identify the specific portions of the proteins that are responsible for the effects, and (4) identify the molecules on the surface of cells that interact with matrix proteins. This strategy is important to achieving this goal for several reasons. First, cell cultures allow for very precise measurements of biological effects at low cost. Detailed knowledge of the effects of matrix proteins on isolated cells is the first requirement for predicting the effects of drugs that either mimic or block the cell-matrix interactions. Second, identification of active portions of matrix proteins and interacting cell proteins will allow for design of new drugs and selection of existing drugs for testing. Third, observations of genetically modified mice place results of cell culture experiments in the context of an intact organism. This is essential because therapies would be applied in humans, where many factors are present that cannot be replicated in cell cultures.

NIH will also employ genetic engineering technology to generate new mouse strains: (1) mice that allow for visualization of matrix proteins in tissue samples, and (2) mice in which the matrix proteins are produced in certain cells at specific stages of development. Using new mouse strains will help to determine the effects of matrix protein-osteoblast interactions at different stages of osteoblast development. This strategy adds to the information gained by the first strategy, placing initial observations in the context of time and place. Knowing where and when matrix proteins are produced in normal mice gives a rough idea of which cells must be targeted in designing a therapy, and at what stage in cell development the effect is most critical. Producing the proteins at specific times and places by genetic technology establishes these parameters more precisely. Although mice wholly deficient in fibronectin are not viable, researchers recently engineered mice in which only a subset of osteoblasts are fibronectin-deficient. Development of this animal model is essential for successful completion of this goal because the model will provide valuable information to researchers as they dissect fibronectin's role in bone formation.

NIH will determine the physical and mechanical properties of bone from genetically modified mice. These measurements are necessary to assess the potential clinical significance of interventions based on interactions between bone cells and matrix proteins. Ultimately, therapies targeting osteoporosis are effective only if they improve the resistance of bone to fracture.

Deficiency of the protein fibrillin-2 causes a genetic disease called congenital contractural arachnodactyly (CCA), one feature of which is reduced bone mass. Recent work suggests that fibrillin-containing structures are necessary for normal bone cell function. Understanding the mechanism of this effect could help in the development of therapies for CCA and could also lead to new ways of stimulating bone formation in more common conditions, such as osteoporosis.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	(FY02) Information on the role of thrombospondin-2 in bone generation is incomplete.	◆					
FY03	*Actual Performance:* (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.						
Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	(FY03) Biochemical pathways that mediate cell survival are unknown.		◆				
FY04	*Actual Performance:* (MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.						
Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	(FY03) Information is incomplete on where thrombospondin-2 is produced; mouse model can provide this data.			→	→	→	
FY05	*Actual Performance:* (EXT) The FY05 target was extended to FY 2007. The stromal cells of bone marrow appear to be the key producers of thrombospondin-2. Technical difficulties have delayed construction of the fluorescent reporter mouse.						
Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor.	(FY04) Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown.				◆		
FY06	*Actual Performance:* (MET) Researchers produced a mouse in which only bone-forming cells are deficient in fibronectin and identified integrin alpha v beta 5 as the cell surface molecule that mediates interactions between the cells and connective tissue growth factor.						
Determine the characteristics of the skeleton in mice deficient in dentin matrix protein 1 (DMP-1), and assess the consequences of DMP-1 deficiency for bone cell function.	(FY06) The skeleton of a mouse lacking DMP-1 exhibits complex defects. It is unknown how this is related to bone cell function.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Determine the properties of bone-forming cells and bones from mice in which fibrillin-2 is absent.	(FY06) Although fibrillin proteins have been studied as structural components of the matrix, it has only recently been recognized that they may influence the function of bone cells.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A genetically modified mouse in which only bone-forming cells (osteoblasts) are deficient in fibronectin has been produced. The effect of this deficiency

is surprisingly mild, given that experiments with osteoblasts in culture indicated an important role for fibronectin in bone formation. One possible explanation is that fibronectin produced by other types of cells contributes to the natural environment of osteoblasts and this lessens the requirement for fibronectin production by the osteoblasts themselves. Studies are now underway to generate mice in which fibronectin production is eliminated in other cell types to test whether cells other than osteoblasts provide fibronectin during normal bone growth. In parallel experiments, samples of bone removed from mice carrying fibronectin-deficient osteoblasts will be maintained in laboratory cultures to test whether blood circulating in a living mouse might be a source of fibronectin for bone formation.

The cell surface molecule mediating interaction between osteoblasts and connective tissue growth factor (CTGF) has been identified as integrin alpha v beta 5. Investigators also showed that interaction between the integrin and CTGF triggered changes in the osteoblast that are related to the cell's ability to spread and move over the matrix surface. The integrins constitute a group of similar proteins with important roles in many different tissues. They are the targets of on-going drug development efforts that potentially could yield new therapies for bone loss and osteoporosis.

Implementation Strategy Advances or Other Highlights

Significant progress has been made on other aspects of this goal. The matrix component dentin matrix protein 1 (DMP1), which is the focus of the 2007 target, has been shown to play a key role in the mineralization of bone by osteoblasts. Mineralization of bone is crucial for its mechanical strength. Mice deficient in DMP1 have poorly mineralized bone, resembling the human disorders known as rickets and osteomalacia. In fact, researchers recently discovered that one inherited form of rickets is due to mutations in the human DMP1 gene. In other work, mechanical testing of bones from mice lacking the matrix component biglycan shows that biglycan-deficient bone is weaker than normal bone, possibly because of differences in the way minerals are incorporated into the matrix.

These insights have implications for future implementation of this goal and for how bone cell-matrix interactions might eventually be exploited in developing therapies for bone loss. Initially, the emphasis of the strategy was on the growth and survival of osteoblasts because making bigger and thicker bones is one way to make bones stronger. But, another way to make bones stronger might be to increase the degree of mineralization. The new results suggest that specific cell-matrix interactions in bone may be important for mineralization. Understanding these interactions could thus furnish the basis for therapies that would make bone intrinsically stronger, improving its resistance to fracture.

SRO-8.4	**By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.**

BACKGROUND

The Institutional Development Award (IDeA) Program was authorized by the NIH Revitalization Act of 1993 to foster health-related research and increase the competitiveness of investigators at institutions located in States with historically low grant awards from NIH. An institution's eligibility to participate in the IDeA Program is determined by the aggregate level of NIH grant funds collectively received by all research institutions within its State over the preceding consecutive 5-year period and/or the average success rate of research applications over that same time span. Between 1997 and 2001, States that received on average less than $75 million in NIH grant awards and/or had a success rate of less than 20 percent were eligible for the IDeA Program.

The IDeA Program was established in FY 1993 at a funding level of $750,000, which slowly increased to $10 million in FY 1999. This limited funding precluded development of major initiatives. However, in FY 2000, funding increased to $38.5 million, which allowed for the development and implementation of a more comprehensive initiative, the Centers of Biomedical Research Excellence (COBRE). The COBRE initiative was specifically designed to enhance the pool of well-trained investigators who could successfully compete for NIH grant awards. This initiative augments and strengthens institutional biomedical research capacities by expanding or modifying research facilities, equipping laboratories with modern research equipment, providing mentoring for promising candidates, and developing research faculty through support of a multidisciplinary center, led by a peer-reviewed, funded investigator with expertise central to the research theme of the center.

The FY 2001 budget for the IDeA Program increased to $100 million and this allowed for the development of a second initiative, the Biomedical Research Infrastructure Network (BRIN). BRIN enhances the pipeline for outstanding students and bolsters the quality of science faculty at baccalaureate and other participating institutions. The BRIN is intended to network research intensive and undergraduate institutions in IDeA states to prepare students for graduate and professional schools as well as for careers in the biomedical sciences. In FY 2004, BRIN was renamed IDeA Networks of Biomedical Research Excellence (INBRE) to better reflect the purpose of the program and to avoid confusion with another program with a similar name.

Rationale

Strong congressional interest in the IDeA Program, along with significant increases in funding, has led to questions about whether the biomedical research capabilities of institutions in IDeA-eligible States will be enhanced and whether this will lead to increased competitiveness of investigators to obtain either NIH research grants or other Federal or non-Federal support. An evaluation will assess the impact of the IDeA Program on the acquisition of NIH research funding as a percent of total NIH funding by the cohort of eligible States and

will determine the factors that have had the greatest impact on enhancing investigator competitiveness.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A database was developed for the annual progress report to collect potential indicators based on previous related NIH evaluations and findings from a pre-COBRE analysis.

Two separate evaluations, one for COBRE and another for INBRE, will be conducted to assess the IDeA Program. Each consists of an evaluation design study followed by the full-scale evaluation. The evaluation design studies included an assessment of data needs, site visits, data collection, data analysis, and a final report. Expert panels will provide advice throughout the evaluations.

Step 1 of the Assessment Methodology for the IDeA Program will consist of completing the evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact and developing a data collection system for INBRE. Step 2 will consist of completing the evaluation design to determine a confirmed list of target indicators to measure IDeA/INBRE impact and assessing the results of the COBRE evaluation design study.

Since the COBRE began before INBRE, the two evaluations will be conducted at different intervals. The evaluation design study for COBRE was completed in FY 2004 and that for INBRE was completed in FY 2005. The full-scale evaluation for COBRE began in FY 2006 and will be completed in FY 2008. The full-scale evaluation for INBRE is anticipated to begin in FY 2007 and be completed in FY 2009.

The purpose of each evaluation design study is to determine the best strategy for evaluating the program. Consideration will be given to determining the indicators that optimally assess whether the research competitiveness and research capacity of the institutions has increased. Some target indicators have been proposed:

INDICATOR	INDICATOR
Publications	Biomedical/behavioral grant submissions and awards
Presentations	NIH biomedical/behavioral grant submissions and awards
Recruited Faculty	Research personnel and research administration staff
Newly Constructed Laboratory Space	Investigators whose research has become independent of COBRE

Further, the annual progress reports that collect potential indicator data will be used to validate the list of indicators developed through the evaluation design study. Whether or not these indicators should be measured at the state, institutional, and/or center level will be determined by the design studies.

Following completion of these evaluation design studies, the full-scale evaluations of COBRE and INBRE will be conducted to determine the impact of the IDeA program.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	(FY02) Indictors from Pre-COBRE analysis and previous evaluations.	◆					
FY03	*Actual Performance:* (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.						
Assessment Methodology for IDeA Program (Step 1): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. -Develop a data collection system for BRIN.	(FY03) Data collection and management system to evaluate impact of IDeA/COBRE in place. (FY04) Indicators from IDeA/COBRE evaluation design.		◆				
FY04	*Actual Performance:* (MET) The COBRE evaluation design, which includes a confirmed list of target indicators, is complete. Data collection and management system is in place for BRIN.						
Assessment Methodology for IDeA Program (Step 2): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. -Assess results of COBRE evaluation design study.	(FY04) Data collection and management system to evaluate impact of IDeA/BRIN in place. (FY04) COBRE evaluation design completed but not evaluated.			◆			
FY05	*Actual Performance:* (MET) The IDeA/INBRE evaluation design was completed in September 2005 and the final report included a confirmed list of target indicators to measure INBRE impact. The results of the COBRE evaluation design study were assessed.						
Full-Scale Assessment of the IDeA Program (Step 1): - Initiate the full-scale evaluation for IDeA/COBRE.	(FY04) COBRE evaluation design				◆		
FY06	*Actual Performance:* (MET) The full-scale evaluation for IDeA/COBRE was initiated when the contract to conduct the COBRE evaluation was awarded on September 28, 2006.						
Full-Scale Assessment of the IDeA Program (Step 2): - Initiate the full-scale evaluation for IDeA/INBRE.	(FY05) INBRE evaluation design.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Full-Scale Assessment of the IDeA Program: --Complete the IDeA/COBRE evaluation and analyze preliminary results.	(FY06) IDeA/COBRE evaluation initiated.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was MET. The full-scale evaluation for IDeA/COBRE was initiated when the contract to conduct the COBRE evaluation was awarded on September 28, 2006. The contractor will conduct a process evaluation which will focus on the 19 COBREs that were initially funded near the end of FY 2000. The purpose of the evaluation is to determine if the program operations and outputs during the centers' first six years have been successful as well as the success of the junior investigators supported during this period. Some examples of the outputs to be assessed include: successful recruitment of new research faculty and technical staff, expansion of core facilities and successful implementation of 3-5 research projects. Although it is an early assessment, enough time has elapsed for the centers to have achieved the program's process goals and for their junior investigators to have made progress in achieving specific outcome goals. Specifically, some of the outcome goals include giving presentations at scientific meetings, publishing research in peer-reviewed journals, applying

for research grants sponsored by NIH and/or other organizations, receiving an external research grant, receiving one or more major research grants as an independent investigator and continuing to participate in COBRE activities after attaining independence. The period of performance for the 19 centers in this cohort will be FY 2001 to FY 2006.

The project consists of 13 tasks identified in the Statement of Work. The technical approach proposed by the selected contractor was designed to minimize the burden on COBRE center personnel as well as the duration and cost of the evaluation by relying primarily on secondary data sources.

Implementation Strategy Advances or Other Highlights

To assist in measuring the impact of IDeA/COBRE on the development of competitive investigators and their capacities to compete for NIH research funding, a contract has been awarded. The contract deals with conducting a process evaluation of the initial 19 COBRE centers funded in FY2000. The contractor will be using the database, which was developed in FY 2003, to confirm the validity of the target indictors needed to determine the impact on research competitiveness and research capacity.

SRO-8.5	**By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.**

BACKGROUND

Conventional clinical and functional measures of disease status do not fully capture the ways in which chronic diseases and their treatment affect individuals. Many aspects of patients' subjective experience, such as symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability are important targets for disease intervention that are not measured by x-rays or laboratory results. Measurement of patient-reported outcomes (PROs) is particularly important in clinical trials, where changes in clinical measurements or imaging results alone may not translate into important benefit to the patients, or in trials in which two treatments may be comparable in limiting or curing disease but have different adverse effect profiles differentially affecting symptoms, functioning, or other aspects of patients' quality of life.

The last several decades have seen a proliferation of tools to measure symptoms, quality of life, functional status, emotional status, and general perception of health. Although many of these instruments have good demonstrated reliability and validity, there are many limitations to current measurement approaches. One critical disadvantage is the inability to compare results across different studies when different measurement tools are used. These instruments may have non-comparable or non-combinable scores because each scale may use a different number of items, different response options, different reference periods, or different item content. For example, progress in clinical pain research is slowed by the use of various pain measurement scales that are not directly comparable. The length and complexity of questionnaires and batteries can also be problematic, creating a level of respondent burden that hampers recruitment, results in too much missing data, or is detrimental to response validity and reliability. The clinical outcomes research enterprise would be enhanced greatly by the availability of a psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics.

Rationale

Increased availability of more precise, efficient and easier to use measures of quality of life and symptom indices will significantly facilitate all forms of clinical research and enhance patient care delivered on the front lines. The development of better health-related quality of life (HRQOL) and symptoms instruments would provide the needed tools for comparing the outcomes of preventive, rehabilitative, and curative interventions.

A new enabling technology, computerized adaptive (or dynamic) health assessments, can yield a more efficient and easier-to-use set of validated clinical research tools. Two critical concepts form the basis of this new technology. The first is that by collecting a large set of questionnaire items in subjects with the widest possible range of severity of disease and levels of health, one can construct reliable models (i.e., item response theory models) that

predict the probability of specific responses by patients based on their answers to initial questions. The second concept uses software programs to control the specific set of questions asked of each patient. Based on the answers to initial questions, the program can focus the remaining questions to more accurately assess the patient's level of functioning. If these standardized instruments and information on their performance in reference populations were widely available, clinical researchers would be able to measure clinical outcomes far more accurately, compare across diseases or populations, account for co-morbid conditions, and ascertain the impact of nonspecific symptoms like fatigue, without the necessity of conducting or having to duplicate, previous validation efforts.

Properly constructed, this repository and supporting technology will lead to more efficient, precise and reliable assessment of quality of life and non-specific symptoms in clinical research, increasing the interoperability of clinical research, permitting the direct comparison of results even from different instruments, using different questions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A multi-disciplinary network of cooperative agreements (PROMIS) has been funded to develop an item bank, test item response theory models of item performance, and develop a computerized adaptive testing system to measure a select number of health-related quality of life (HRQOL) domains and non-disease specific symptoms in patient with chronic illnesses. In FY 2006, the network characterized the ability of commonly used instruments to capture these domains. The strengths, deficiencies, gaps, and redundancies in the most common instruments for these domains were described. Network experts guided the process of developing a set of items to be tested, some new and some from existing instruments, with input from patients. Data collection using this item set has been initiated in a wide range of patients suffering chronic diseases and conditions, and enrollment is anticipated to be completed in May 2007. In FY 2007 and 2008, the results of this large data collection effort will be analyzed to determine a variety of item characteristics and psychometric properties, select the most useful items for the final item bank, and plan additional data collection as needed to address any remaining questions about item bank psychometric properties.

In order to achieve this goal, NIH has proposed an ambitious roadmap project that included plans to systematically perform a comprehensive analysis of domains of health-related quality of life in chronic disease. This NIH project has developed and is administering these instruments to a chronic disease patient sample.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify specific domains to be measured, evaluate existing measures and items, and develop instrument(s) and assessment methods for use in diverse chronic disease patient samples.	(FY04) Highly valid, reliable, and broadly usable assessment tools are needed to enhance clinical research on patient-reported chronic disease outcomes.			◆			
FY05	*Actual Performance:* (MET) Preliminary item pools to measure the chosen domains (Pain, Fatigue, Physical Functioning, Emotional Distress, and Social Role Participation) have been created based on exhaustive review of existing measures. Initial instruments and methodologies have been developed.						
Initiate administration of instrument(s) to a large demographically diverse patient sample representing a wide range of chronic disease type and severity.	(FY05) An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 05 target.				◆		
FY06	*Actual Performance:* (MET) Administration of the PROMIS item pool to a diverse sample representing a wide range of conditions was initiated in July, 2006.						
Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and social role participation.	(FY06) Preliminary data analyses undertaken.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Conduct primary data analyses of item responses in pain, fatigue, physical functioning, emotional distress, and social role participation domains obtained from large, diverse samples of the general population and chronic disease patients to calibrate items and refine item banks for the PROMIS instrument.	(FY07) More data needed from large, diverse samples of chronic disease patients using the test item pool.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. Administration of the PROMIS item pool to a diverse sample representing a wide range of conditions was initiated in July, 2006. The PROMIS item pool consists of 784 items representing 14 distinct item banks in five measurement domains (physical functioning, pain, fatigue, emotional distress, social role participation). A sample of 11,500 is planned, with 7,500 from the general population and 4,000 from clinical populations including conditions such as heart disease, cancer, rheumatoid arthritis, osteoarthritis, outpatient psychiatric, spinal cord injury, and chronic obstructive pulmonary disease. Many in these clinical populations will have comorbid conditions. Each patient, however, is only counted once based on their primary condition, and additional analyses will be performed to assess the effects of comorbid conditions. As of November 15, 2006, over 3,000 participants have been administered blocks of items within the full item pool.

Implementation Strategy Advances or Other Highlights

An Internet panel is being utilized to recruit the general population sample and some of the clinical samples. The original plan for this project was to obtain a general population sample of 1000 from random-digit dialing telephone surveys. Changes in telephone communications (e.g. caller ID screening of calls, cellular phones as the primary phone), however, have made it increasingly difficult to obtain large representative samples using this methodology. With a large Internet panel, the project was able to increase the general population sample from 1,000 to 7,500 without additional resources and specify demographic targets to insure

adequate representation across gender, race, and ethnic groups. This revised data collection strategy will likely enable the project to efficiently meet the FY07 performance target.

SRO-8.6	By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).

BACKGROUND

The NIH collaborated with the National Center for Health Statistics to develop a vision component for the National Health and Nutrition Examination Survey (NHANES). After collection of baseline data through 2004, changes were made to the future survey, including revised questions to capture information on severe visual impairment, the extent of uncorrected but correctable refractive errors, the methods selected by study participants to correct their diagnosed refractive error, and vision-related quality of life questions. Additionally, a retinal component will be added to the vision component for 2005-2006, and the survey will be extended to 2007-2008. These changes will provide better estimates of the extent and nature of vision impairment in the U.S. Knowledge about the nature and extent of visual impairment in the United States will allow public health officials to more efficiently tailor surveillance activities to identify individuals in need, health providers to better supply corrective modalities to individuals whose vision can be improved and rehabilitation services to those with uncorrected visual impairment, and health economists to allocate sufficient resources to this effort. The end result will be to provide more Americans with normal vision allowing them to more safely perform activities for which vision is required, including driving, occupational, and recreational activities.

Disease Burden

Vision impairment is one of the most feared disabilities. Although it is believed that half of all blindness can be prevented, the number of people in the United States who suffer vision loss continues to increase. The leading causes of vision impairment and blindness in the U.S. are primarily age-related eye diseases. The number of Americans at risk for age-related eye diseases is increasing as the baby-boomer generation ages. These conditions, including age-related macular degeneration, cataract, diabetic retinopathy and glaucoma, affect more Americans with age-related eye disease. The vision impairment that results is expected to double within the next three decades. As of the 2000 census, there were more than 119 million people in the United States in this age group.

Refractive errors are the most frequent eye problems in the United States. Nearsightedness (myopia) and farsightedness (hyperopia) are the most common refractive errors. Most infants have some degree of hyperopia, but vision becomes more normal with age usually leveling off by age 6. While some children may be farsighted early in life, most myopia occurs later during adolescence. Other common refractive errors include astigmatism (uneven focus) and presbyopia (an age-related vision problem with near focus). Fortunately, almost all refractive errors can be corrected by eyeglasses or contact lenses. It is estimated that more than 150 million Americans use corrective eyewear to compensate for their refractive error. Americans are estimated to spend over $15 billion each year on eyewear, supporting an optical industry in the U.S. worth more than $30 billion. Uncorrected or under-corrected refractive error can result in significant vision impairment.

Rationale

There are no reliable and consistent national estimates of the prevalence and incidence of visual impairment, the extent of uncorrected but correctable refractive errors, and the impact of vision on quality of life activities. Several studies have reported prevalence and incidence data for diseases that can cause visual impairment and blindness, but there are no solid national estimates of the prevalence or incidence of visual impairment and the attendant disability, loss of productivity, and the impact on quality of life.

The NIH collaborated with the National Center for Health Statistics to develop a vision component for NHANES in support of the vision objectives in Healthy People 2010. After collection of baseline data through 2004, changes were made to the 2005-2006 survey, including revised questions to capture (better) information on severe visual impairment, as well as extending the vision-related quality of life questions to ages 20 and older (compared to those 50 and older for NHANES 1999-2004). As a nationally represented survey of Americans with both interview and examination components, NHANES is uniquely suited to gather, in a cost effective manner, information on vision and ocular health from both a quality of life and medical perspective. Because NHANES encompasses a range of health and nutritional components, the opportunity exists to identify other health conditions that may be related in some manner to visual impairment or be experienced by individuals with visual impairment. Insights about concomitant conditions can help foster further research efforts to better understand disease and can assist in the design and implementation of comprehensive health and vision promotion programs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NHANES survey collects a wealth of data during the personal interview and lengthy medical examination. The vision component will consist of questions about visual impairment and quality of life activities as well as examination data on visual acuity, refraction, and keratotomy. The CDC is planning to include a retinal assessment of the optic disc and macular areas. Integrating data form these two sources will allow for differentiation of cause of visual impairment for those individuals whose vision cannot be corrected to normal levels. Obtaining vision and retinal data on the same study participants makes both components more comprehensive. The survey will be extended to 2007-2008 to provide better estimates of the extent and nature of vision impairment in the U.S., as well as allowing assessment of the impact of Healthy People 2010 on the vision health of the Nation. CDC expects to continue the retinal component in 2007-2008.

Approximately 7,000 people will be sampled in a multi-stage probability sample of the US civilian, non-institutionalized population in a manner designed to be nationally representative. NHANES is the only nationally representative survey incorporating questions about vision in a personal interview as well as an assessment of vision in an examination setting.

NHANES has an internal process for deciding which components are included during each survey cycle. It is conceivable that inclusion of a vision component will be requested in 2009-2011 to provide baseline data for Healthy People 2020. Alternatively, resources may be focused on developing specific community-based approaches to promote health vision in

demographic groups shown by the survey to be in greatest need of corrective services to preserve vision. NHANES staff will determine when data from the survey will be released. Co-sponsoring agencies, such as NIH, and the public will gain access to the data at the same time, most likely in late 2009.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Extend NHANES and survey approximately 3,500 people.	(FY06) Very little reliable data on the prevalence of visual impairment in the U.S.	-	-	-	-	◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Continue collecting data for the vision component of NHANES to reach a target of surveying approximately 7,000 people in total.	(FY07) Approximately 3,500 people surveyed in FY 2007.	-	-	-	-	-	◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SRO-8.9.1	**By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).**

BACKGROUND

Disease Burden

Mediated through the brain, mood disorders disrupt every facet of a person's life: emotions, thought processes, behavior, social relationships and physical health. In addition to the inherent effects of depression on health through sleep and appetite dysregulation and other physiologic disturbances (e.g., sticky platelets) that are just beginning to be understood, major depression can significantly influence the outcome of general medical illnesses that are commonly comorbid with depression. Depression is seen frequently among people with coronary heart disease (CHD) and other cardiac illnesses. The prevalence of major depression in patients after a stroke is approximately 20 percent, and estimates of lifetime rates of depression among persons living with HIV range from 22 to 45 percent. Untreated depression increases the risk of dying from heart disease by as much as six-fold. Similarly, the presence of concurrent medical illnesses often complicates the treatment of depression. People with comorbid diabetes and depression have an eight times greater relapse rate than those with depression but without other medical conditions.

Rationale

The premise of this goal is that targeted research on these topics will have a significant impact on the overall reduction of years lost to disabilities (YLDs) associated with depression in two ways. First, although effective treatments benefit millions of persons with major depression, a significant proportion (50%) of persons are not helped or do not fully recover when given a standard pharmacological or psychosocial intervention. The quality of care available to persons with treatment-resistant depression, as well as treatments for persons with depression comorbid with other medical illnesses, will improve as (1) knowledge of the causes and processes of depression expands, including the genetic, environmental, behavioral and cultural risk and protective factors; (2) treatments—both psychosocial and pharmacological—become more refined and targeted; and (3) strategies are developed for protecting individuals from relapse and recurrence of depression. Secondly, achievement of this goal will contribute to a capacity for reducing YLDs as research addresses questions about the close association between depression and physical illnesses. Despite the increased risk of depression in the presence of a number of other medical illnesses, depression is not sufficiently recognized or adequately treated, particularly over the chronic course of the illness. To prevent depression, research is under way to try to understand the relationship between this brain disorder and physical illnesses.

Although effective depression treatments are currently available, only an estimated 20 percent of patients obtain adequate treatment. Rates of underutilization are higher for persons of color, elderly persons, youth, and young and middle-age males. Although several models of care have proven effective in delivering adequate depression treatment, the uptake and

maintenance of these patterns of delivery of care remain poor.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH investigated basic mechanisms underlying depression that may serve as important targets for intervention, such as the role of vascular changes in aging towards development of depression. Research has improved upon the definition and assessment of depression treatment outcomes and identified predictors of treatment response at various points throughout the course of illness. NIH is testing interventions that produce longer recovery periods for those most at risk for relapse in community populations, such as the elderly. Research will identify factors that have an impact on effective and sustainable dissemination and implementation of scientific findings at multiple environmental levels. Finally, NIH anticipates identifying the mechanisms and processes by which depression has a relatively large influence on the course or outcome of a comorbid disorder associated with disability or premature mortality. Depression often co-occurs with other physical disorders. For example, depression is frequently diagnosed in patients with heart disease, epilepsy and diabetes. To date, however, little is known about the interactions between depression and comorbid disorders. Do they share a common pathophysiology? Does one disorder affect the outcome of the other? How do preventive and treatment interventions for one disorder affect the other? In a time of rapid technological advancement in biomedical and behavioral research, there are a number of promising new tools to address basic and translational research on co-morbidity between depression and other physical disorders. Family studies applying genetic epidemiological methods may be employed to elucidate the genetics of co-morbidity. New technologies for assessing gene expression could be used to examine molecular mechanisms that may underlie interactions between co-morbid disorders. Widely shared animal models could lead to insights into the causation, prevention and treatment of comorbid conditions. Targeted preclinical and clinical studies on the development of improved imaging markers may advance diagnosis and treatment of comorbid disorders. The application of new methodologies will advance the ability to identify specific mechanisms of comorbidity that will inform development of new targets for intervention.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify at least one biological (gene-environment) interaction that has high probability of contributing to depression.	(FY02) Known that stress linked to depression but interaction not known.	◆					
FY03	*Actual Performance:* (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.						
Determine whether vascular changes related to aging contribute to depression.	(FY03) Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression.		◆				
FY04	*Actual Performance:* (MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.						
Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	(FY04) A series of clinical trials are currently underway that match patients' responses to different treatments.			◆			
FY05	*Actual Performance:* (MET) Characteristics that influence the efficacy of pharmacological and behavioral treatment for depression have been identified. The characteristics range from genetic variation to psychosocial factors.						
Identify at least one effective strategy for treating depression in the elderly in a variety of settings.	(FY05) A number of interventions to treat depression in the elderly are currently being developed and tested.				◆		
FY06	*Actual Performance:* (MET) Several new effective strategies for treating depression in the elderly have been identified.						
Determine the relative efficacy of combined treatment strategies or sequential treatment algorithms in treating chronic depression.	(FY05) Studies are underway to test the efficacy of differing treatment combinations or sequences for depressed patients.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Identify at least two methodologies for examining interactions between depression and other comorbid physical disorders.	(FY07) New methodologies may be applied to address interactions of depression with co-morbid physical disorders.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. Significant progress has been made in identifying quality treatment strategies for long term depression care management and outcomes among elderly via efficacy and effectiveness studies. The effectiveness of depression treatment and management is strengthened by the application of findings from numerous studies, including the PROSPECT and maintenance treatment studies described below.

In FY 2006, a collaborative study undertaken to examine the effect of an intervention on reducing suicidal ideation and depression in geriatric patients was concluded. The Prevention of Suicide in Primary Care Elderly Trial (PROSPECT) examined the extent to which an intervention that combined treatment guidelines with care management reduced rates of depression and suicide ideation, maximized treatment adherence and enhanced clinical follow-up among older primary care patients. From a mental health services research perspective, findings indicate that a key "effective strategy" for treating depression for the elderly in primary care settings is incorporating a depression management specialist in a collaborative care approach to treatment. Essentially, creating a multidisciplinary treatment team with a depression management specialist assists both the patient and the physician provider in conducting guideline-based care, maximizing treatment adherence and clinical follow-up.

Another study examined alternatives for maintenance treatment of older adults who reach recovery from depression (and sustained remission) via a combination of antidepressant medication and interpersonal therapy. Continuation of the medication in the maintenance phase was found to be critical for this group to sustain recovery and avoid recurrence of depression; those who received either continued combination treatment or continued medication alone experienced significantly less recurrence of depression over a 2-year follow-up than did those given psychotherapy alone or pill placebo (which did not differ). Thus, for older adults who have gotten well with antidepressant medication, continuation of the medication regimen well past the point of recovery is an effective strategy for maintaining and extending their subsequent period of wellness. Monthly maintenance sessions of interpersonal therapy were not effective in preventing recurrent depression. These results differ somewhat from those obtained in an earlier, similarly designed maintenance therapy study in older adults by the same group, which indicated added value for maintenance psychotherapy. In the earlier study, the antidepressant medication was nortriptyline. Other differences included that the older adults studied in the recent study as compared to the earlier one were on the average older and more medically burdened, and included individuals with late-onset forms of geriatric depression as well as recurrent depression (which typically has considerably earlier ages of onset).

Implementation Strategy Advances or Other Highlights

NIH has supported several recent efforts to improve the diagnosis of depression in patients with other neurological disorders or injuries. One group of researchers developed a rapid and accurate screening instrument to identify symptoms of major depression in people with epilepsy. Another research team demonstrated that a brief questionnaire was effective in identifying depression in stroke survivors. The NIH Work Group on Depression and Parkinson's Disease established new diagnostic criteria for depression in Parkinson's Disease patients that are easier to use and more broadly applicable than earlier criteria.

SRO-8.9.2	By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation in minority communities.

BACKGROUND

Disease Burden

Although stroke remains the third leading cause of mortality in the United States and the leading cause of adult disability, the burden of stroke is greater among minority racial/ethnic groups by virtue of its higher incidence and mortality in these populations. The incidence of ischemic and hemorrhagic stroke is disproportionately high in the African American population and occurs at younger ages; moreover, these disparities may be increasing. Mortality from stroke among African Americans is nearly twice that of Caucasian Americans, and among Native Americans and Alaska Natives, has increased significantly during the 1990s. Moreover, among several minority racial/ethnic groups (including African Americans, Hispanic Americans and Native Americans), the disparity in stroke mortality (both ischemic and hemorrhagic) is especially evident among younger individuals ages 45 to 64 years. African Americans may experience more severe strokes and greater residual physical deficits, although these deficits may not be fully reflected in impairment of the ability to perform activities of daily living.

Rationale

There is a wide range of hypothesized causes of the excess stroke mortality in the southeastern United States and among African Americans. The prevalence of stroke risk factors and the potential impact of reducing those factors vary among racial/ethnic groups, with potentially greater impact associated with reduction or elimination for minorities. For example, hypertension, one of the most important risk factors for stroke, is disproportionately prevalent and less effectively controlled in African Americans. A recent report based on a national probability sample of over 600,000 persons identified hypertension as the single initiating cause of death independent of socioeconomic status that contributed the most to the racial disparity between African Americans and Caucasians in potential life-years lost. Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, minorities are less likely to use the emergency medical system when experiencing a stroke. The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood. Prevention programs are a preferred strategy for reducing or eliminating racial/ethnic disparities in stroke and include both primary and secondary approaches.

The DHHS Research Coordination Council (RCC) has identified the research theme Understanding Health Disparities—Closing the Gaps as a priority. In addition, eliminating health disparities is one of the two stated goals of Healthy People 2010, the disease prevention agenda for the Nation.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has established a program to create Nursing Partnership Centers to reduce health disparities. These centers established collaborations between research-intensive schools of nursing and minority-serving university schools of nursing to address health disparities, including stroke. The Centers focus on influential factors that reduce health disparities, such as ways to promote healthy behaviors, reduce risks that contribute to chronic diseases, and develop ethnically and culturally sensitive health care interventions. Qualifying minority-serving institutions, either in the United States or in territories under U.S. jurisdiction, are those in which students of minority groups who are underrepresented in nursing research (e.g., African American, Hispanic American, Native American, Alaska Native, Native Hawaiian, Pacific Islander, Asian American, and Philippine nurses) constitute a significant proportion of the enrollment and have a track record of commitment to the special encouragement of minority faculty, students, and investigators.

NIH has established an acute stroke research and care center at the Washington Hospital Center (WHC), a private community hospital in Washington, D.C., where more than 75 percent of stroke patients are African American or Hispanic. The WHC has begun building a database to gather epidemiological data on its stroke population. The WHC will use these data to identify new risk factors and measure rates of previously reported risk factors. Information on risk factors is necessary to identify populations to be targeted by stroke prevention programs. The data will also serve as a baseline against which to measure the effectiveness of future stroke prevention programs.

To develop sustainable, replicable, and culturally appropriate prevention and intervention research programs targeted to minority populations and designed to decrease the incidence and prevalence of stroke, NIH established a Stroke Prevention/Intervention Research Program (SPIRP) at a minority institution. The Program will identify more effective methods of implementing, within diverse communities, stroke prevention programs. The first phase of the program established an infrastructure for the SPIRP. The second phase will establish collaborative stroke prevention research projects to include community-based interventions, epidemiology, and/or outcome measures. Ultimately, the SPIRP will identify effective, community-based stroke prevention and intervention strategies for export to and adaptation in other diverse communities.

NIH has established an Alaska Native Stroke Registry at the Alaska Native Medical Center (an Indian Health Service supported health care system for Alaska Natives) to monitor stroke incidence, prevalence, mortality, and risk factor data that could be used to improve stroke prevention and the quality of stroke care provided to Alaska Natives. This multiyear, long-term project will populate the pilot stroke registry, targeting Yupik Eskimos living in the Yukon-Kuskokwim Delta and Bristol Bay regions, to establish registry infrastructure and data gathering methods. If successful, the registry will be expanded statewide to all regions and include all Alaska Native subgroups. Ultimately, registry data will be used to identify strategies to reduce risk factors for stroke and develop statewide prevention intervention programs.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Establish a 5-year program to create about 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	(FY02) Piloted programs to build nursing center research capacity focused on health disparities	◆e					
FY03	*Actual Performance:* (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.						
Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	(FY03) Acute stroke center exists but is not focused on stroke disparities or in a minority community		◆				
FY04	*Actual Performance:* (MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.						
Establish the infrastructure for a Stroke Prevention and Intervention Research Program (SPIRP) at a minority institution.	(FY03) Minority institution research /training programs exist but not on stroke prevention/intervention			◆			
FY05	*Actual Performance:* (MET) Established research infrastructure and advisory committees, and hired director for SPIRP.						
Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives.	(FY04) Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke				◆		
FY06	*Actual Performance:* (MET) Established the infrastructure for the Alaskan Native Stroke Registry, began enrolling patients.						
Initiate at least two collaborative, community-based prevention projects at the Stroke Prevention and Intervention Research Program (SPIRP).	Cooperative agreement awarded establishing SPIRP infrastructure, but stroke prevention projects have not yet begun					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Establish a database of stroke patients and collect data for the purposes of identifying new stroke risk factors and developing effective stroke prevention strategies.	WHC lacks patient data needed to identify stroke risk factors, evaluate stroke prevention programs						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. NIH awarded funding to the Alaska Native Medical Center for an Alaskan Native Stroke Registry in September 2005. This registry builds on the Medical Center's extensive experience with chronic disease registries and will provide critical information on the disparity in stroke mortality. A Scientific Advisory Committee for the registry project has been formed and has met five times. This committee has developed a list of data elements pertinent to Alaskan Natives that live in a rural setting, including culturally unique risk factors. A web-based data collection tool has also been created. The registry began entering patient data on October 1, 2005. As of June 2006, 71 patients had been enrolled in the registry.

Implementation Strategy Advances or Other Highlights

NIH has made progress toward the overall GPRA goal through several different programs. Researchers have already recruited approximately 22,000 out of a projected 30,000 individuals for the NIH-funded REasons for Geographic And Racial Differences in Stroke (REGARDS) study, an observational study that is exploring the relationships between race and geography and stroke prevalence, incidence, and mortality in a region of the southeastern United States with particularly high stroke mortality rates. This rapid progress represents a

major achievement in clinical study recruitment of both minorities and non-minorities.

The Northern Manhattan Study of Stroke (NOMAS) is identifying stroke risk factors in whites, African Americans, and Hispanics in a different community than REGARDS. Recently, NOMAS researchers have demonstrated that there are significant race-ethnic differences in ischemic stroke incidence. Relative rates for certain stroke subtypes are particularly elevated in African Americans and Hispanics, as compared to whites. Although differences in conventional risk factors among these populations may be responsible for some of these disparities, variability in genetic makeup, risk factor control, and other unmeasured risk factors may also contribute.

In September 2004, the NIH awarded five research grants to evaluate clinical interventions to control hypertension in African Americans. The projects have completed their planning and pilot work and are entering the participant recruitment phase. Annual meetings and regular conference calls serve as forums to share experiences, exchange ideas, and plan publications. The investigators held their second meeting in June 2006.

Another notable achievement relevant to the overall goal is the establishment of twelve performance-based, education outreach projects, called Enhanced Dissemination and Utilization Centers (EDUCs), to improve cardiovascular health in high-risk communities (defined as communities with coronary heart disease and/or stroke death rates that rank in the top 15% nationwide). The NIH funded six in 2001 (EDUCs I) and an additional six in 2002 (EDUCs II). Health disparities and strong community involvement were also key elements of the projects. EDUCs planned, implemented, and evaluated well-defined educational and behavioral strategies, such as the use of trained community health workers, enhanced continuing medical education sessions, awareness-raising town-hall meetings, community-based screening and referral programs, nutrition and physical activity programs, and working with physicians to improve the implementation of clinical practice guidelines. Phases I and II were completed as of January 2006. A comprehensive report of the results, both qualitative and quantitative, as well as instruments and materials will be posted on the NIH website. Additional phases of EDUCs are under discussion.

SRO-8.9.3	**By 2011, characterize the progression of normal, healthy brain development in a nationally representative sample of children in the United States by creating a database of MRI and clinical/behavioral data and analytical software.**

BACKGROUND

Before magnetic resonance imaging (MRI) technologies, relatively little was known about healthy brain development in humans. MRI has made it possible to safely study normal brain development in all age groups, including healthy infants and young children. Different MRI technologies are available including anatomic MRI to measure structural brain development, Magnetic Resonance Spectroscopy (MRS) to examine metabolic brain development, and Diffusion Tensor Imaging (DTI) to characterize white matter fiber tracts, the pathways connecting different brain regions.

In 1990, the first findings on structural brain development showed age-related changes in gray and white matter volumes and in the development of critical inner brain structures. In addition, limited longitudinal studies have allowed researchers to identify some subtle developmental brain changes. Researchers are also finding some relationships between certain regions of the brain and specific cognitive abilities in children. These findings have yielded insights into brain development; however, their role in clinical and behavioral development is unclear.

Limitations of these earlier studies make it difficult to identify subtle differences between normal and abnormal brain development and to apply the findings to the general pediatric population. Many studies examined children of different ages all at one time and/or were based on small sample sizes. Furthermore, little information is available on children younger than age six, when brain growth and development is the most rapid.

Understanding normal brain development is important in finding the causes of a myriad of childhood disorders related to mental retardation, mental illness, drug abuse, and pediatric neurological diseases, which can continue in adulthood. To define the healthy ranges in brain growth and development patterns in children as they mature, longitudinal studies that have representative samples of healthy children using state-of-the-art MRI technologies are needed. Such a study is extremely challenging given the difficulties in acquiring anatomic, MRS, and DTI brain images in young children. Despite major challenges, NIH is leading an ambitious large-scale effort, the first of its kind, to develop a database and analytical tools to characterize normal, healthy brain development and its relationship to behavioral development.

The NIH Clinical Exemption Committee approved the study protocol and consent forms. In addition, each data collection site received Institutional IRB Committee approval to perform scans on and to collect behavioral and physical data from children and adolescents. There are no known adverse effects of undergoing an MRI scan, including during pregnancy. Following prudent clinical practice, pregnant women will remain outside of the scanning suite.

Rationale

At this time, no single standardized and comprehensive source of information exists on MRI measurement of normal brain development over time in children and adolescents in the United States. This project will create the nation's first such research database using state-of-the-art technologies by bringing together the expertise of basic scientists and clinicians. These standardized data are critical because they will provide a basis for determining deviations in brain development associated with a variety of brain diseases, disorders, and conditions. In addition, the database will include comprehensive longitudinal neurobehavioral assessments including medical and family history, demographic, behavioral, neurocognitive, and school achievement measures. Moreover, the database will provide researchers with an effective means for developing standardized comparison groups when examining brain disorders, psychopathology, or brain-based disabilities, which will, in turn, facilitate clinical and translational studies in the future.

The project was designed with 20 percent compounded attrition across the data collection phases. This ensures that a sufficient number of children remain enrolled in the study to detect growth and changes in key brain structures in a representative sample of children in the United States as they develop over time.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH is bringing together a diverse array of researchers to design and support a large-scale longitudinal study that uses state-of-the-art brain imaging technologies and that collects clinical and behavioral data, which will be used to develop analytical software tools.

This effort is highly ambitious in the number of children to be enrolled (approximately 500) at a wide range of ages (7 days to 18 years). In addition, researchers will combine data collected from complex technologies--magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy--scanning the same children over a period of approximately 6 years. This will require retaining every family's participation in the project and collecting extensive demographic, medical, cognitive, and behavioral data at every visit.

Obtaining brain images from healthy children is a challenge in itself. The scans will be conducted in healthy, unsedated children who will be required to remain motionless for different lengths of time. To conduct the study, researchers had to develop new and adapt existing techniques to scan children of different ages, the most difficult being toddlers. Approaches include studying children during their sleeping periods and training children to lie motionless in brain imaging scanners.

As the data are collected, researchers will create normal pediatric growth curves of the whole brain and of specific regions of interest and will establish normal white matter fiber tract development. In addition, analytical software will be developed to automatically generate the volume and area of specific brain regions and of white matter fiber tracts in children. A special effort will be made to disseminate these data and as a result, the scientific community will have access to a web-based, user-friendly resource that integrates

neuroanatomical and clinical/behavioral data to examine brain-behavior relationships and relationships between physical maturation and brain development. This effort is also expected to serve as a model for new NIH neuroinformatics initiatives that can link to the anatomic MRI database.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Prepare and disseminate the first of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	(FY04) First of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.			◆			
FY05	*Actual Performance:* (MET) Enrolled 504 children, and prepared and disseminated the first stage of scans, demographic, medical, cognitive, and behavioral data collected from 430 children, age 4.5 to 18, to the research community.						
Complete the second of three stages of neuroimaging scans and data collection of approximately 500 children across the United States.	(FY05) The first of three stages of scans, demographic, medical, cognitive, and behavioral data were collected from 500 children and disseminated to research community.				◆		
FY06	*Actual Performance:* (MET) A total of 514 children have been enrolled in the study. Ninety-five percent of the children between the ages of 4.5 to 20 years old who completed the first stage of data collection have completed the second stage of neuroimaging scans, demographic, medical, cognitive, and behavioral data collection.						
Complete preliminary analyses of changes of brain growth in children over time and share findings with research community.	(FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Prepare and disseminate all three stages of anatomical neuroimaging scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	(FY07) Preliminary analyses of changes of brain growth in children over time completed.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET. A total of 514 children have been enrolled in the study. Ninety-five percent of the children between the ages of 4.5 to 20 years old who completed the first stage of data collection have completed the second stage of neuroimaging scans, demographic, medical, cognitive, and behavioral data collection. In addition, 98 percent of these children have completed diffusion tensor imaging scans as well as the anatomical MRI scans. All of these data have been added to the database and are currently undergoing quality control processes. Recruitment, scans, and data collection are also ongoing for 116 children younger than age 4.5 because brain growth and development are more rapid compared to the older age group. The data from 75 of these younger children have been made available to the research community in a database. In addition, a report in the journal Neuroimage (in press) will show: data indicating that the demographic distribution of the study sample is similar to the distribution in the 2000 U.S. Census; examples of the high-quality scans collected; and the protocol for collecting the high-quality scans.

Implementation Strategy Advances or Other Highlights

Data from the 116 children in the younger age group (up to 4.5 years old) will be available to the research community in mid-2007. Of these younger children, 77 percent completed three or more assessments and scans. In addition, the final, or third, stage of data collection for the older age group (4.5 to 20 years old) is nearly complete. The overall project attrition rate remains at four percent, which is outstanding and maintains the number of families needed in the study to represent the full spectrum of ethnic, minority, and socio-economic statuses in the United States.

SRO-9.4	**By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.**

BACKGROUND

Congenital cytomegalovirus (CMV) is the most common viral infection passed from a mother to her unborn child. Approximately one percent of newborns, or about 40,000 infants each year, are born infected with CMV. Children born with CMV infection who have symptoms of infection, such as hearing loss, seizures, visual impairment, and cerebral palsy, are usually identified at birth and receive appropriate medical care. However, the majority of CMV-infected children—roughly 90 percent—have no symptoms at birth. These children have what is called a "silent" infection, which often goes unnoticed. In addition, CMV is a leading cause of progressive hearing loss in children in the United States. Approximately 10% to 15% of children with congenital CMV infection have some degree of hearing loss that has delayed onset and worsens during childhood. Although few population based studies of the etiology of hearing loss in infants have been performed, when such studies have included assays for congenital CMV infection, they have strongly suggested that congenital CMV infection is a leading cause of sensorineural hearing loss in children. In addition, even though a majority of infants born in the United States are already screened for hearing loss, most infants are not tested for CMV unless they already show signs of the disease. Further, newborn hearing screening cannot detect or predict hearing loss that will occur later in childhood. While the causes of childhood hearing loss remain largely unknown, estimates indicate that as much as 20% to 30% of childhood hearing loss is caused by CMV infection.

Rationale

Due to the compelling but limited data on congenital CMV infection and hearing loss in infants, in March 2002, the NIH convened a workshop with a panel of experts on congenital CMV infection and newborn hearing and metabolic screening. The panel made several recommendations regarding future research priorities in the area of congenital CMV infection and hearing loss. Based on the workshop recommendations, the NIH published a Request for Proposals (RFP) and, in 2005, funded the University of Alabama School of Medicine, Birmingham, to lead a multicenter study, entitled the CMV and Hearing Multicenter Screening (CHIMES) Study, on the role of congenital CMV in the development of hearing loss in children. Identifying asymptomatic children and following their progress to determine if hearing loss develops is a major focus of this research. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. Those who test positive for CMV will undergo follow-up diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. The scientists will analyze the data to better understand the relationship between CMV infection and hearing loss and to determine the extent to which CMV screening together with hearing testing can improve the detection and prediction of permanent hearing loss in children.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH has developed a strategy to implement neonatal screening for CMV infection to permit the identification of infants who will develop CMV-induced hearing loss. Initially, the NIH supported scientists plan to develop clinical protocols and other needed study documents, such as patient information brochures (FY 2006). The NIH-supported scientists then plan to compile the Manual of Procedures (MOP) and deliver the MOP to all hearing screening sites (FY 2007). Third, the NIH-supported scientists will initiate patient enrollment at all hearing screening sites (FY 2008). Based on the outcome of patient enrollment, the NIH-supported scientists will proceed to the pilot phase of the CHIMES study. By developing a neonatal screening test for CMV infection, the NIH will continue its goal to improve the health of individuals with hearing loss.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Design and develop clinical protocols and other needed study documents.	(FY05) Previous studies have strongly suggested that congenital CMV infection is a leading cause of sensorineural hearing loss in children.				◆		
FY06	*Actual Performance:* (MET) NIH-supported scientisists designed and developed needed clinical protocols and other needed study documents, such as patient brochures for the CMV & Hearing Multicenter Screening (CHIMES) Study.						
Compile Manual Of Procedures (MOP) and distribute to all hearing screening sites.	(FY06) Clinical protocols and other needed study documents are available.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Initiate patient enrollment at 7 hearing screening sites.	(FY07) Manual of Procedures (MOP) delivered to all hearing screening sites.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target has been MET because NIH-supported scientists successfully developed clinical protocols and other needed study documents, such as patient information brochures for the CMV & Hearing Multicenter Screening (CHIMES) Study. These documents will be used to implement neonatal screening for CMV infection to permit the identification of infants who may develop CMV-induced hearing loss.

Implementation Strategy Advances or Other Highlights

The primary advances made during FY 2006 include the development of basic study documents, such as patient information brochures for the CMV & Hearing Multicenter Screening (CHIMES) Study. Each document displays the newly-developed CHIMES study logo with the motto 'A Sound Tomorrow Starts Today'. NIH-supported scientists developed the following documents in both English and Spanish: 'CMV - Information for Families,' 'CMV - Information for Parents,' 'Developmental Milestones of Hearing and Speech,' and form letters for participating families whose infants tested either positive or negative for CMV infection. The NIH-supported scientists have also developed clinical protocols and forms, including a sample screening script, hearing evaluation forms, and clinical screening forms. These standardized clinical protocols and forms are critical for ensuring that data is collected in a uniform manner.

COMMUNICATION AND TRANSFER OF RESULTS

Without the flow of information, important scientific findings would languish at the researcher's bench. The fruits of NIH's research activities - new knowledge about the causes and courses of diseases and the means to prevent, diagnose, and treat them - cannot affect human health unless that knowledge is disseminated. Scientific knowledge is the bedrock of evidence-based prevention and treatment programs. Thus, a core NIH function is to facilitate the communication of research findings to clinicians, the public health system, voluntary health organizations, and the public. Equally important is transferring knowledge to the private sector so that it can be used to develop products and technologies that benefit health. NIH's technology transfer program is one of the most active in the Federal Government.

The Public Health Service Act of 1944 authorized NIH and the other U.S. Public Health Service (PHS) agencies to collect and make available, through publications and other appropriate means, information relevant to the practical applications of research [Title III, Sec. 301 (1)]. In addition, the legislation that enables and directs the development of NIH programs emphasizes the important role NIH plays in informing the public about the results of health-related research. Similarly, the authorizing legislation for the NIH Institutes and Centers (ICs) includes "dissemination of health information" as an integral part of each IC's basic mission. All of the NIH ICs conduct programs to collect, disseminate, and exchange information on medical and biological science, medicine, and health. The National Library of Medicine (NLM), the world's largest medical library, is a component of NIH and works closely with the ICs to ensure the effective communication of research results.

The broad purpose of NIH's technology transfer activities is to facilitate and enhance the development of new drugs, other products, and methods of treatment that benefit human health by promoting the efficient transfer of new technologies resulting from NIH research to the private sector. Federal legislation empowers NIH to interact directly with industry to expedite the transfer of technological discoveries into commercial products that will benefit the public. In addition to improving public health, technology transfer contributes to the global competitiveness of the Nation's businesses and to the Nation's economic prosperity.

NIH patents technologies invented by its intramural scientists and issues licenses to organizations in the private sector that are willing and able to commercialize these inventions. NIH has forged numerous partnerships with industry and other external research organizations, thereby enhancing its capacity to expedite the commercial application of these new technologies with the ultimate goal of improving public health and advancing the research enterprise.

Partnerships are as crucial to the communication and transfer of results as they are to generating new knowledge. Community-based and international partnerships are especially featured in the goals that follow, and these partnerships are important vehicles for gathering as well as for disseminating information.

CTR-1	**By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).**

BACKGROUND

Sudden Infant Death Syndrome (SIDS) is a syndrome of unknown cause and is defined as the sudden death of an infant under one year of age, which remains unexplained even after a thorough case investigation, autopsy and review of the clinical history. SIDS is the leading cause of post neonatal mortality in the U.S. According the National Center for Health Statistics, the 2002 SIDS rate is 0.57/1,000 live births. The national Back to Sleep public health education campaign was launched in 1994 after the American Academy of Pediatrics (AAP) recommended back sleeping as the safest sleep position for infants under 1 year of age. Stomach sleeping is a major risk factor for SIDS. The campaign promotes placing babies on their backs to sleep to reduce the risk of SIDS. It is led by the NIH in collaboration with the following campaign sponsors: AAP, Maternal and Child Health Bureau of HRSA, First Candle/SIDS Alliance, and the Association of SIDS and Infant Mortality Programs.

Rationale

Since the launch of the campaign, the SIDS rate has dropped by 50 percent. However, despite the overall success of the campaign, African American infants are placed to sleep on their stomachs more often than white infants. The SIDS rate for African American infants is two times greater than that of white infants.

The NIH and other campaign sponsors hosted a meeting of experts to identify strategies for reaching African American communities with the Back to Sleep campaign messages. Representatives from various organizations including the Alpha Kappa Alpha Sorority, Inc. (AKA), Women in the National Association for the Advancement of Colored People (WIN), National Coalition of 100 Black Women (NCBW), National Medical Association, and the Congress of National Black Churches, Inc. and others proposed outreach and education strategies aimed at eliminating the racial disparity in SIDS rates. As a result, the NIH and partner organizations developed the Resource Kit for Reducing the Risk of SIDS in African American Communities, which is designed to help organizations initiate SIDS risk reduction programs in their local communities. It contains materials such as facts sheets and brochures to encourage people to lead discussion groups on ways to reduce the risk of SIDS in various community settings.

The Partnerships for Reducing the Risk of SIDS in African American Communities was a project with the AKA, NCBW, and WIN. The leaders of these three organizations committed to hosting three summits featuring the NIH SIDS risk reduction information and materials. The following is a list of the summit locations that were held in FY ‘03: Tuskegee, Alabama; Los Angeles, California; and Detroit, Michigan.

The goal for the summit meetings was to encourage regional leaders to engage in SIDS risk reduction activities, build alliances within communities to assist in SIDS risk reduction activities, educate those with the power to make a change in policy or behavior, and create

collaborative models and resources that can remain within communities. A "train-the-trainer" approach was used so that participants could transfer the knowledge to their local settings. Culturally appropriate materials were developed for African American communities. After the regional summits were completed, the NIH conducted informal interviews to determine subsequent outreach strategies that developed as a result of their participation.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Comprehensive strategies have been developed to satisfy the overall goal of SIDS reduction in African American communities. First, NIH launched a multi-year project to disseminate the AAP safe sleep guidelines in Mississippi. The project has multiple components including training public health workers on the conveying SIDS risk reduction messages, developing partnerships with state and local stakeholders, and providing mini-grants to community and faith-based organizations to assist in their outreach efforts. Second, a continuing education curriculum was developed for nurses on the safe sleep guidelines and effective ways to convey the risk reduction message. This curriculum is being implemented at regional and national conferences.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	(FY02) No regional summit meetings were held prior to 2003	◆e					
FY03	*Actual Performance:* (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.						
Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in FY 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	(FY03) No interviews have been conducted for this purpose		◆e				
FY04	*Actual Performance:* (MET) Interviews were held with participants from each summit and 150 outreach activities resulted from each of the summits.						
Continue to extend 'Back to Sleep' campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	(FY03) Three participating national organizations			◆e			
FY05	*Actual Performance:* (MET) NIH extended the 'Back to Sleep' campaign messages to African American populations through community-based collaborations with eight national organizations in SIDS training and educational activities.						
Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the Back to Sleep campaign messages.	(FY03) There are no known efforts to systematically educate the nursing community on a national level about SIDS risk reduction.				◆e		
FY06	*Actual Performance:* (MET) The Nurses Continuing Education Program was presented at eight national and four regional nurses conferences. Approximately 5,250 nurses participated in the training.						
Extend the continuing education module for nurses in appropriate community-based clinical settings in African American communities in the Mississippi Delta region.	(FY05) There are no known efforts to systematically educate nurses on a community level about SIDS risk reduction.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Achieve goal of reducing the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).	(FY06) TBD Baseline disparity between African American and white infants in back sleeping.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and exceeded. In 2006, continuing education courses were conducted at 8 national nursing conferences: 1) National Association of Pediatric Nurse Practitioners (Mar. 30), 2) Association of Women's Health and Neonatal Nursing (June 24), 3) National Black Nurses Association (Aug. 8), 4) National Perinatal Conference (Sept. 28), 5) Professional Nurse Educators 33rd Annual Conference and Annual Meeting (Oct. 25), 6) National Association of Neonatal Nurses (Nov 8), 7) American Academy of Nursing (Nov. 8), 8) National Alaska Native Indian Nursing Association (Nov. 12). In addition to these eight national conferences, the nurses continuing education program was presented at four regional conferences: the NY-NJ Regional Nurses Meeting, the Wisconsin National Nursing Association, the Mississippi National Nursing Association and the National Alaska Native American Indian Nurse Association. Nurses often have sustained contact with women and families just after the birth of a child. The messages that nurses give to new families in this

period about the importance of placing an infant on his or her back to sleep can help reduce the risks of SIDS. The continuing education courses highlighted the fact that the SIDS rate for African American infants is two times greater than that of white infants. The intervention that nurses provide to African American mothers and families at the time of birth can help reduce this disparity. Approximately 5,250 nurses participated in the training. Of those, 425 have completed the self-administered test and have received continuing education credit. This program will continue through FY 2007.

Reducing the SIDS rate requires knowledge and action by parents, caregivers, and health care providers. Nurses who care for newborns are important role models for new parents. By consistently placing infants to sleep on their backs and using other safe sleep practices while infants are still in the hospital, and by educating new families about SIDS risk reduction, nurses play a critical role in modeling the safest sleep position and disseminating information to reduce the risk of SIDS. The NIH, in collaboration with First Candle/SIDS Alliance, developed a Nurse Continuing Education Program on SIDS risk reduction. The actual product consists of a 40-page manual that a trainer can present or that nurses can read on their own, and a self-administered test. The goal of the program is to increase the capacity of nurses to educate families and caregivers about ways to reduce SIDS risk factors. NIH developed the program, designed the workbook, and conducted the program at national and regional nursing organizations. The Maryland Nursing Association is providing the continuing education credit.

Implementation Strategy Advances or Other Highlights

The implementation strategy for the continuing education module consists of a two-tier approach. As part of the first tier, the continuing education module is being promoted at national and regional nursing conferences. This involves submitting an abstract, often up to a year in advance, and having it peer reviewed. In addition to presenting the program to nurses for continuing education credit, NIH arranges for a booth at the conference to continue promoting the CE program. In the second implementation tier, nurses who attended the training at their conferences are encouraged to conduct the training for other nurses in their work place such as a hospital, clinic, HMO or practice group using the 40-page training manual.

Efficiency

The NIH surpassed its target of promoting the continuing education module with at least six national nursing organizations by conducting continuing education courses at eight national nursing conferences. In addition the NIH presented the continuing education program at four regional nursing conferences.

CTR-2	**By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the campaign, '*Know Stroke. Know the Signs. Act in Time.*'**

BACKGROUND

Rationale

Stroke places a major health burden on U.S. society in death, disability, and economic costs. About 700,000 new strokes (first and recurrent) are reported every year in the United States. Stroke is the third leading cause of death and is a leading cause of serious, long-term disability among adults. Stroke costs the United States an estimated $57.9 billion per year in direct and indirect costs.

To bring important health messages to the public and in response to the mandate by Congress in the FY 2001 House and Senate Appropriations Committee reports, NIH created the multifaceted communication effort *Know Stroke. Know the Signs. Act in Time.* The campaign aims to increase awareness of the symptoms of stroke and the need for urgent action. In 2004, as an extension of the *Know Stroke* campaign, NIH partnered with the Centers for Disease Control and Prevention to launch a grassroots education program called *Know Stroke in the Community*. The program is designed to identify and enlist the aid of "Stroke Champions" who will educate communities about the signs and symptoms of stroke. This program focuses on reaching populations at high risk for stroke – African Americans, Hispanics, and seniors – in communities that have the health care systems in place to treat them.

Stroke is a medical emergency. Rapid identification of a stroke is essential to treatment and positive outcomes. When given within 3 hours of the onset of symptoms, a clot-busting drug called tissue-type plasminogen activator (t-PA) can reduce and even reverse the impact of a stroke by dissolving the blood clot that causes damage to the brain. A NIH study found that patients who received t-PA were at least 30 percent more likely to recover with little or no disability after 3 months. Without t-PA, stroke patients often suffer disabilities that require extensive rehabilitation. The window of opportunity to start treating stroke patients is 3 hours from the onset of symptoms, but to be evaluated, patients should arrive at the hospital within 60 minutes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The *Know Stroke* campaign is a multiphase effort. In the first phase, NIH developed materials in collaboration with key stakeholders in the stroke community, and focused efforts on reaching health care providers. In the second phase, NIH developed and executed public service advertising in communities across the country where stroke has a particularly negative impact. In the third phase, NIH, working with the Centers for Disease Control and Prevention, launched the *Know Stroke in the Community* program. In 2004, NIH completed a pilot phase of the program in five cities – Houston, Richmond, Chicago, Birmingham, and

New Orleans. In less than six months, the program identified 71 Stroke Champions who conducted more than 350 education events and delivered stroke education messages and materials to tens of thousands of people.

In 2005 and early 2006, the *Know Stroke in the Community* program expanded to Boston, St. Louis, Cleveland, and Jacksonville, bringing the total number of Champions to 135. In May 2006, NIH conducted its tenth *Know Stroke in the Community* training session in Atlanta, Georgia, adding another 15 Stroke Champions for a total of 150. In November 2006, NIH conducted its 11th *Know Stroke in the Community* training session in Minneapolis-St. Paul, Minnesota, adding another 18 Stroke Champions for a total of 168.

Throughout FY 2006, NIH continued to work with national organizations such as the CDC, the National Council of La Raza (NCLR), and the General Federation of Women's Clubs (GFWC), to develop community-based programs for extending stroke messages to Hispanics and African Americans in the 11 markets that are part of the *Know Stroke in the Community* program. To reinforce the work of the Stroke Champions, NIH distributed English-language television and radio public service announcements (PSAs) and Spanish-language radio PSAs to these markets. NIH worked with NCLR to develop and distribute a toolkit that includes a video, flipchart, and other materials in Spanish for use by NCLR's promotores de salud (lay health educators) in conducting stroke education. Additionally, NIH worked closely with GFWC through a variety of activities that thus far have included presenting *Know Stroke* workshops and distributing *Know Stroke* materials to GFWC members and constituents. NIH has conducted a special mailing of its community education kit to GFWC's 4,520 chapters and other key contacts across the U.S. for a total of 4,524 kits distributed.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Work with partners in five communities with at least 15 percent African American audiences to extend the Know Stroke campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 Know Stroke community education kits and 100,000 Know Stroke brochures (25,000 will be distributed to African American audiences).	(FY03) National partnerships developed; no current comprehensive local partnerships		e				
FY04	*Actual Performance:* (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.						
Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 Know Stroke community education kits (1,000 will be through African American partners).	(FY03) Five Partnerships developed in FY 2004.			e			
FY05	*Actual Performance:* (MET) Planned outreach programs in 5 U.S. cities. An additional 5,686 Know Stroke community education kits are being distributed (approximately 1,000 through African American partners). Distribution efforts are under budget by $142,000 and 686 kits over the projected target.						
Complete goal of increasing awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least 5 communities and extending the impact of the campaign, "*Know Stroke. Know the Signs. Act in Time.*"	(FY05) Extended outreach program to five additional communities nationwide.				e		
FY06	*Actual Performance:* (MET) Exceeded goal of increasing awareness among the general public in 5 communities by conducting *Know Stroke* outreach activities in a total of 25 communities. These activities were executed through NIH *Know Stroke in the Community* training sessions in 3 cities, as well as 14 presentations through local GFWC chapters and 8 stroke-related presentations conducted at GFWC regional meetings.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target was MET and the goal was ACHIEVED. In FY 2006, NIH completed *Know Stroke* outreach programs in 3 additional U.S. cities; completed presentations through local GFWC chapters in 14 U.S. cities; as well as provided educational materials to 4,520 GFWC representatives across the country. In addition, 8 stroke-related presentations were conducted at GFWC regional meetings. NIH continued beyond the original goal of 5,000 to distribute an additional 4,524 kits through the partnership with GFWC. In addition to the *Know Stroke* video, facilitator's guide, brochures and posters, the kits included a stroke statistics booklet with facts about stroke rate and risk factors by state from CDC. The kit also included a feedback form and pre-paid envelope for the clubs to return to GFWC with their thoughts on the materials and stroke awareness events they have hosted.

Since its inception in May 2001, the NIH campaign, *Know Stroke. Know the Signs. Act in Time.* has surpassed its original goal of increasing stroke awareness in cities across the country. NIH has done this by partnering with providers and volunteers in at least five communities annually. Through the creation and building of meaningful partnerships during the past five years, NIH has successfully raised awareness and engaged providers and volunteers through a variety of activities, including *Know Stroke* educational trainings and presentations. NIH partnerships include the American Stroke Association, the National Stroke Association, the Centers for Disease Control and Prevention, the National Council of La Raza, and the General Federation of Women's Clubs. NIH also achieved an increase in public education and awareness about stroke through the distribution of hundreds of thousands of *Know Stroke* brochures, as well as the development and placement of television and radio public service announcements, and feature articles, which were targeted to the general public, African American and Hispanic communities. In addition, NIH has exceeded its goal of disseminating 5,000 *Know Stroke* kits, leveraging its partnerships to plan and execute strategic, meaningful distribution of the materials, thus ensuring further reach of the *Know Stroke* messages.

Throughout the past five years, NIH has been able to demonstrate the impact of the *Know Stroke in the Community* campaign on increasing stroke awareness in communities through activity reports and feedback forms provided to NIH. To date, 168 *Know Stroke* Champions have conducted 650 outreach events, including health fairs, blood pressure screenings and other community gatherings. In total, the Champions have reached more than 150,000 individuals through peer-to-peer interactions in small and intimate community venues. Such settings are particularly effective in fostering communication between communities of color and advisors they trust. Evaluations showed that Champions considered the stroke information helpful and culturally appropriate, leading to greater acceptance and retention of stroke messaging.

Partner groups including the GFWC have also been providing NIH with feedback on their use of the community education tool kit through feedback forms. NIH has received 40 feedback forms thus far from GFWC affiliates across the country, and the forms continue to

come in. All GFWC representatives shared the stroke information kit with their clubs. More than a quarter of the representatives passed on the stroke awareness kit to their local library, community organization or health events after sharing with their members. While NIH will continue to engage in public and professional stroke education aspects of its mission, its original goal has been successfully achieved.

Implementation Strategy Advances or Other Highlights

In FY 2006, NIH continued to provide support to the Stroke Champions from the pilot cities (Birmingham, Houston, Chicago, Richmond, and New Orleans) as well as those from the program's expansion (Boston, St. Louis, Cleveland, Atlanta, Jacksonville, and Minneapolis-St. Paul).

- To reinforce the efforts of the Stroke Champions, NIH re-released the "Ambulance" television public service announcement (PSA) in March 2006, focusing airplay in *Know Stroke in the Community* cities as well as other markets in the "Stroke Belt," an area in the southeastern United States where stroke incidence is particularly high. Between March and October 4, 2006, the PSA was broadcast more than 2,007 times in 37 markets, resulting in a total audience of 17.6 million.
- In May 2006, NIH conducted two radio media tours (RMTs). The first was targeted to stations with large African American audiences. An African-American stroke expert from NIH completed 13 interviews with local and national radio stations. The interviews were run a total of 66 times reaching an estimated audience of 17.8 million. The second RMT was targeted to stations serving Hispanic audiences. A Spanish-speaking stroke expert from NIH completed five interviews that ran a total of 13 times, including on CNN's national Radio Noticias. This RMT reached an estimated audience of 10.6 million.
- NIH released three pre-packaged newspaper articles each targeting a different audience--African American, Hispanic, and general. As of October 24, 2006, the African American matte release has generated 312 articles in 17 different states with a readership of 17.9 million; the Hispanic matte release has generated 44 newspaper articles in 5 different states with a readership of 9.9 million; and the general audience matte release has generated 516 newspaper articles in 20 different states with a readership of 29.9 million.
- NIH developed two 30- and 60-second radio PSAs in Spanish. Each PSA conveys the story of a real-life stroke survivor whose family member recognized the signs of stroke and called 9-1-1. NIH is preparing to formally launch the PSAs in FY2007, but the spots have already aired on ABC Radio Networks.
- In June 2006, NIH and the General Federation of Women's Clubs (GFWC) launched their partnership at the annual GFWC convention. NIH has since conducted a special mailing of its community education kit to GFWC's chapters and other key contacts across the U.S., with 4,524 kits distributed.
- In February 2006, NIH presented the *Know Stroke in the Community* program in a poster session at the American Stroke Association's annual International Stroke Conference. The poster highlighted the program's success to date and the session generated a number of inquiries among conference participants for further information.
- In July 2006, NIH distributed 1,235 *Know Stroke* posters to 247 JCAHO-certified

hospitals each of whom received five posters.

Efficiency

FY 2006 activities were completed for an estimated $150,000, which is less than the $377,000 originally budgeted for these activities. Distribution of the community education kits have surpassed the target of 5,000, with the additional 4,524 kits distributed through the partnership with GFWC and other key contacts. NIH was able to complete these activities, including distribution of the additional kits, due to the creative and innovative partnership it secured with the GFWC, through whom NIH was able to leverage existing events and opportunities to conduct stroke-related education and awareness presentations as well as organize and execute a distribution of kits to all of the GFWC chapters across the country. By maximizing existing GFWC resources and working collaboratively with GFWC to leverage those resources and opportunities, NIH was able to complete its goals.

CTR-3	By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.

BACKGROUND

NIH has a longstanding tradition of promoting science with the ultimate goal of improving the public health on a global scale. One manner in which this is accomplished is by ensuring the availability of new therapeutic drugs, vaccines, devices, and other products that improve human health by linking technologies resulting from NIH and FDA intramural research with the private and public sectors through Public Health Sector (PHS) technology transfer activities. In this regard, NIH, on behalf of HHS, is one of the most active agencies in the Federal Government, participating in infrastructure and policy-building workshops hosted in the U.S. and overseas. OTT's participation in symposiums and workshops usually includes meetings and discussions with foreign delegations interested in replicating or adapting the successful partnerships among government, industry, and academia occurring within the United States.

To more fully utilize these partnerships to meet the NIH mission, there is a need to enhance the capacity of key personnel in developing countries to adapt and build the infrastructure for transferring laboratory discoveries to the bedside. Capacity building, within countries, is best achieved with active participation by local experts. Sometimes, however, local expertise first must be developed. This can be achieved by establishing a program for providing technical assistance and specific information to scientific and administrative personnel in developing countries on technology transfer activities and operations. This program can be carried out first with countries identified through previous collaborations as having the foundation (e.g., R&D experience, cadre of scientists, and government interest in science, technology and commercialization) necessary to establish technology transfer offices.

Rationale

The mission of the NIH, an Agency of the Department of Health and Human Services (HHS), is to support "science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability." Thus, promotion of science at NIH has the goal of not only improving the health of the American public but also ultimately enhancing human health on a global scale.

The OTT supports this goal by ensuring through its technology transfer activities that PHS health-technologies become available to the public in the U.S. an abroad. Moreover NIH institutes and centers are increasing their efforts worldwide by supporting centers of excellence in developing countries. The proposed international capacity building program will join in the NIH effort to be sure that countries receiving NIH funds have the ability to appropriately handle patents and licenses arising from NIH funding. It is a requirement that NIH grantees comply with Bayh–Dole provisions and thus need training on handling such matters appropriately consistent with the terms of their grants, the law, and U.S. policy interest. This is also in the U.S. public interest and, ultimately, results in improvement in

public health.

As noted in the NIH Roadmap, "public-private partnerships have become a model for advancing science and communicating results of medical advances to improve the quality of life for all people." In its routine functions relating to intellectual property, patents and licensing, and through its daily interactions with NIH scientists, universities and industries, OTT has been at the forefront of this endeavor. Thus, undoubtedly, OTT can provide leadership through this technical assistance program in building bridges worldwide "among researchers in academia, government and the private sector" to move research results and to make technologies accessible to the public in form of products.

HHS is committed to "finding and sharing solutions to shared health problems with our global partners". This goal of strengthening the capacity of developing countries to identify technologies and pursuing their development into products fits within the spirit of the HHS Office of Global Health Affairs, which is charged with the mission of "promoting the health of the world's population by advancing the Department of Health and Human Services' global strategies and partnerships" including those global efforts targeted to reduce the burden of diseases such as HIV/AIDS, tuberculosis, and malaria.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Establishing an in depth and long-term technology transfer assistance (TA) program to provide guidance and information related to technology transfer to scientific and administrative personnel in the appropriate institutions within developing countries will require extensive preparation. NIH plans to establish a working group in the Office of Technology Transfer (OTT) that will formulate recommendations. The recommendations will serve as the basis for a proposal for a needs assessment study that can be supported through the NIH One Percent Evaluation Set-Aside Program. This formal need assessment will systematically detail the nature and extent of issues that the technical assistance program should address and determine appropriate program goals and outcomes.

The strategy for program design (including selection of training personnel) is dependent on the outcome of the needs assessment which was conducted in FY 2004. NIH will identify appropriate institutions in developing countries that are in need of targeted technical assistance to address national and regional public health needs, and will administer appropriate capacity-building activities.

Securing potential partners is critical for full implementation of the technical assistance program. Thus, during FY06, potential partners from international organizations, private foundations, other federal agencies and professional societies were identified. Identifying and acquiring these partners will require intensive dialogue and negotiations with numerous organizations and agencies, and relating the aim of the technical assistance program to their respective objectives, goals, missions, and strategic plans. Additionally, must commit to providing guidance and support throughout the development and implementation of the technical assistance program. As partners sign on to the goal, the program is likely to sustain itself and expand.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	(FY03) No known needs assessment studies exist for developing technology TA program.		◆				
FY04	*Actual Performance:* (MET) Developed a 'needs' assessment study for a technical assistance program.						
(Target 2) Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	(FY03) No personnel.			◆			
FY05	*Actual Performance:* (MET) Personnel joined OTT to design and implement the TA program based on the results of the needs assessment study.						
(Target 3) Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	(FY03) Limited access to targeted training in developing countries.			◆ᴱ			
FY05	*Actual Performance:* (MET) OTT identified and targeted appropriate institutions in seven developing countries for participation in either an educational and technical assistance internship program (China, South Africa, India, and Brazil) or an on-site training seminar (Ghana, Zambia and Korea).						
(Target 4) Complete goal of through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.	(FY05) OTT identified and targeted appropriate institutions in seven developing countries.	-	-	-	◆ᴱ		
FY06	*Actual Performance:* (MET) OTT efficiently achieved the FY2006 goal of strengthening capacity of developing countries to identify technologies and pursue their development, through education/technical assistance.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was efficiently MET. The 2006 goal to strengthen the capacity of developing countries to identify technologies and pursue their development into products through education and technical assistance program has been ACHIEVED. Upon completion of the goal, representatives of developing countries were provided education and technical assistance so as to facilitate the development and expansion of technology transfer programs at their respective institutions. Such programs assist in the identification of technologies for commercialization and development into products.

In FY06, OTT continued to expand the International Technology Transfer Training Program by providing technical assistance and training to scientific and administrative personnel in developing countries on Intellectual Property Management and Technology Transfer activities and operations. International Technology Transfer Interns at OTT included representatives from at least four developing countries (six institutions), including India (the Indian Institute of Technology, Medical Research Council from India, and the Indian Department of Biotechnology); the Philippines (the Patent Office of the University of the Philippines, Manila); Hungary (the Hungarian Biotechnology Association); and Mexico (the University of Nuevo Leon). During FY06, the training program was expanded to include rotations and visits to other relevant NIH Institutes and Centers; federal agency international affairs offices at the Food & Drug Administration, the Patent & Trademark Office, and the State Department; technology transfer offices at four US universities and four non-profit foundations; and Product Development Partnerships. Finally, the Senior Advisor for International Technology Transfer developed, implemented and teaches a new course, 'International Strategic Partnering and Biomedical Business Development,' at The

Foundation for Advanced Education in the Sciences (FAES) Graduate School at the NIH, which further supplemented the internship program. Upon completion of the comprehensive Technology Transfer Training Program, the interns from developing countries returned to their respective institutions to develop Technology Transfer and Intellectual Property Management programs. The training program encompasses a wide range of activities, including the development of patent portfolios and the marketing of technologies to industry.

Correspondingly, in FY06, NIH continued its outreach educational programs, whereby staff members contributed to educational programs and conducted on-site training sessions for representatives from many developing countries. First, in partnership with public, international and non-profit organizations, OTT coordinated and assisted in the implementation of workshops aimed to enhance local capacity and infrastructure on Intellectual Property and Technology Transfer issues pertaining to biomedical research and development and public health in nine countries (China, India, Tanzania, Egypt, Argentina, Croatia, Czech Republic, Hungary, and Chile). Second, on-site training sessions were conducted for representatives from five countries (Brazil, the Philippines, Ghana, Senegal, and Korea). These training sessions provided extensive information and support on technology transfer-related issues, including intellectual property (e.g., patenting of inventions) and commercialization avenues (e.g., marketing of technologies to industry).

Finally, multi-media educational and training resources have been developed to supplement the Technology Transfer Training program that is also available more broadly throughout developing countries. The multi-media resources include website based training, publications, and handbooks that not only served as resources in FY06 but may be updated in subsequent years so as to effectively continue and enhance the technology transfer capacity in developing countries.

In sum, through comprehensive International Technology Transfer Training Program and the substantial outreach programs, OTT has MET and EXCEEDED its FY06 target/goal, to complete the goal to "by 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products."

Implementation Strategy Advances or Other Highlights

While completing the FY06 target (and the goal) to strengthen the capacity of developing countries to identify technologies and pursue their development, multi-media strategies were developed to provide educational and technical assistance. The resources not only supplement technology transfer training programs (e.g., internships, workshops, and on-site training sessions), but also serve to deliver technology transfer educational materials more broadly to developing countries. First, OTT developed a database of resources pertaining to intellectual property and technology transfer operations and training available at NIH; other US Government agencies (e.g., the US Department of Energy, Federal Laboratory Consortium, and the US Department of Commerce/National Institute of Standards and Technology); international organizations (e.g., the World Health Organization, World Intellectual Property Organization, and United Nations Industrial Development Organization); and non-profit foundations (e.g., the Gates and Rockefeller Foundations). The database is available at the OTT website and is expected to be a key tool for technology

managers of universities and research centers in developing countries and worldwide. Similarly, in partnership with US universities, a database was developed for neglected diseases (which primarily affect people in developing countries) that serve as an additional resource for technology managers in developing countries.

Second, OTT Senior Staff have authored or collaborated on publications and resource tools directed to international technology transfer. For example, as part of the Curriculum Planning Working Group of the Technology Managers for Public Health, OTT's Senior Advisor for International Technology Transfer collaborated on the publication entitled, 'Academic Licensing to Global Health and Product Development Partnerships.' This August 2006 publication by the Centre for the Management of Intellectual Property in Health Research and Development (MIHR) serves as a resource tool for technology managers in the US and internationally. In addition, OTT's Director, Senior Advisor for International Technology Transfer and Monitoring and Enforcement Branch Chief authored three chapters pertaining to global health and technology transfer for the "Handbook of Best Practices for Management of Intellectual Property in Health and Agriculture Research & Development" (2d ed.), published by MIHR and the Rockefeller Foundation. The handbook is expected to serve as a textbook for technology transfer courses at universities and research centers in developing countries.

Efficiency

The FY06 target, comprising completion of the goal to, by 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products, was met efficiently in at least two ways. First, the international technology transfer interns were sponsored by partner-institutions in their home countries, thereby defraying some of the costs to OTT. Second, the development of multi-media educational resources served as a cost-effective method to provide education and technical assistance that is accessible to a broader audience in the developing world, while also enhancing the International Technology Transfer Training Program, workshops and on-site training sessions.

CTR-4	**By 2008, increase the percentage of Small Business Innovation Research (SBIR) program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.**

BACKGROUND

Established under the Small Business Innovation Development Act of 1982 (Public Law 97-219), the Small Business Innovation Research (SBIR) program was initiated to stimulate technological innovation, use domestic small businesses to meet Federal research/research and development (R/R&D) needs, foster and encourage participation by socially and economically disadvantaged persons and women-owned small businesses in technological innovation, and increase private sector commercialization of innovations derived from Federal R/R&D.

The SBIR program is a highly competitive, three-phase award system. In Phase I, the objective is to establish the technical merit and feasibility of the proposed R/R&D efforts and determine the quality of performance of the small business awardee organization prior to providing Federal support. In Phase II, the objective is to continue the R/R&D efforts. In Phase III, the objective is for the small business to pursue, with non-SBIR funds, the commercialization objectives resulting from the research conducted in Phases I and II. Early-stage financing of innovation through public-private sector partnerships, such as those in the SBIR program, plays an instrumental role in supporting the development of new technologies and is an effective means for accelerating the progress of the technology from the laboratory to the market. The small business research community often lacks the expertise, contacts, and funds necessary to support the commercialization of products/processes/services that are developed with NIH SBIR funds.

Rationale

To facilitate the translation of SBIR innovations into commercially viable products that will have societal benefit, NIH will develop a program of technical assistance services. These services will assist SBIR awardees in their transition from the 'test tube to the medicine cabinet' and will serve as a means for leveraging NIH resources (SBIR funds) to foster new public-private sector partnerships. Because areas of need are varied and numerous, NIH envisions providing a 'menu' of services from which SBIR awardees can choose to address their individual needs. Through the development of technical assistance programs, NIH will be able to catalyze the matching of SBIR recipients with the resources/partners needed for them to bring their concepts to commercialization.

By consolidating the funds available through individual awards, NIH can create a program to assist SBIR awardees as they address the technical challenges that arise during the conduct of SBIR projects. NIH has already conducted two pilot assistance programs and has completed one year of a trans-NIH fully implemented program. These programs offered Phase II awardees business planning assistance and opportunities to 'marry' their technologies with potential targeted strategic alliances and investors, and Phase I awardees to learn of possible additional applications of their technologies thereby possibly opening up additional markets.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Several technical assistance programs aimed toward commercializing SBIR-developed products will be developed over a three-year period to meet the SBIR GPRA goal. The intent is to develop a menu of assistance programs from which SBIR awardees may choose to enroll that will help them fill a void in their ability to commercialize their federally-funded technologies. To achieve this end, modules expected to assist in the commercialization of SBIR products will be piloted. Effective pilots will be transitioned into programs. At that time, critical elements for monitoring performance will be identified. These critical elements will be monitored over time to report on performance and to make adjustments as needed to enhance the services.

NIH will first pilot programs that expand the availability of business planning and strategizing assistance to small businesses. These pilots will target specific commercialization issues such as business planning, technology valuations and niche assessments, manufacturing issues, regulatory hurdles (for biologics, therapeutics, new drugs, and devices) and licensing. Programs that are successful in their pilot phases will be introduced to the greater pool of SBIR awardees the following year. For example, NIH used the results of the completed FY03 Pilot Commercialization Assistance Program (CAP) to develop a trans-NIH CAP Program in FY04. The program included one-on-one business counseling; development of a business/strategic plan; and identification of key customers, investors, and business partners. Fifty SBIR awardees participated in the business planning portion of the pilot. Of these participants, 35 presented their business opportunities at an investment event with the intention of attracting and/or obtaining investment funding and/or strategic alliances. These companies will be tracked for a period of 18 months to determine if they did in fact make an investment or partnering deal.

While the trans-NIH CAP programs are being implemented, a new pilot assistance program will be launched in another business area of need. A pilot Technology Niche Assessment Program was offered to a group of Phase I SBIR awardees. This program assisted with identifying the niche markets that may be applicable for the individual technologies being developed. From the lessons learned from the pilot, a trans-NIH niche assessment program was implemented in late FY 05; the pilot proved to have addressed the needs of the participants.

Using this model of pilot testing programs one year and implementing trans-NIH programs over the next three years, by the end of FY 08, it is anticipated that a minimum of three programs will then be items on the Technical Assistance Program menu. If each is successful in becoming a menu item, the final menu could consist of CAP, Technology Niche Assessment, and Manufacturing Assistance Program. Implementation of these programs will be done through solicited contracts with business consulting firms specifically trained to provide such services.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing Assistance (extended to FY 07) (FY 07) Manufacturing Assistance	No current programs.		◆	◆[e]	→	◇	
FY04	*Actual Performance:* (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.						
FY05	*Actual Performance:* (MET) Completed pilot Niche Assessment Program with 100 participants.						
FY06	*Actual Performance:* (EXT) Pilot test for MAP has been extended to FY2007						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 2) Implement effective piloted programs to create a menu of technical assistance programs (FY04) CAP 1st Yr. (FY 05) CAP 2nd Yr., Niche 1st Yr. (FY 06) CAP 3rd Yr., Niche 2nd Yr. (FY 07) Niche 3rd Yr., Manufacturing 1st Yr. (FY 08) Manufacturing 2nd Yr.	Pilot Assistance Programs (i.e., CAP, Niche, etc.).		◆[e]	◆[e]	◆	◇	◇
FY04	*Actual Performance:* (MET) Initiated trans-NIH CAP with 130 participants.						
FY05	*Actual Performance:* (MET) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at an investment forum.						
FY06	*Actual Performance:* (MET) 122 awardees participated in the second year trans-NIH CAP program and 72 presented their business opportunities at an investment forum. All 150 participants in Niche Assessment Program received their TNA™ reports.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 3) Report critical elements to assess advances of each technical assistance program (FY 04) None (FY 05) CAP 1st Yr. (FY 06) CAP 1st Yr., CAP 2nd Yr., Niche 1st Yr. (FY 07) CAP 1st Yr., CAP 2nd Yr., CAP 3rd Yr., Niche 2nd Yr., Manufacturing Pilot (FY 08) Niche 3rd Yr., Manufacturing 1st Yr.	Pilot programs converted to program implementation.		◆	◆[e]	◆	◇	◇
FY04	*Actual Performance:* (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.						
FY05	*Actual Performance:* (MET) Pilot CAP -- 40% of forum presenters received additional private investments or sales. Cumulative private sector funding/sales received was $37,764,520 with most received by five firms.						
FY06	*Actual Performance:* (MET) First Year CAP -- 87% of participants showed commercialization progress. Contacts with investors increased 18%, negotiations 68%, and deals 87%. Second Year CAP -- 88% of participants showed commercialization progress.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 4) Complete goal of increase the percentage of Small Business Innovation Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.	Results of pilot programs converted to program implementation						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The target in FY 06 for piloting a Manufacturing Assistance Program has been extended into FY 2007. Options to contract with a business consultant for this project were investigated in FY 06 but many unexpected challenges arose in the contracting process. Discussions were held with staff members of Manufacturing Extension Partnership (MEP) at the National

Institutes of Standards and Technology (NIST) and a collaborative plan was developed to implement the program through a NIST contract. This resulted in NIH pursuing a GSA contract. A statement of work has since been prepared and a GSA Request for Quotations has been released with selection of a contractor in December 2006. The pilot program is expected to be completed by August 2007 and if deemed successful, the contract will immediately be renewed and a trans-NIH program will be implemented. The target will then be back on its originally planned schedule. The major accomplishment to date is the release of an RFQ for a GSA business consulting contractor to help implement the program.

Target 2

The FY 06 target of implementing a trans-NIH CAP and trans-NIH Niche Assessment Program was MET.

First Year Trans-NIH CAP – Feedback for the nine months following completion of the first year CAP was received by 77 participants (an encouraging 71% response rate). Analysis of the data showed that 87% of the 77 companies had made commercialization progress. When compared with their baseline data, contacts with investors increased 18%, negotiations with investors and partners increased by 68%, and an 87% increase was seen in deal completions. 38% of the companies experienced revenue growth and none reported negative total revenue.

Second Year Trans-NIH CAP– Again this year, individualized business counseling and mentoring was provided by Larta Institute, the NIH contractor assisting with implementing the NIH CAP, to 122 NIH SBIR Phase II awardees (111 fully completed and 11 partially but substantially completed the program). During the program, each company prepared: (1) a business model for generating revenue, (2) presentation materials consisting of an executive summary and PowerPoint presentations for specifically targeted, and (3) an 18-month strategic action plan. Seventy-two companies presented their business opportunities at the program's culminating investment/partnership event. The commercialization baseline data were collected and will be used for comparing participants' progress over the next 18 months. Baseline statistics include: 88% of the 75 respondents have made commercialization progress. Fifteen deals were made. 31% of the companies indicated increases in revenue.

Trans-NIH Niche Assessment Program – 150 NIH FY 2005 & 2006 Phase I SBIR awardees provided technical information to the contractor, Foresight Science and Technology about their ideas and the markets they were expecting to enter. Foresight performed due diligence and prepared reports specific to each company's technology indicating the needs and concerns of the end-users, the competitive advantages of their technologies, additional possible markets, and a market-entry strategy. Possible partners and/or investors were identified for consideration. All 150 participants received their reports in FY 2006. Feedback is still being collected, but of the 68 respondents so far, 81% felt they have a more realistic understanding of their target markets.

Target 3

The FY 06 target for reporting critical elements for the CAP and Niche Assessment Program was MET. As evidenced by the number of Confidentiality Disclosure Agreements , negotiations, and deals, many of those who completed the first and second years of the CAP have made progress with their commercialization efforts. Feedback received so far from those completing the first year of the Niche Assessment Program shows that the Technology Niche Analysis (TNA™) reports have been beneficial in helping companies better understand their technology's niche market.

CTR-5	**By FY 2013, improve marketing and management of NIH intellectual property assets by building text mining capability.**

BACKGROUND

The mission of the NIH is to support 'science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.' Thus, promotion of science at NIH has the goals of pursuing knowledge as well as transferring that knowledge and related technology to the private sector for further development. The attainment of those goals, ultimately, can lead to significant improvements in human health and the quality of life and ensure a continued high return on the public investment in research.

Technology transfer is a vehicle through which the fruits of NIH intramural research are transferred to industry to be developed ultimately into preventive, diagnostic, and therapeutic products to advance public health. For the United States to remain a world leader in technological and scientific innovation, both the public and private sectors must work together to foster rapid development and commercialization of useful products to benefit public health, stimulate the economy, and enhance our international competitiveness, while at the same time protecting the taxpayers' investment and safeguarding the principles of scientific integrity and academic freedom.

Evaluating, protecting, monitoring, and managing the NIH invention portfolio is accomplished largely through overseeing patent prosecution, negotiating and monitoring licensing agreements, and providing oversight and central policy review. The marketing and management of the vast and varied portfolio of intramural inventions is a critical aspect in translating scientific discoveries into products that can benefit public health.

NIH will establish a knowledge management (KM) system, composed of software, hardware and databases, to enable professional staff to keep pace with, explore, gain knowledge, and bring meaning and relevancy to large sets of scientific, technical, and legal documents using one single KM interface to access real-time information relevant to the NIH intramural inventions. NIH will focus immediate efforts to leverage text mining software to perform needed high-powered analyses. Text mining technology relies on finding patterns, not single facts, and is analogous to data mining. The difference is that it mines unstructured text, where data mining extracts patterns from numeral records stored as structured data in relational databases.

Rationale

Approximately 90 percent of the scientific community's explicit information currently is found in text documents that describe the existing state of knowledge, technology, and scientific innovation, and the potential partners for further development and commercialization of NIH's intramural invention portfolio. Without an integrated way to process or 'mine' all this information, the ability of NIH to utilize information currently available to assist in licensing efforts is severely compromised.

Establishing a real-time KM system will improve marketing and management of NIH intellectual property assets. Using text mining tools to create a single KM interface to access real-time information relevant to NIH's intellectual property assets and related information will increase the efficiency and effectiveness of technology transfer operations.

The long-term benefits to NIH of adopting such technology include: (1) improved management of NIH technology portfolio; (2) expanded outreach efforts for licensing of NIH technologies, including foreign entities; (3) increased partnering through identification of Cooperative Research and Development Agreements (CRADA) and academic or for-profit collaborators; (4) identification of materials and research tools worldwide for use by the NIH research community; (5) enhanced fiscal management related to patenting; and (6) improved reporting capabilities and ability to provide better responses to questions from the Congress and the public.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Establishing an in-depth and long-term technology transfer marketing and management program for intramural intellectual property will require extensive coordination. It is critical to identify and target those individuals and businesses most likely to be interested in licensing available technology. In order to accomplish this, NIH plans to focus on leveraging a text mining software engine (NIH currently owns a 10-year internal use license for this software technology) to perform needed high-powered analyses.

Initially, the project will concentrate on text mining the following data sources: PubMed, science news wires, TechTracS, and CRISP. Using a knowledge management system, NIH can more quickly and easily identify potential licensees and, for each available technology, electronically transmit an abstract describing the technology and instructions for licensing. Additionally, such targeted marketing allows NIH to determine quickly whether further research and development are needed before a technology is ripe for licensing.

Text mining of additional data sources was accomplished in FY 2006, including RaDUIS (the RAND Federal Database of Research and Development); NIH Office of Rare Diseases; patents applications filed at the US Patent & Trademark Office (USPTO); and industry leads databases.

In FY 2007, NIH intends to establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually. Some technologies have limited applicability and licensing ability as a single technology. By identifying complementary technologies held by other entities and marketing them as a single package, there is a greater likelihood that the combined technologies will be attractive to a licensee and that they could be developed into a product that benefits the public health.

The knowledge management system will also allow NIH to quickly and easily identify those technologies that are too early stage for licensing and, thus, require further research

and development before they are marketable. Decisions can be made at an earlier stage regarding whether to abandon the patents or whether NIH should pursue additional collaborations to advance the technology to the point of marketability. Additionally, the system would enable NIH to identify and contact potential CRADA partners for these critical collaborations.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Identify and text mine at least four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	(FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.			◆E			
FY05	*Actual Performance:* (MET) Identified and text mined five relevant data sources: TechTracS, CRISP, PubMed, Science News Wire, and the USPTO's patent database (2001-present).						
Identify and text mine an additional four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	(FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.				◆E		
FY06	*Actual Performance:* (MET)Identified and text mined an additional four data sources, comprising RaDUIS, NIH Office of Rare Diseases, USPTO patent applications, and industry leads databases. The target was met efficiently by accomplishing task with minimal cost and expanded scope.						
Establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually.	To be determined by results of FY06 target.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
To further refine the automated computer system by exploring other relevant data sources and developing portfolio synthesis and visualization tools to assist in the identification of prospective licensees and matching of technologies to those potential licensees, and by continuing to beta-test the system to allow for it eventually to be more widely distributed.	To be determined by results of FY07 target.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target to identify and text mine an additional four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing was MET efficiently. NIH's Office of Technology Transfer (OTT) identified and text mined an additional four relevant data sources for automated distribution, comprising RaDUIS (the RAND Federal Database of Research and Development); NIH Office of Rare Diseases; patents applications filed at the US Patent & Trademark Office (USPTO); and industry leads databases. The continued development of the text mining tool called Synapse (previously identified as GovPatents.com) has allowed NIH and FDA technologies to be more efficiently marketed to industry.

Implementation Strategy Advances or Other Highlights

The text mining tool, Synapse, has been demonstrated worldwide and has been overwhelming endorsed as a leading edge tool by both industry and academia. In its second year, Synapse has been used extensively to match company in-licensing needs to the NIH/FDA intramural technology portfolios (market pull) as well as to perform targeted marketing (technology push). More specifically, the text mining of the additional four data sources advanced the software tool so as to enable OTT to present its technology portfolio in an integrated manner to approximately fifteen companies, encompassing large pharmaceutical as well as small biotechnology entities, thereby facilitating the eventual licensing of NIH/FDA technologies.

Efficiency

The FY06 performance target was MET EFFICIENTLY in at least the following three ways. First, the identification and text mining of the USPTO's patent applications database was accomplished with minimal additional cost. The USPTO granted access to its patent application portfolio gratis, thereby limiting the cost to processing the data source. Second, the identification and text mining of RaDIUS was accomplished with minimal cost while the additional data have proven to be of significant value by enabling the bundling of technologies across federal agencies for licensing. Third, the FY06 performance was not limited to successful completion of the FY06 target (the identification and text mining of an additional four data sources), but also extended to worldwide implementation, thereby fostering further development of the tool and facilitating more effective marketing of NIH and FDA technologies to industry, including large and small companies. Implementation of the software tool has also drastically reduced the time required for analysis of technology portfolios from a period of several months (as reported by industry) to minutes.

CAPACITY BUILDING AND RESEARCH RESOURCES

Developing a research infrastructure is essential for continual scientific observation, discovery, and advancement. The NIH infrastructure encompasses the appropriate combination of trained scientific investigators, technologies, and research facilities. The productivity of the research enterprise depends in large measure on the strength of the talent pool and on technological and other research resources available for use in investigations. Collectively, NIH seeks to (1) recruit and train qualified investigators, (2) implement data automation and streamlined business processing where possible, and (3) expand the availability of resources by implementing Web-based tools, grant applications, and administrative portals.

Research Training and Career Development

NIH's training activities are designed to increase the Nation's ability to attract and retain the best and brightest minds and develop a cadre of well-trained, highly skilled investigators who are ready to generate the scientific discoveries of the future. To nurture the talent base of investigators, NIH provides research training support at the pre-doctoral and postdoctoral levels, primarily through the National Research Service Award (NRSA) Program and career development support. The NRSA is authorized under Public Law 93-348, Section 487, of the Public Health Service Act. (Note: Effective with the enactment of Public Law 107-206 on August 2, 2002, the NRSA Program was renamed the Ruth L. Kirschstein National Research Service Award Program as a tribute to the exceptional contributions Dr. Kirschstein has made to NIH and the Nation.) The following training and career development opportunities are offered:

Pre-doctoral Training. At the pre-doctoral level, students who are beginning graduate training need to learn the conceptual and theoretical aspects of the science they hope to practice. Most NIH support at this level is provided through grants to institutions so that they, in turn, can provide broad, multidisciplinary training programs for a critical mass of students.

Postdoctoral Training. At the postdoctoral level, NIH supports an extension and expansion of the apprenticeship approach. For individuals continuing their formal education in the biomedical or behavioral sciences, NIH offers training grants, fellowships, and research assistantships to fund this period of intense research activity. The primary focus at this level is on the acquisition of the knowledge and skills necessary to launch an independent research career.

Career Development. Career development awards provide support for acquiring specialized new skills to trained investigators (postdoctoral researchers) just commencing independent research careers or well established researchers looking to expand into new areas.

Mechanisms of Support. Extramurally, NIH offers a flexible and varied series of high-quality training opportunities tailored to the career needs of recipients who are at different stages of education and career development. The Web site at the following link provides information on the various extramural training and career development awards: http://grants2.nih.gov/training/extramural.htm. Intramurally, many training and career development opportunities also are available in NIH laboratories. The Web site at the following link provides information on the different intramural training positions: http://www.training.nih.gov/.

Loan Repayment. NIH Loan Repayment Programs are a vital component of the Nation's efforts to attract health professionals to careers in clinical, pediatric, health disparity, or contraceptive and infertility research.

Research Resources

The availability and accessibility of essential research tools, cutting-edge technologies, adequate facilities, animal models, reagents, and other repositories are fundamental to the productivity of the research enterprise. This is because research resources often set the boundaries as to which questions can and cannot be investigated. Within research resources, new information technologies (IT) to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

NIH has an active history of using IT to contribute to the success of its mission as well as to the efficiencies of all aspects of its administrative and scientific functions. For example, in February 2000 NIH launched ClinicalTrials.gov, a Web-based database that provides patients, family members, health care professionals, and members of the public with easy access to information on government- and industry-sponsored clinical trials. NIH also developed an IntraMall, a Web-based system for easily locating, ordering, and recording purchases of scientific supplies, computer equipment, and office supplies. IntraMall is the Federal Government's largest online purchasing system.

The promise of IT continues to be realized. Currently, NIH is involved in three major IT initiatives, known collectively as enterprise systems. They are the NIH Business System (NBS), the Clinical Research Information System (CRIS), and electronic research administration (eRA). In addition to contributing to the NIH mission, each of these systems, in its own way, supports the President's Management Agenda (PMA) and the Secretary's One HHS initiative. For example, the eRA is playing a major role in supporting the HHS E-Grants initiative. E-Grants are intended to put a single, simple face on the currently complex tasks of finding Federal grant opportunities and applying for Federal grants. Moreover, the eRA will create a unified electronic mechanism for grant application and administration to eliminate the redundant, paper-based processes currently required.

Expanding electronic government (e-gov) is one of the five key elements of the PMA and was initiated to make better use of IT investments to increase efficiency, reduce the paperwork burden, and improve government response time. The Secretary has embraced the PMA by moving to implement a "One Department" philosophy across HHS, that is, a vision to help HHS evolve from a collection of distinct and separate agencies into 'One Department.' To achieve his goal of managing HHS IT on an enterprise basis, the Secretary directed the development and execution of the Draft HHS Enterprise Information Technology Strategic Plan, FY 2003-2008 (March 2003). The Plan outlines strategic goals and strategic objectives that will advance the best and most effective HHS IT resources and will drive progress for public health and human services. All the NIH enterprise systems dovetail with the Draft HHS Enterprise IT Strategic Plan.

CBRR-1	**By 2012, recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.**

BACKGROUND

A critical part of the NIH mission is the education and training of the next generation of biomedical, behavioral, and clinical scientists. The overall goal of the training program is to maintain a population of scientists that is well educated, highly trained, and dedicated to meeting the Nation's future health-related research needs.

The extramural grant programs of the NIH support a broad range of research education, training, and career development activities that utilize a variety of support mechanisms to meet the NIH research training and career development goals. Although other Federal agencies and private philanthropies support research training, none provide the focus, breadth, or depth required to ensure capacity for research personnel across the biomedical, behavioral, and clinical sciences.

Building and maintaining a comprehensive scientific research workforce are inherently ambitious activities. The evolving nature of biomedical, behavioral, and clinical research; the long-term investment in research training; and the global mobility of the research workforce all challenge efforts to align needed expertise with public health demands. Training for a career in research generally requires an investment of 8 to 12 years of pre- and postdoctoral education, during which time science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented. To be successful, trainees must have an aptitude for research, be highly committed as well as agile in their ability to address emerging research questions, and also possess the organizational skills and acumen required to manage complex research projects.

Success of NIH training programs can be measured, in part, by the number of trainees and fellows that apply for and receive subsequent NIH support; subsequent support is an indicator of retention success in the research arena, and reflects the impact of NIH-funded training on the ability of trainees and fellows to be competitive and sustain a research career with independent funding.

Rationale

The NIH is dedicated to improving the health of Americans by supporting biomedical research that will help prevent, detect, treat and reduce the burdens of disease and disability. In order to achieve these goals, it is essential to ensure a diverse available pool of highly trained scientists in adequate numbers and in appropriate research areas to address the nation's biomedical, behavioral and clinical research needs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A number of activities are conducted to support the achievement of this goal. These include: issuing new and updated research training and fellowship initiative announcements to ensure that the needs of the scientific research community are served; engaging the National Research Council of the National Academies to periodically perform evaluative studies of the National Research Service Award program; informing the scientific research community of new, updated and ongoing training and career development opportunities through presentations at national, regional, and local meetings; and communicating with other Federal agencies that support similar research training goals.

In particular, NIH seeks to retain newly-trained investigators and aid their transition to independent research careers through strategies such as:

• Encouraging training in laboratory and project management for postdoctoral trainees

• Providing career development awards that explicitly target the transition process, such as the K22 Career Transition Award and K99/R00 Pathway to Independence Award

• Offering loan repayment opportunities for newly-trained scientists committed to research careers.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%		◆	◆	◆	◇	◇

FY04	*Actual Performance:* (MET) Award rate to comparison groups exceeded by 12%
FY05	*Actual Performance:* (MET) Award rate to comparison groups exceeded by at least 14%
FY06	*Actual Performance:* (MET) Award rate to comparison groups exceeded by at least 13%
FY07	*Actual Performance:* Performance results will be reported in February 2008.
FY08	*Actual Performance:* Performance results will be reported in February 2009.

(Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12% *Previous Target:* (Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%. The baseline and will be re-examined and may be adjusted based on data available in the future so that each year our target is to achieve at least the average. (FY06) 12% (FY07) 12% (FY08) 12% (FY09) 12% (FY10) 12% (FY 11) 12% (FY 12) 12%	◆	◆	◆	◇	◇
FY04	*Actual Performance:* (MET) Award rate to comparison groups exceeded by 14%.						
FY05	*Actual Performance:* (MET) Award rate to comparison groups exceeded by at least 13%						
FY06	*Actual Performance:* (MET) Award rate to comparison group exceeded by at least 13%						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY 2006 target to retain NRSA predoctoral trainees and fellows in research relative to comparison groups of Ph.D.s was MET. In contrast to other doctoral students at the same institution over the same time period (Comparison Group A) and doctoral students at institutions not receiving NRSA support (Comparison Group B), NRSA trainees and fellows from 1985 through 1995 were more likely to remain active in biomedical research, as indicated by the greater percentage applying for and receiving NIH research project grant support within 10 years of completing their Ph.D.s.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Trainees and Fellows	32.4% (4,679/14,455)	20.2% (2,913/14,455)
Comparison Group A	13.9% (9,716/69,873)	7.1% (4,977/69,873)
Comparison Group B	6.6% (1,355/20,641)	2.8% (573/20,641)

Target 2

The FY 2006 target to ensure the retention of postdoctoral fellows receiving research training through the NRSA program relative to comparison groups was MET. In contrast to postdoctoral fellows that applied for, but did not receive NRSA research fellowship support during the same time period, NRSA postdoctoral fellows from 1985 through 1995 were more likely to remain active in biomedical research, as indicated by the greater percentage applying for and receiving NIH research project support within 10 years of completing their training.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Fellows	48.9% (5,147/10,520)	32.2% (3,390/10,520)
Other Postdoctoral Fellows	32.5% (3,557/10,963)	18.8% (2,065/10,963)

Implementation Strategy Advances or Other Highlights

During FY 2006, NIH revised the requirements for its major institutional research training grant program to encourage instruction in grant writing for trainees and to ensure that postdoctoral trainees, in particular, develop the requisite skills in laboratory and project management to remain in research and become successful independent investigators.

In addition, NIH issued more than 50 new or updated education, research training, and career development funding opportunity announcements in FY 2006, including the announcement of the new, trans-NIH K99/R00 Pathway to Independence Award. The K99/R00 Award complements the existing K22 Career Transition Award offered by a number of NIH Institutes and Centers, and will aid an additional 150 to 200 exceptionally promising new investigators a year transition to independent research careers.

To foster the retention of newly trained investigators in research, NIH's loan repayment program made awards of up to $35,000 to more than 1,650 individuals in FY 2006. By reducing the burden of educational debt, these loan repayment awards allow recipients – many of whom are clinical investigators – to concentrate on launching their research careers.

PART

This goal was included in the FY 2008 PART of the Extramural Research Training and Research Career Development Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

CBRR-2	**Promote data sharing and provide information in real time by implementing and monitoring the NIH Business System. (By FY 2010, the NBS will be in an ongoing status.)**

BACKGROUND

The core mission of the NIH is to conduct and support biomedical research. After an extensive review of its administrative processes and current information technology support, the NIH began implementing an enterprise resource planning system known as the NIH Business System (NBS). The NBS Project will replace the NIH administrative and financial core operations systems, including the general ledger, finance, budget, procurement, supply, travel, and property management systems. The NBS will enable administrative/scientific support that is cost effective, provide more accurate and timely information, and facilitate the scientific mission of the NIH. The NBS will reduce the amount of time required by NIH scientists to complete administrative tasks (for example, related to travel requests or acquisition), thereby freeing these valuable resources in direct support of NIH's core research mission.

Rationale

Deployment of the NBS should position the NIH to meet the Chief Financial Officers (CFO) Act and Government Management Reform Act (GMRA) requirements and OMB's timeframes. The successful implementation of the NBS general ledger module for FY 2004 reduced the need for previously constructed adjustments required to prepare financial statements. This was a critical step for the NIH meeting the tighter timeframes for annual financial statements and other financial reporting while maintaining the accuracy of the reports. Implementation of the general ledger module and follow-on modules will strengthen the NIH's compliance with accounting standards for recording transactions in the appropriate ledger accounts, providing subsidiary ledgers for all appropriate general ledger accounts, and for identifying intra-governmental partners. Complying with accounting standards will help facilitate the reconciliation process and provide more effective analysis of general ledger account balances.

The NBS is an important component of the One HHS initiative and a major element of the DHHS Unified Financial Management System (UFMS). As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS. The NIH staff actively participates on DHHS UFMS teams to meet common goals, address Department-wide challenges, and ensure that the NBS will become an integral part of the UFMS.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NBS Implementation is a phased approach, as recommended by JFMIP, to incorporate individual modules as they are completed. Modules of the NBS will serve similar functions to the legacy ADB system. In FY 2007, the NBS is upgrading the general ledger/budgeting and travel modules already in production and plans to deploy the contracts/ acquisition, property, supply, accounts payable and receivables modules and the agreement and real property solutions. Post deployment support will be provided for the property and

contracts/acquisition/accounts payable and receivable/supply modules through FY 2008. Billing and cost accounting for Central Service and Supply operations will be deployed at a later date. Additional modules may be developed and implemented beyond the original seven functional areas of ADB.

The FY 2005, FY 2006 and FY 2007 NBS implementation and deployment activities that the functional, technical and change management teams will undertake include the ongoing design, configuration, and testing of the baseline system and the system at the integration phase including workflow management. An overview of the tasks follows:

a) identifying business rules to be applied and functionality that have policy change implications;
b) testing each function to assure that the configurations are accurate, that business rules are being applied properly and reporting test results for potential change management issues;
c) developing workflows for each function and identifying all interfaces with other functions;
d) testing integrated functionality to determine that business rules and workflow operate as expected and report the results
e) defining all existing integration with remaining ADB function(s) or other systems, as required;
f) developing acceptance test criteria and translating the acceptance test criteria into test scripts for the end user training and for the functions to be deployed;
g) collaborating with Change Management staff to develop technical training materials and user documentation for each function to be deployed;
h) training approximately 6200 users for an estimated 32 roles;
i) providing access to all authorized NIH users of each new function and providing pre and post deployment support to end users.

DHHS currently has a goal of deploying e-Travel throughout the Department. The intent is that the e-Travel system will provide functionality, integration with financial components and real-time support similar to that currently implemented by NIH. The NIH is currently analyzing the actions and resources necessary to include NIH travel needs into the consolidated eTravel system, while mitigating disruption or degradation to NIH travelers and administrators. The NBS roll-out phase will support integration activities to UFMS finance systems.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	(FY03) NBS without contracts/acquisition/accounts payable/supply modules		◆	→	◆	◇	
FY04	*Actual Performance:* (MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.						
FY05	*Actual Performance:* (EXT) The program steps a-g 'Integration' is being re-planned. Extended to 2006.						
FY06	*Actual Performance:* (MET) Completed CRPs 2 and 3, user acceptance testing (UAT) and production of training materials is underway. The program steps a-g 'Integration' has been completed.						
FY06	*Actual Performance:* (EXT) The program steps h-I 'Final review' is being extended to 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	(FY03) NBS without service and supply fund activities module		◆	→	→	→	◇
FY04	*Actual Performance:* (MET) Identified solutions for automated amortization for Real Property and Agency Agreements.						
FY05	*Actual Performance:* (EXT) The program steps a-g 'Integration' deployment for service and supply fund modules are being extended to 2008.						
FY06	*Actual Performance:* (EXT) The program steps h-I 'Final review' is being extended to FY 2009.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 3) Report critical elements of General Ledger and Travel Module performance.	(FY04) NBS performance with General Ledger and Travel Modules deployed				◆	◇	◇
FY06	*Actual Performance:* (MET) Performance metric mapping directly to the HHS strategic goals and objectives were reported against FY2004 baseline.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 4) NBS roll-out and post deployment support.	(FY05) NBS without contracts/acquisition/accounts payable and receivable /supply modules					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 5) Commencement of NBS/UFMS migration activities.	(FY06) NBS without the UFMS migration					◇	◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 6) Continue to provide NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules.	(FY06) No NBS post deployment support currently exist						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY2006 program steps a-g 'Integration' target to deploy the property and contracts/acquisition/accounts payable and receivable/supply modules was MET. The NBS built and executed CRP3 testing, user acceptance testing (UAT) and developed the training

and communication plans that support workforce transitions, developed training materials and conducted a numerous Executive Officer, Scientific Director, NIH-wide Town Hall and other end user meetings introducing the property and contracts/acquisition/accounts payable and receivable/supply modules. The project team also conducted the data collection component of data conversion and completed two mock data conversions of master data.

Target 2
The FY2006 program steps h-I 'Final review' target to develop the service and supply fund activities module was extended to FY2009. Deployment of the service and supply fund activities module will not occur before FY2008. This is no reportable activity currently due.

Target 3
The FY06 target to report critical elements of General Ledger and Travel Module performance was MET. Critical elements of General Ledger and Travel Module performance were reported in FY2006 to include the number of NBS Help Desk tickets (per module), percent of total NBS tickets closed by Level 3 personnel, number of purchase orders approved, number of days to close the books and captured percent of server uptime statistics. These elements map directly to the HHS Strategic Goals and Objectives FY 2003 - 2008, Goal 8: "Achieve excellence in management practices"; Objective 8.1 to "Create a unified HHS committed to functioning as one Department."

The NBS Travel module is used daily by all NIH Travel administrative personnel. Approximately 444,000 records have been processed in the NBS Travel module since deploying for FY 2004. For FY 2006, approximately 135,464 travel authorizations and voucher transactions were entered online in real time. The NMC takes a proactive approach for intercepting document errors in both the travel and financial modules. The goal is to achieve "same-day resolution" for system and document errors that immediately affect user access and/or traveler reimbursements.

In addition, the NBS provides enhanced sponsored travel tracking and reporting. The process aids with the identification of outstanding receivables and allows for more efficient collection, as evidence by a significant reduction in sponsor-related billing requests since deployment of the NBS.

The NBS updates patient records every 5 minutes, seven days a week. This automated process coupled with real-time interfaces between the travel and finance systems enables Clinical Center staff to enter patient authorizations and pay travel vouchers as patients complete their stay at the Center. Approximately 22,629 patient trips were processed by the Clinical Center Travel Office during FY2006.

The NBS Management Center (NMC) supports the deployed General Ledger and Travel modules by employing standard escalation protocols for assisting users who are experiencing difficulty. In FY06 the NMC saw a 40% reduction in the number of user call assistance tickets, totaling 9,165 down from 15,178 in FY04. This can be largely attributed to system stability, continued user comfort with the system, and NMC education outreach efforts that include emails as well as supplementary training seminars. There were three such seminars in FY06, whose topics were derived from trend analysis from monitoring NBS user call

assistance tickets as well as direct user feedback.

Implementation Strategy Advances or Other Highlights

The NBS automated and linked the DHHS EHRP to the NBS Human Resources database for all employee-based transactions. This information is used to support portal access, travel manager transactions and review and approval processing flows. This solution has been adopted by the UFMS for their organization and people data base needs.

CBRR-3	**By 2007, streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS).**

BACKGROUND

The NIH Clinical Center has been a pioneer in the use of computer technology for the advancement of research and the improvement of care. The present Medical Information System (MIS) was implemented in 1975 and gave NIH physicians access to tools such as physician order entry and a point-and-click interface that are still not implemented in many academic health care settings. Unfortunately, the system was built around a proprietary database, and its capabilities no longer meet the needs of the institution for providing data in both the research and clinical care settings. For some functions such as pharmacy, surgical services, and consent management, no automation is currently in place.

To address the limitations of the present system and to fully automate clinical care information, NIH has embarked on the CRIS project. Specific functionality that will be provided by the CRIS includes:

- Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and regulations of the Privacy Act of 1974
- Interfacing with ancillary systems to provide integrated data and eliminate paper-and-pencil transfer of data among systems
- Reduction of potential medical errors through the implementation of a pharmacy and surgical scheduling, management, and documentation system
- Management and display of radiologic, anatomic, pathologic, and ultrasound images and other image-based data
- Interfacing to IC research databases
- Support for standardized medical vocabularies
- Support for analyzable electronic documentation (i.e., physician notes)
- Support for protocol-based provision of care
- Provision of management information for resource allocation and cost attribution
- Provision of longitudinal patient data
- Provision of historical patient data for research analysis
- Comprehensive support for patient appointing
- Support for bed management
- Support for nurse acuity assessments

Rationale

Historically, research data have been recorded in stand-alone systems or on paper. Because these research data could not be provided directly from the hospital system, they were typically copied from hospital system computer screens into the local electronic or paper-based research record. Such a process, when multiplied over the research enterprise of NIH, represents a substantial loss of productivity and a major risk of error. Implementation of the CRIS will reduce the life-cycle costs of these clinical information technology projects and obviate the need for IC-specific systems.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

CRIS includes several functional modules that will be phased in once they are completed. The core hospital system was developed to include modules that streamline business processes and automate data movement among multiple systems. Staff time for redundant data entry was reduced with the implementation of the core system in FY 2004. In FY 2005, a surgery and anesthesia management system as well as an augmentation of the pharmacy system and patient registration system were implemented facilitating records management for Clinical Center staff. Additionally, a clinical data warehouse was developed and used across NIH. The warehouse directly supports the PMA goals of expanded electronic government and improved financial performance. The CRIS project represents the nucleus of clinical informatics for NIH, with the goal of collecting clinical information for patient care and research in one place. For centralized reporting and monitoring, the completed system will serve as a model for other health care organizations. In 2006 the goal was the integration of Clinical Center data systems. The successful completion of this goal now ensures that patient data flows into a central transactional system for more efficient patient care, and central collection of data for analysis and research. Working together with CIT to identify multiple clinical systems, ensuring compliance with CHI standards, HL7 compliance and interoperability will ensure meeting the larger goals of the NIH Roadmap and DHHS.

The development of the CRIS (Clinical Research Information System) is key to complying with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). It is an ambitious undertaking and requires a number of enterprise process and system changes to deliver the goal. In FY 2006 the CRIS project moved closer to the goal of systems integration by interfacing ancillary patient care systems to the central electronic health record.

The CRIS project scope included a new hospital information system to support clinical practitioner order entry (CPOE), results retrieval, and electronic clinical documentation. Ancillary departmental systems were included in the project scope to support radiology, lab, nutrition, surgery, medical records, admissions and the pharmacy. In addition, the original scope included a data repository to allow intramural institutes to access clinical data by patient and protocol. The ability to merge clinical data with research data fully supports the need for investigators to analyze data by protocol and across protocols. As of 2007, the entire scope of the project (all systems) will be complete. All aspects of the program are due to be completed within FY 07. The project will enter an operations and maintenance phase in FY 07.

The original goal of the CRIS project was to collect all clinical data once for clinical care and for research. This goal will be fully realized with a fully functional hospital information system. The need to manually move data from a clinical system to a research system will be mitigated. In the future, clinicians will have all data and images necessary for patient care centralized in one application and researchers will be able to access both clinical and research data within individual institute systems.

The CRIS project will continue the process of integrating diverse clinical care systems into the CRIS. These types of integration are highly dependent on changing technologies and the ability to interface various data collection systems with the core CRIS.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Implement a core hospital system.	(FY03) 28 year old legacy system		◆e				
FY04 *Actual Performance:* (MET) The core hospital system, CRIS, went live and the legacy system was retired.							
Implement a surgery and anesthesia management system.	(FY03) No current system exists			◆			
FY05 *Actual Performance:* (MET) Surgery and anesthesia management system implemented; project is on task and within budget.							
Implement a clinical data warehouse.	(FY03) No trans-NIH clinical data warehouse currently exists			◆			
FY05 *Actual Performance:* (MET) Implemented a clinical data warehouse; project is on task and within budget.							
Integrate clinical systems across the NIH Clinical Center.	(FY04) Multiple clinical systems exist, but information is not retrievable in a central system.				◆e		
FY06 *Actual Performance:* (MET) CRIS has interfaced clinical systems across NIH Clinical Center and has gone from 3 integrated systems in 2000 to 19 integrated systems.							
Complete goal of streamlining business processes and automation of data movement by implementing , monitoring and updating the clinical research information system (CRIS).	FY06 results					◇	
FY07 *Actual Performance:* Performance results will be reported in February 2008.							

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY2006 target to integrate clinical systems across the NIH Clinical Center was MET efficiently. The Clinical Research Information System began as an enterprise in 2000 and 2006 represents the completion of the CRIS project as an enterprise. Prior to the CRIS project, the legacy medical information system was interfaced with two other clinical systems within the Clinical Center - the laboratory information system and the legacy Nutrition System. Over the past 6 years, the goal of the CRIS enterprise was to replace the medical information system, replace the nutrition system and build new systems to create a comprehensive system for managing patient care and research data within the Clinical Center. Since 2000, the CRIS has gone from 3 integrated systems to 19 integrated systems. Connected by HL7 interfaces, clinical care and research data is now seamlessly included into the CRIS enterprise from radiology, surgery, admissions, medical records, consultations, the blood bank, scheduling as well as institutes systems for echocardiograms, and electromyelograms. The CRIS system represents the positive impact of using technology to create efficiencies. CRIS integrates care across disciplines, eliminates manual transfer of data between systems, and reduces the potential for medical errors.

Efficiency

Efficiencies have been achieved by decreasing manual data entry between systems. Additional systems have added additional costs, but have also allowed the systematic collection of additional and more complex research data.

CBRR-4	**By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic Research Administration (eRA) system.**

BACKGROUND

The eRA is NIH's infrastructure for conducting interactive electronic transactions for the receipt and review of applications, and the monitoring and administration of NIH grant awards to biomedical investigators worldwide. Public Law 106-107 requires Federal agencies to migrate from paper-based to electronic systems, thus improving the delivery of services to the public. Therefore, the overall objective of the eRA is to provide a two-way electronic interface for the submission and processing of grant applications and reports in compliance with Public Law 106-107. eRA system development incorporates government wide standards and will integrate with the other NIH, DHHS, and e-grants systems. DHHS is the agency partner in the development of the government-wide Grants.gov effort. NIH eRA staff is also involved in this effort. In 2004, DHHS designated eRA as a Center of Excellence for all DHHS research grant processing. In response NIH has undertaken the responsibility of integrating the electronic grants systems of The Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), The Substance Abuse and Mental Health Administration (SAMHSA), and the Health Resources and Services Administration (HRSA).

eRA developed the eRA eXchange, a business-to-business system, by which it can electronically receive grant applications from Grants.gov, the DHHS e-Grants storefront initiative. It is also being used for other grants-related activities with commercial service providers and research institutions who establish system-to-system capabilities with NIH. The eXchange uses eXtensible Markup Language (XML) and PDF attachments. XML is the next generation beyond HyperText Markup Language (HTML), and provides independence from proprietary development tools. XML enables a single data entry point, more efficient maintenance, and higher quality products. This places the NIH eRA system in a strategic position to integrate with Grants.gov, and ultimately to achieve the ability to execute end-to-end electronic processing between NIH and the external community using shared electronic resources.

Rationale

A significant goal for eRA is moving internal work flows from paper-based business processes to electronic processes. The electronic submission and receipt of grant applications through Grants.gov is currently an intense effort and when completed will permit a revitalized refocusing on the administration of grants from application through grant closeout. This will include substantial improvements to Receipt and Referral processes, peer review facilitation, and project oversight. The availability of applications on-line eliminates the need for multiple copies of applications for each reviewer. Financial and progress reporting can now largely be done electronically, and by the end of FY07 or FY08 it is anticipated that most aspects of the grant administration process will be done electronically, which will increase the efficiency of the process and lower the costs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Electronic reporting was implemented in institutions participating in the Federal Demonstration Partnership (FDP) through a Web-based progress-reporting system. A pilot of this system began in November 2002, and was tested throughout FY 2003 by making it available to FDP institutions that requested to use it. After ensuring acceptable performance of the progress reporting system once all FDP institutions have been invited to use it, its availability was expanded to all grantee institutions and a formal announcement was publicized on the NIH Commons during the third quarter of FY 2004. The ability for a grantee institution to submit progress reports through the Commons is now in the hands of the institution's business official.

In terms of developing XML capability, NIH started building pilot software to accept competing grant applications from the grant community in FY 2003. This pilot software has focused initially on competing applications for simple research mechanisms. The initial version of this pilot software was completed successfully in FY 2004, and has since been further refined and improved over the course of several subsequent receipt cycles. These competing grant application pilots have produced several positive results for the NIH. Most notably, these efforts have resulted in a robust and extensible technical infrastructure for receiving and handling XML transactions. In FY2006, this capability was expanded to enable to NIH to accept grant applications via Grants.gov system-to-system interface. NIH will continue to expand upon the types of grant applications it receives through Grants.gov via the exchange. Also, efforts are underway for extending and applying this existing infrastructure to an even broader array of services, such as sending out notice of grant awards via XML data streams.

Migration of existing client/server applications will be completed by implementing an eRA J2EE Migration Plan. This plan stages the transition of proprietary client/server applications to a standard, multi-tier, component-based technology. The J2EE architecture complements the XML technology, transforming eRA into a non-proprietary, secure enterprise system.

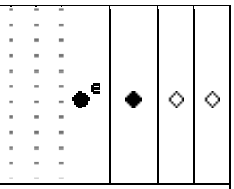
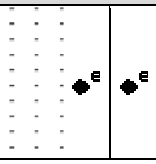
The overall implementation strategy for the integration of electronic grant processing for HHS Operating Divisions (OPDIVs) is to identify OPDIV integration requirements and, where there are gaps, determine whether OPDIV business processes need to be changed or whether eRA business processes/system modifications need to be made. To this end, a 'fit/gap' analysis of OPDIV requirements was finalized in FY05. An eRA-led working group, with participation from the integrating OPDIVs, met bi-weekly and finalized a list of issues that require changes to existing business processes or system modifications. Coding and testing of OPDIV grant processing was ongoing in FY05, and FDA, SAMHSA, HRSA, and CDC (non-research) began processing grants through eRA by the end of FY05. Full grant processing for the OPDIVs by eRA was achieved during FY06, and the completion of the migration of legacy data will be completed in FY07.

The transition from a paper-based business process to fully electronic processing has been part of the eRA vision for several years. The conversion of paper applications to electronic format has been fully implemented, and the system is capable of accepting electronic

applications and doing 'Internet Assisted Review'. Other conversion activities are currently underway, and other processes will be converted as time, budget resources and other priorities allow. It will likely be several years before most of the conversion is completed. Even though NIH is targeting increased conversion to electronic processing of documents, it may not be cost-effective or desirable to expect a 100% conversion of the individual pieces that comprise end-to-end processing of grants. NIH plans to achieve most of this effort by FY08 or FY09. eRA continues to map electronic processes to existing business models, but as these continue to change, eRA efforts will require greater adaptability. These unknowns make it difficult to commit to a specific schedule for completion of paperless processing. Each year the NIH expects the capability for paperless processing to expand and this progress will be reported.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership[2].	(FY99) No institutions using electronic reporting	◆e					
FY03	*Actual Performance:* (MET) Electronic reporting available to the 65 FDP participating institutions.						
(Target 2) Begin pilot-testing of progress reporting for multi-project mechanisms.	(FY99) 14 simple competing grant applications received	→	→	→	→	→	
FY03	*Actual Performance:* (EXT) XML development needed. Extended to 2007.						
(Target 3) Expand availability of electronic progress reporting to all grantee institutions	(FY02) 145 FDP institutions given access to electronic reporting.		◆				
FY04	*Actual Performance:* (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.						
(Target 4) Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	FY03) Need for system to conform with OMB/Federal Enterprise Architecture		◆				
FY04	*Actual Performance:* (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.						
(Target 5) Develop plan to integrate OPDIV's	No plans in place for OPDIV Integration.		◆e				
FY04	*Actual Performance:* (MET) eRA has developed plans for adding the FDA and components of the CDC.						
(Target 6) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. Goals: FY05 - 50% of eligible HHS OPDIV's FY06 - 100% of eligible HHS OPDIV's	Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's AHRQ and CDC/NIOSH			◆e	◆		
FY05	*Actual Performance:* (MET) The Target was exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) are using eRA to process new grants.						
FY06	*Actual Performance:* (MET) 100% of the eligible HHS OPDIVs (AHRQ, CDC, FDA, and SAMHSA) are using eRA for administration of research grants.						

[2] Target was carried over from previous eRA goal and was met for FY 2003.

(Target 7) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 - 25% electronic business processing FY06 - 40% electronic business processing FY07 - 55% electronic business processing FY08 - 80% electronic business processing	10% of business processes being done electronically					
FY05	*Actual Performance:* (MET) Approximately, 33% of business processes & financial status reports are done electronically.					
FY06	*Actual Performance:* (MET) Approximately 40% of the transactions in the business processes are now being done electronically.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
FY08	*Actual Performance:* Performance results will be reported in February 2009.					
(Target 8) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 - 50% code conversion FY06 - 75% code conversion FY07 - 100% code conversion	(FY03) Migration plan developed. Current architecture is client-server mix with web					
FY05	*Actual Performance:* (MET) 60%of the code has been converted. This efficiency was accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.					
FY06	*Actual Performance:* (MET) The target was met and exceeded. 100% of the code was converted before the end of FY06, and all of the Web-based applications were deployed by the end of FY06					

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 6

The FY06 target of integrating 100% of the eligible Health and Human Services (HHS) Operating Divisions (OPDIVs) as eRA users for administration of research grants by the end of FY06 was MET. The Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Substance Abuse and Mental Health Services Administration (SAMHSA) are all using eRA to administer process their research grants. NIH has worked extensively over the past year to fully integrate SAMHSA, FDA and CDC into the eRA/IMPACII grant processing system. CDC is currently integrated and is making discretionary grants using the system as is SAMHSA. FDA requirements are complete enabling FDA to process grants through the system by the end of the Fiscal Year 2006. NIH provided access to all eRA modules requested by the OPDIVs and linked to the financial system used by the Agencies. The Health Resources and Services Administration (HRSA) chose to use another service provider, so all of the OPDIVs that chose to use eRA have successfully been integrated as eRA users.

Target 7

The FY06 target goal of 40% of the business processes being conducted electronically was MET. The use of electronic notification was expanded in FY06 with a significant increase in the percentage of progress reports and financial status reports (FSRs) that were submitted electronically. Internet (electronic) Assisted Review is being used for the review of all NIH applications. All of the Small Business Innovation Research (SBIR) applications were received electronically. All paper applications are converted to electronic format and processed electronically. Significant process was made in preparing the system to receive Individual Basic Research Grant (R01) applications in February 2007, which make up a majority of all the applications that are received each year.

Target 8

The FY06 target of 75% code conversion for the complete migration of existing client/server applications to Web-based technology was MET and exceeded. Hundred percent (100%) of the code was converted before the end of FY06, and all of the 11 applications have been deployed as web-based applications. In completing this goal before schedule, the FY07 target, has been met as well; thereby creating efficiency.

Implementation Strategy Advances or Other Highlights

As a result of NIH's demonstrated ability to integrate new users, the Veterans Administration (VA) has signed an agreement to use the eRA system to administer their research grants, and that process is well underway. As a result of the OPDIV integration, five HHS OPDIVs are now using the same computer system to process their grants instead of having to maintain five separate computer systems.

Efficiency

Complete code conversion was achieved sooner than expected because one contractor was employed to convert all of the applications instead of assigning the code conversion to the current operations and maintenance contractors. This allowed the actual code conversion to be completed sooner than originally planned. Integrated testing and implementation took a little longer with that approach, but the conversion time save far exceeded the extra testing and implementation time originally planned, and the overall elapsed time was reduced.

CBRR-5	**By 2007, expand by 15,000 the pool of researchers and clinicians NIH has trained in biomedical informatics, bioinformatics, or computational biology.**

BACKGROUND

The availability of high-powered, sophisticated computational tools and high-bandwidth communication networks has revolutionized basic biomedical research, clinical practice, and public health administration. Organizing, linking, mining, and analyzing large heterogeneous data sets are fundamental to cutting-edge research in the biological sciences, public health services, clinical medicine and translational research. The development, effective enhancement, and creative application of customized or general-use information tools requires sustained involvement of people who are trained in computational/information sciences as well as a biomedical/behavioral/biological science domain.

Biomedical informatics, bioinformatics and computational biology are terms that are often used interchangeably to describe scientific work that is the intersection of computational and informational sciences with an application domain in the biomedical, biological or biochemical sciences. The term 'biomedical' is used in its broadest sense, encompassing health care and public health administration as well as basic fundamental research into the nature of the human body, its components and processes. In the text describing this goal, informatics training is used to mean any and all of these things.

Rationale

The potential value of informatics within clinical and basic biomedical sciences has been recognized for several decades. And, in the post-genome era, the promise of informatics for linking genotype to phenotype has engendered considerable excitement. The need for at least two kinds of training has been identified: (1) training that expands the informatics knowledge of biologists, clinicians, and public health officials so that they can participate meaningfully in the design, deployment, enhancement, and evaluation of information tools and (2) training that expands the pool of research informaticians who can work at the nexus of informatics and a biomedical application domain. By supporting a range of informatics training opportunities, including short courses, internships, mentored research, and formal academic programs, NIH helps fulfill this important need and advance its mission to foster fundamental, creative discoveries that protect and improve health.

Often, the academic training of biomedical scientists, doctors, nurses, and public health officials includes hands-on 'information literacy' training for the use of basic computers and software, but not an introduction to the concepts and methods of informatics or to the sophisticated computational systems and tools they will design, select, and use in professional settings. NIH sponsored training opportunities that address this deficiency include short courses, intensives, internships, and rotations. Short-term informatics training for scientists, clinicians and public health officials allows them to participate actively in the design and enhancement of tools they use, such as working with computer scientists to develop retrieval algorithms for microarray data gathered in their own research, guiding the design of a program for computer-aided surveillance of outbreaks in a local population, or

evaluating effectiveness of new record system at a health center's pediatrics clinic.

As research in biomedical sciences increasingly involves the design and use of computational tools, modeling and simulation, it could be argued that graduate curricula in the basic biomedical sciences, and the support of graduate students on individual research grants will meet short-term informatics training needs, but that is not the case. Courses and graduate assistantships in laboratories provide some hands-on experience with tools, experience that could eventually lessen the need for short-term training; but they do not provide conceptual or methodological training in informatics and computational biology. With a focused and continuing program of short-term informatics training, NIH can help to assure that clinicians and researchers will be able to work effectively, that information tools needed for science and medicine will be developed with speed and in a way that meets domain needs, and that the biomedical research workforce will include a sufficient number of scientists whose discoveries can be made in silico. NIH short term training programs provide a solid starting point, reaching several thousand people each year.

There is a growing pool of graduate students whose academic interests center on informatics and computational biology. As biomedical science becomes more computation- intensive, scientists and clinicians already active in their careers wish to expand the scope of their research to include informatics research questions. Additionally, the emerging importance of large scale association studies and other translational research that links genotypic and phenotypic information further increases the demand for informaticians. Core strategies used by NIH for meeting these informatics training needs include pre- and post-doctoral training and mentored research awards.

Research training in informatics or computational biology expands the research work force that advances knowledge in the biomedical computational and information sciences. Their research leads to important breakthroughs such as intelligent tools for clinical decision making, computational methods to organize and mine large, heterogeneous research data sets, and novel approaches for automated linking of clinical findings and genomic data, and for modeling complex cellular processes. Current pre- and post-doctoral training programs bring scores of graduate students, scientists, and clinicians each year into biomedical informatics, bioinformatics, or computational biology.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH meets its informatics training goal through an array of annual training activities in two areas described below. Because the informatics and computational biology training needs of scientists and clinicians differ from those of individuals who seek research careers in informatics, an array of training opportunities is needed, including some that can be done without leaving one's home institution and some that allow short-term intensive 'immersion' experiences elsewhere.

NIH will increase the number of clinicians and researchers who receive short-term informatics or computational biology training. NIH is committed to supporting short-term informatics training, including short courses, internships, summer programs or other intensive training opportunities for undergraduates, graduate students, scientists and

clinicians, to provide them with basic knowledge of the concepts and methods of informatics.

NIH will increase the number of pre-doctoral and post-doctoral trainees who receive funding for formal academic coursework or mentored research training in informatics or computational biology. NIH is committed to increasing the pool of trained research informaticians, who work at the nexus of informatics and an application domain. These opportunities involve acceptance into a training program, receipt of a fellowship or mentored research award. Many of these trainees spend several years in training.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	(FY05) 8,716 people received short-term training in informatics or computational biology.			◆[e]	◆[e]	◇	
FY05	*Actual Performance:* (MET) NIH provided short-term training for 8,716 people in informatics or computational biology.						
FY06	*Actual Performance:* (MET) NIH provided short-term training for 8,028 people in informatics or computational biology.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	(FY05) 365 trainees enrolled in pre- or post-doctoral training in informatics or computational biology.			◆[e]	◆[e]	◇	
FY05	*Actual Performance:* (MET) NIH enrolled 365 people in pre or post-doctoral training in informatics or computational biology.						
FY06	*Actual Performance:* (MET) NIH enrolled 358 people in pre or post-doctoral training in informatics or computational biology.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 targets were MET and exceeded. For Target 1, NIH provided short-term training for 8,028 people, well in excess of the target of 4,500 people. Because enrollment in three of the largest courses vastly exceeded expectations, NIH exceeded the target. Short-term informatics training encompasses participation in hands-on training classes or mini courses or technical workshops whose duration may be several hours to several days. These educational experiences increase knowledge and skills about informatics tools and concepts. This target tracks 13 programs offered by NIH.

For Target 2, NIH enrolled 358 people in pre or post-doctoral training in informatics or computational biology, exceeding the target of 220 people. These are educational experiences that prepare people for informatics research careers, including fellowship awards, a visiting faculty/postdoctoral program, and traineeships at 18 university-based training programs funded by NIH. This target tracks six programs offered by NIH.

This goal has been ACHIEVED one year sooner than expected. NIH has met the goal of training 15,000 researchers and clinicians in biomedical informatics, bioinformatics, and computational biology. This goal was initially developed to expand interest in this important

training area, and to increase the number of people who receive informatics training. Due to the unanticipated high demand for this type of training, the goal has been met early. Informatics training is very popular and future demand is hard to predict but is likely to grow. Trans NIH initiatives such as the National Centers for Biomedical Computing and Clinical Translational Science Awards include significant informatics training components. All fields of biomedical research now employ sophisticated informatics tools to capture and analyze data. In an era of comparative genomics and personalized drug design, it is difficult to predict when demand curve will level off. Performance targets were exceeded in both target areas of this goal. For example, in the short-term training, target 1, the three largest short courses each had more than 1,000 attendees. In one course, enrollment was more than 30% greater than expected; in another, it was nearly 3 times the expected enrollment; and in the third, nearly twice the expected number of people enrolled.

Although NIH will no longer report on this GPRA goal since it has been achieved, due to the strong interest and need for informatics training, NIH will continue to offer both short-term and pre or post-doctoral training in informatics and computational biology.

Implementation Strategy Advances or Other Highlights

For short-term training, a mixed strategy has been successful, offering informatics training in a variety of locations, using a variety of teaching methods including lecture, internship, hands-on training and one-on-one consults. Recruitment primarily takes place through list-serves, newsletters, word-of-mouth, and web pages. Use of videocasts has increased the reach of the lecture-style programs. For NIH-based programs, advertising is done through the NIH calendar and email listservs.

For pre or post-doctoral training in informatics or computational biology, training is offered through several grant mechanisms, including institution-based training programs that admit their own trainees, and fellowships awarded to an institution on behalf of an individual. NIH-funded informatics research training programs are housed at 18 different academic centers around the U.S.: Harvard University, Yale University, Columbia University Health Sciences, University of Pittsburgh, Johns Hopkins University, Medical University of South Carolina, Vanderbilt University, Regenstrief Institute - Indiana University, Indianapolis, University of Wisconsin Madison, University of Minnesota Twin Cities, University of Missouri Columbia, Rice University, University of Utah, University of California Irvine, Stanford University, Oregon Health Sciences University, University of California – Los Angeles, and University of Washington.

Efficiency

The FY 2006 performance target for short-term training was exceeded. In FY 2006, 8,028 people were trained; nearly 80% greater than the target of 4,500 people. Of the 13 programs included in this target, three large short courses account for 91% of attendees. Because these courses are delivered in lecture format in large auditoria, adding space, providing video feeds and real-time Internet videocasting can greatly increase attendance capacity without requiring additional sessions or instructors.

The FY 2006 performance target for pre or post-doctoral training in informatics or computational biology was exceeded. In FY 2006, 358 people were enrolled; nearly 63%

greater than the target of 220 people. This is due in part to individual budget decisions at the collaborating institutes that protected funds for training activities. Five of the six programs included in this goal exceeded their FY06 targets, in one case by five times the expected number of trainees. The 2006 performance target for the institutional training program was conservative due to budget constraints and previous year slot freezes already instituted.

CBRR-6	**By 2010, build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.**

BACKGROUND

The National Institutes of Health's (NIH) extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. The extramural construction grant program supports the costs of designing, constructing and/or renovating non-Federal basic and clinical research facilities to meet the biomedical and behavioral research, research training, or research support needs of an institution or a research area at an institution.

Although there are ten NIH Institutes and/or Centers (IC), including the Office of AIDS Research, that have construction or modernization grant authority, in FY 2005 only two ICs had appropriated funds for extramural construction and have actively awarded construction grants over the past 5 years. The National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases (NIAID) actively support the program through the issuance of grants and/or cooperative agreements (hereafter referred to as grants).

The principal objective of NCRR's program is to facilitate and enhance the conduct of PHS-supported biomedical and behavioral research by supporting the costs of designing and constructing non-federal basic and clinical research facilities to meet the biomedical or behavioral research, research training, or research support needs of an institution or a research area at an institution.

The principal objective of NIAID's program is to support the construction of National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) at research institutions across the country. The NBLs will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the RBLs will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support the research activities of NIAID's Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

Rationale

The Research Facilities Improvement Program (RFIP) of NCRR's extramural construction program, makes awards to construct and renovate research facilities and thereby builds capacity to conduct biomedical and behavioral research. The RFIP needs to takes certain factors into account when making award decisions in order to ensure that the RFIP helps to meet NCRR's mission and provide support for construction and renovation of biomedical and behavioral research facilities that is the most beneficial to the research community. These factors include: ensuring that the facilities constructed or renovated are geographically

disbursed, promoting interdisciplinary collaborations; facilitates the institution's ability to conduct, expand, improve or maintain biomedical or behavioral research and the ability of the facility to meet an unmet health need.

NIAID's Extramural Biocontainment Facilities Construction Program's purpose is to build biocontainment facilities to support translational, product development-related and clinical research in biodefense and emerging infectious diseases. Under the program, awards have been made to support construction of 15 facilities, including 2 BSL-3/4 National Biocontainment Laboratories (NBLs) and 13 BSL-3 Regional Biocontainment Laboratories (RBLs). These facilities will provide high-level biocontainment for more advanced stages of biodefense and emerging infectious disease research that were anticipated as a part of the expansion of NIAID's research in these areas following September 11, 2001. These more advanced stages of research play a critical role in supporting NIAID's role in the biodefense effort to conduct research and develop biomedical countermeasures to potential agents of bioterrorism in order to protect the Nation's public health. The facilities will provide centralized research space access for NIH-funded researchers across the country who are conducting biodefense and emerging infectious disease research. The facilities will also be available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH not only ensures research infrastructure is available but makes sure that the infrastructure is safe and sound. Therefore, throughout the construction process, NIH staff provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects. At the completion of the building or renovation, NIH may conduct a site visit to ensure the building was built properly with all of the latest codes met. NIH staff will work closely with institutions that have had difficulty completing the project on time. In some cases, delays are unavoidable therefore the completion of the construction may also be delayed. However, NIH staff monitors these grants to ensure that delays are kept to a minimum and provide expedited review of construction designs as needed.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research. (FY06) 44 to be completed (FY07) 48 to be completed (FY08) 30 to be completed (FY09) 22 to be completed (FY10) 9 to be completed	Number of projects proposed to be completed annually: (FY06) 0 (FY07) 44 (FY08) 92 (FY09) 122 (FY10) 144	-	-	-	◆	◇	◇
FY06	*Actual Performance:* (MET) 43 of the 44 construction grants were completed either early or on time. One site was unable to begin construction due to unforeseen circumstances, and NIH is seeking a legal opinion regarding final disposition of the funds.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 2) Completion of 15 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. (FY07) complete 2 facilities (FY08) complete 4 facilities (FY09) complete 8 facilities (FY10) complete 1 facility	Number of biocontainment facilities proposed to be completed annually: (FY06) 0 (FY07) 2 (FY08) 6 (FY09) 14 (FY10) 15	-	-	-	-	◇	◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY06 target was MET. 43 of the 44 construction grants were completed either early or on time, and one grantee was unable to begin construction due to unforeseen circumstances. Specifically, 20 grantees completed construction early and 23 grantees completed construction in 2006. For the one site that was unable to begin construction, construction costs escalated dramatically due to an unanticipated increase in the cost of all construction materials, especially concrete and steel. Additionally, over the past 18 months a complete and unpredicted change occurred in the senior administrative leadership at the University, which placed a hold on all construction projects.

Implementation Strategy Advances or Other Highlights

Once the funds are awarded, a grantee has five years to obligate the federal funds. In the case of the one unfinished project the award was made in 2001 and the grantee had until the end of 2006 to obligate the funds. Since construction on the project has not begun yet due to unforeseen circumstances, NIH is seeking a legal opinion regarding final disposition of the funds.

PART

This goal was included in the FY 2008 PART of the Extramural Construction Program. NIH will continue to achieve this goal's annual requirements as indicted by the PART Improvement Plan.

CBRR-7	**By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.**

BACKGROUND

The NIH represents the largest and most significant public investment in AIDS research in the world. The response to the pandemic requires a unique and complex multi-institute, multi-disciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every Institute and Center (IC). The AIDS-related research portfolio includes research relating to HIV infection, co-infections, opportunistic infections, malignancies, and metabolic, cardiovascular and other clinical complications. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds. The Office of AIDS Research (OAR), located within the Office of the Director, coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program.

OAR develops the annual Trans-NIH Plan for HIV-Related Research, in collaboration with the ICs, and with non-government experts from academia, foundations, industry, and community representatives. The Plan and the processes instituted to ensure its implementation allow NIH to pursue a united research front against the global AIDS epidemic. The Plan is used to: 1) frame the development of the NIH AIDS research budget; 2) determine the use of NIH AIDS-designated dollars; 3) define those research areas for which AIDS-designated funds may be allocated; and 4) track and monitor AIDS research expenditures. OAR has supported the AIDS Research Information System (ARIS), a 15-year old mainframe system to track and monitor AIDS research expenditures.

Rationale

In FY 2006, a critical new element was added to the annual planning and budget development process -- a multi-tiered comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds. This review: 1) established a new model to ensure that AIDS research dollars support the highest priority science; 2) allows OAR to direct the transfer of funds to better manage the AIDS research portfolio; 3) ensures that resources are focused on the highest scientific priorities, taking into account the ever-changing domestic and international AIDS epidemic, as well as the evolving scientific opportunities; and 4) assists in developing the trans-NIH AIDS research budget from the commitment base. The trans-NIH AIDS research budget, developed by OAR, is explicitly tied to the objectives of the strategic plan.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The process was designed to review AIDS funded projects with the goal of ensuring that the projects supported with AIDS-designated dollars are devoted to the highest priority areas of AIDS research. The review is intended to identify dollars that can be redirected to higher priority AIDS research projects. Within each scientific coordinating committee (Natural

History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science Research) a grant-by-grant review is initiated of all NIH extramural projects supported with AIDS-designated dollars, concentrating on those grants eligible for recompetition in the fiscal year of the strategic plan. Working with relevant IC program staff, grants are identified that are now of lower priority than when they were originally funded. This does not mean that these grants should not have been funded or were not of high priority at the time. However, as the science has evolved, and the priorities of the epidemic have shifted, these areas no longer represent the highest priorities. For example, many grants were awarded to address basic research on then-common opportunistic infections. Over the past few years, with the advent of combination antiretroviral therapy, these infections are no longer common among HIV-infected individuals, and thus now deemed of lower priority for AIDS-designated funding.

Then a small group of eminent non-government scientists is convened to provide expert advice, review each scientific area and all of the grants now deemed of lower priority, and to provide recommendations for redirecting funds to catalyze future initiatives and multi-disciplinary endeavors. The IC is notified when a grant is identified as now too low a priority for future support with AIDS-designated dollars. Each IC has an opportunity to reinvest those dollars in higher priority AIDS programs in their portfolio. For those ICs who cannot identify higher priority projects, those dollars are shifted to other ICs with higher AIDS research priorities needing additional support. The IC may renew the highly-meritorious grants that fall into the low priority category with non-AIDS dollars.

This process has been implemented as a part of the annual trans-NIH strategic planning and budget processes, to enhance NIH's ability to ensure that resources are focused on the highest scientific priorities, taking into account the evolving scientific opportunities to address the domestic and international AIDS epidemic.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Initiate redesign of ARIS by hiring a contractor.	Existing ARIS, a 15-year-old mainframe system used to track and monitor AIDS research expenditures.		◆				
FY04	*Actual Performance:* (MET) Contractor was hired to initiate the redesign and reformatting from a mainframe to a web-based system with improved data entry and reporting capability to more efficiently accommodate evolving scientific priorities and needs for information.						
Improve existing ARIS by converting its mainframe system into a web-based system designed by OAR and IC representatives in consultation with a contractor.	Mainframe system allows coding of each project according to functional categories and the 7 original scientific categories of the NIH AIDS strategic plan. Periodic monitoring of the portfolio utilizing ARIS system with limited capability to allow comprehensive trans-NIH portfolio assessment. Strategic planning process determined that AIDS vaccine research is highest scientific priority.			◆			
FY05	*Actual Performance:* (MET) Assessed existing coding system to determine necessary changes to collect program and budget data to meet reporting needs; established the ARIS Working Group, including OAR and key IC staff, to better coordinate development and implementation of converted system.						
Track, monitor, and budget for trans-NIH AIDS research, utilizing the enhanced ARIS database, to more efficiently conduct portfolio analysis of 100% of expiring grants to determine reallocation of resources for priority research.	(FY06) 723 expiring grants eligible for renewal/recompetition				◆	◇	◇
FY06	*Actual Performance:* (MET) 100% of the 723 expiring grants eligible for renewal or recompetition were reviewed.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY06 target was MET. Utilizing ARIS, in the portfolio analysis process, the OAR reviewed 100% of the 723 grants eligible for renewal or recompetition. OAR conducted the assessment in concert with the ICs, and convened a panel of outside experts. Of the grants assessed in this process, approximately 20 percent (141 grants) were determined to now be of low priority for funding with AIDS-designated dollars, allowing support to be redirected to higher priorities . For example, these included a number of grants related to the basic pathogenesis of opportunistic infections. At the time they were awarded, these grants were of high priority to AIDS research. However, in the past years, with the success of NIH research and the development of multi-drug antiretroviral regimens, some of these infections are now longer common among HIV-infected individuals. Similarly, some of the low priority grants were in the area of basic research on AIDS-related malignancies, some of which are no longer common in HIV-infected individuals utilizing antiretroviral therapy. The highest priorities in AIDS research were vaccine research and the development of other prevention strategies.

It is important to reiterate that the determination of "low priority for AIDS funding" is not related to the scientific or technical merit of the projects, but only to their relevance within the current AIDS research agenda, as it relates to the changing demographics of the epidemic, scientific advances, and new opportunities. Should the investigator choose to submit a renewal application that is determined to be highly meritorious in the peer review

process, the IC may choose to fund the project with non-AIDS dollars.

PART

This goal was included in the FY 2005 PART of the HIV/AIDS Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

CBRR-8	**By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.**

BACKGROUND

The National Institutes of Health (NIH) is dedicated to improving the health of Americans by conducting and funding biomedical research that will help prevent, detect, treat, and reduce the burden of disease and disability. To achieve these goals, NIH supports the preparation of investigators through research training and career development programs and monitors the size and distribution of the research workforce to ensure that scientists are available in adequate numbers and with appropriate training to address the Nation's biomedical, behavioral, and clinical research needs.

For participants in the NIH's largest research training program – the Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants – training-related information is captured and reported to the NIH annually on paper forms. For more than 14,000 participating students and postdoctorates every year, NIH Institute and Center personnel manually enter data from paper appointment and termination forms into the agency's IMPAC II information management system. Capturing data on NRSA trainees this way is a time-consuming process that is susceptible to data entry errors, but is essential for program management and evaluation.

Rationale

As part of its commitment to electronic research administration, NIH is designing and testing a system that will allow NRSA-related data to be directly entered at research training sites and transmitted to the NIH electronically. By 2012, NIH aims to transform the existing, cumbersome NRSA paper process into a streamlined, end-to-end electronic flow of data that will not only increase the efficiency of program administration for NIH and its university partners but also enhance data integrity for program monitoring and assessment.

Through a new system, known as X-Train, research training grant directors will be able to electronically appoint students and postdoctorates to NRSA training grants and report to NIH when their training is complete. Ultimately, X-Train will replace the paper forms that have been used since the beginning of the NRSA program in 1974 and will help NIH Institutes and Centers identify program gaps in a timelier fashion and manage their research training portfolios more effectively.

Because X-Train is currently under testing and development and not anticipated to be introduced until FY 2008, the annual targets for this goal are designed to allow for its gradual adoption by universities and other research training sites and provide NIH an opportunity to fine-tune the system, if necessary, in response to feedback from its users.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The team designing X-Train, which includes experts in research training and grants management, computer programmers, and systems analysts, has been meeting regularly since the summer of 2006 and will present plans for the system to advocates from the extramural community at the next meeting of the Commons Working Group, in January 2007. Following feedback from the Commons Working Group, NIH expects to test X-Train at selected research training sites, prior to its broader introduction in FY 2008. NIH typically phases in new electronic research administration practices and procedures, and X-Train will adopt the same approach over the period from FYs 2008 to 2012.

To facilitate the implementation of X-Train, the system's development is incorporated into the performance plans of the NIH Research Training Officer and Research Training Coordinator.

PART

This goal was included in the FY 2008 PART of the Extramural Research Training and Research Career Development Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
By 2012, ensure that 100% of trainee appointment forms are processed electronically. (FY08) 5% (FY09) 25% (FY10) 50% (FY11) 75% (FY12) 100%	(FY07) 0% processed electronically						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Performance Results for the FY08 GPRA Performance Target will be reported in February, 2009.

CBRR-9	**By 2010, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.**

BACKGROUND

The National Institutes of Health's (NIH) extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. The extramural construction grant program supports the costs of designing, constructing and/or renovating non-Federal basic and clinical research facilities to meet the biomedical and behavioral research, research training, or research support needs of an institution or a research area at an institution.

Although there are ten NIH Institutes and/or Centers (IC), including the Office of AIDS Research, that have construction or modernization grant authority, in FY 2005 only two ICs had appropriated funds for extramural construction and have actively awarded construction grants over the past 5 years. The National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases (NIAID) actively support the program through the issuance of grants and/or cooperative agreements (hereafter referred to as grants).

NIAID's extramural construction program supports the construction of two groups of biocontainment laboratory facilities for biodefense and emerging infectious disease research. The National Biocontainment Laboratories (NBLs) will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the Regional Biocontainment Laboratories (RBLs) will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support NIAID's biodefense and emerging infectious diseases research program, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

NIAID uses two electronic tools to make the management of its extramural construction program more efficient: Buzzsaw, an internet based project collaboration tool that provides a platform to organize, manage and share information among designated project participants and Webex, an internet based virtual conferencing tool that provides a method for participants to share, view, edit and modify complex electronic files (such as blueprints) and information remotely.

NCRR primarily supports NIH-funded research that spans the entire continuum of biomedical research, from basic discovery to patient-oriented research as defined in Section 479 of the Public Health Service Act. The extramural Research Facilities Improvement Program (RFIP), which began in 1994, helps NCRR achieve its cross-cutting mission to increase the Nation's capacity to conduct biomedical and behavioral research by building and enhancing a strong research infrastructure as defined in Section 481A of the Public Health Service Act. The NCRR construction program provides laboratory scientists and clinical

researchers with biomedical facilities and fixed equipment they need to understand, detect, treat, and prevent a wide range of diseases that would be otherwise unavailable or inadequate to conduct the research necessary to advance human health. These grants enable institutions to construct or renovate facilities that contain basic and clinical research laboratory space, improve research imaging capabilities, augment informatics capabilities, and support animal research. Since its inception, this program has supported 340 construction projects in 45 states and Puerto Rico, demonstrating broad and comprehensive geographic distribution to build the Nation's capacity as a whole to conduct biomedical research.

In order to enhance the management of its large and diverse extramural construction program, NCRR has developed the Construction Grants Management System (CGMS) database to perform critical data management functions, including tracking when necessary documentation is required.

Rationale

Since the administration of construction grants involves management of complex information and interactions of many partners, electronic management tools offer critically needed data management capability to program managers. Use of electronic tools for the management of extramural construction programs during the pre-construction, construction and post-construction/compliance monitoring stages the projects saves the government time, money and materials.

The following describes the pre-award, award and post-award requirements that are unique to the NIH extramural construction program and demonstrates the need for a sophisticated electronic system to accurately track and monitor pre-construction, construction and post-award compliance related data and allow for enhanced interaction between project partners.

The additional pre-award requirements, beyond those found in NIH's intramural construction program, are associated with the availability of matching funds, the applicant's compliance with additional public policy requirements and ensuring sufficient title to site. Unless otherwise waived, the NIH must ensure that the applicant has sufficient funds available to meet the matching requirement in order to ensure sufficient funds are available to complete the project. In addition, the applicant must also comply with additional public policy requirements and be able to ensure they have sufficient title to site to ensure an undisturbed use of grant-supported space throughout the usage obligation that is associated with the award.

After award, the awardee must obtain NIH approval of all plans and specifications at each stage of design to ensure the grant-supported space is designed in accordance with NIH Design Policy and Guidelines and Good Laboratory Standards. The proper design of the facility will ensure the safety of NIH grant-supported researchers who will occupy the completed facility. During the design phase, complex documents must be viewed and shared between government managers and the grantees. In addition, at the time construction begins the awardee is also required to file a Notice of Federal Interest (Notice) in the local land records in the jurisdiction in which the property is located. Filing of this Notice results in a lien on the property to ensure that the property will not be: used for any purpose inconsistent with that authorized by the grant program statute, mortgaged or otherwise used as collateral,

or sold or transferred to another party without written permission of the NIH. The Notice ensures the Federal interest in the property will not subordinated to those of non-Federal parties unless a deviation is approved.

Lastly, after construction is complete, the grantee must ensure that the property is protected from physical destruction and that they are using the grant-supported space for its intended purpose throughout the usage obligation. Therefore, immediately upon completion of the construction project, a grantee is required to provide a certification that the property is adequately insured against physical destruction or provide a certification that the grantee is self-insured against the risks involved. This requirement safeguards the government's investment in case of natural disaster or other eventuality. In addition, the authorization and/or appropriation language for construction grant programs requires construction grant recipients to use the grant-supported space for the research purposes for which the space was built for a 20 year period after completion of construction. In order to ensure the grantee's compliance with the usage obligation and to protect the NIH's interest in grant-supported property, NIH monitors this usage in a variety of ways, including periodic facility use certifications or reports, site visits, or other appropriate means for the duration of the required usage period.

To better monitor all phases of the construction projects, track the large number of documents associated with each project and facilitate communication among the grantees and NIH staff, NIAID uses the Buzzsaw and Webex electronic tools mentioned above, and NCRR has developed the NCRR Construction Grants Management System (CGMS) database to track and notify NCRR staff when necessary documentation is required.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIAID efficiently manages its extramural construction program with use of two electronic tools: Buzzsaw, an internet based project collaboration tool and Webex, an internet based virtual conferencing tool. These electronic tools decrease the amount of travel needed in order for NIH staff to manage grants. These tools also save on costly Fedex and shipping charges by allowing groups to view, review and mark up documents such as blueprints remotely, limiting the need to ship documents.

NCRR uses the Construction Grants Management System (CGMS) to better monitor grantees compliance with the requirements of the extramural construction awards. The CGMS was created as a tool for grants management staff and program staff to enhance their governance of public funds. To increase its efficiency and accuracy, the CGMS automatically downloads relevant data from the NIH IMPAC system. The CGMS also automatically determines which construction phase (pre-award, award-design, award-construction and post-award) a project is in based on reported or outstanding data thus, improving the monitoring efficiency of the program. Alerts and notifications are automatically sent via email to appropriate NCRR staff informing them that self-certifications and other program documentation are due.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Achieve average annual cost of managing construction grants	Proposed annual costs: (FY06) $35,643 per grant (FY07) $35,837 per grant (FY08) $36,419 per grant (FY09) $36,530 per grant (FY10) $36,703 per grant	-	-	-	◆	◇	◇
FY06	*Actual Performance:* (MET) Achieved average annual cost of $35,643 per grant.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

NIH achieved an average annual cost of managing construction grants of $35,643 per grant through the use of electronic project management tools.

PART

This goal was included in the FY 2008 PART of the Extramural Construction Program. NIH will continue to achieve this goal's annual requirements as indicted by the PART Improvement Plan.

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

Performance-based results have become a central theme in human capital management efforts at NIH. NIH is developing a strategic, performance-based approach to workforce management by generating performance goals and measures that will (1) align individual performance with organizational goals, (2) provide seamless leadership continuity and succession planning, and (3) appropriately allocate rewards and incentives. Efforts are being invested to develop a clearly articulated workforce plan to address strategic alignment, results orientation, performance measurements, interdisciplinary team building, and workforce succession planning.

NIH is developing a methodical process that provides managers with a framework for making human resource decisions based on the organization's mission, strategic plan, budgetary resources, and a set of desired workforce competencies. Management is currently discussing longer-range resource priorities and staffing needs based on realistic resource improvement goals and staffing requirements. Plans are being developed to allocate funding to improve operating efficiencies and improve technical skills and competencies. NIH is in the process of determining current and future workforce needs, assessing how its current workforce and anticipated future workforce compare with these needs, and developing effective strategies to fill the gaps. The successful implementation of the plan will be critical to achieving program objectives, thus providing a basis for justifying budget allocation and workload staffing needs.

NIH values employees as an essential organizational asset and strives to provide them with the tools they need to be successful. The workforce plan is designed to match the right person with the right job by ensuring more efficient and effective recruitment, training, and retention. In high-performing organizations, employees see a direct connection between their work and accomplishing the organization's mission. Toward this end, NIH places a heavy emphasis on the education, development, and training of its employees. The plan will enable employees and managers to identify training and career development needs, link training with performance goals, provide meaningful performance incentives, and foster a diverse workforce.

To meet the challenge of workforce management, NIH has delayered management levels and consolidated human resource management functions. In addition, NIH has achieved great success in reaching competitive sourcing goals in a variety of commercial areas. While all these initiatives are under way, NIH managers are confronted with the need to balance the certainty of short-term requirements with long-term planning. The workforce plan is central to achieving NIH's long-term objectives and will be the foundation for policies that reshape the workforce over time.

SMHC-3	**Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the agency's programmatic objectives and projected future needs. (ongoing)**

BACKGROUND

The first item on the President's Management Agenda is the strategic management of human capital, which seeks to create a more effective Government that depends on attracting, developing, and retaining top-quality employees from diverse backgrounds and ensuring that they perform at high levels. Strategic human capital management is the transformation of how to employ, deploy, develop, and evaluate the workforce. It focuses on results, not processes. It places the right people in the right jobs to most effectively perform the work of the organization.

Rationale

NIH is deeply committed to creating and sustaining a trained and motivated workforce to carry out the mission of the Agency and has taken a number of major steps to improve human capital management. NIH staff developed an initial strategic workforce plan; drafted a transition strategy to re-train and ultimately assign-employees who are not placed in new organizations as a result of competitive sourcing initiatives; consolidated human resource management functions; developed a major initiative to assess and modify the NIH infrastructure of key NIH administrative-management functions; implemented performance contracts for senior executives and managers; and initiated a major effort that will result in recommendations for improving the effectiveness of recruitment, development, and succession planning processes for key scientific positions within the NIH Intramural Research Program. The ongoing study of key positions within the NIH Intramural Research Program will provide a potential framework for the initiation of a future study of key positions within the NIH Extramural Research Program during FY 2006. All of these major activities demonstrate an unwavering commitment on the part of the NIH to the principles behind the PMA and DHHS management initiatives.

Ultimately, the strategic human capital management plan will capture the workforce needs based on NIH's scientific agenda, identify areas of staff expansion and contraction, address competencies and/or success profiles for key NIH Intramural and Extramural positions, incorporate succession planning and leadership development programs to ensure that viable candidates are available for critical positions, and fully integrate human resources policies to shape the NIH workforce according to the mission and direction of the Agency.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Key activities are underway to achieve the annual targets, improve the strategic management of human resources, and aid in the development of a comprehensive human capital plan. The NIH staff conducted a major study of key positions within the NIH Intramural Research Program (IRP), to include the identification and evaluation of industry best practices related to key IRP positions; development, piloting, conduct, and analyses of

incumbent interviews regarding current IRP succession planning processes and systems associated with eight categories of key IRP positions; development of competencies or success profiles of eight roles and four tiers of key IRP scientific roles; analysis and comparison of incumbent interview/competency criteria to industry best practices; and validation of the IRP competency model. An assessment of NIH strengths and weaknesses regarding succession planning for key IRP positions was conducted considering the scientific agenda and future workforce needs. A study of key IRP positions was also conducted to determine dynamics of the positions and associated competencies; gaps in positions were identified; and an assessment of the gaps will establish future impact. An additional framework of quantitative and qualitative information related to key IRP positions will also be derived from the conduct of annual studies of average age, years of service, retirement eligibility, retention, recruitment strategies and activities, and points of concern about the recruitment and selection processes. Findings from major and annual studies will be utilized to improve the strategic management of human resources. An associated system of performance indicators will be established to assess human capital management of key positions within the IRP.

An implementation plan will be developed to address the most significant challenges, gaps, policies, and systems needed to improve recruitment, development and succession planning processes for key IRP positions. Human capital needs of key positions within the NIH Intramural Research Program will be projected for 3 to 5 years. Findings, conclusions and initiatives will be incorporated into the NIH strategic workforce plan and other programmatic documents.

It is anticipated that the IRP human capital initiatives will serve as an initial framework for an overlapping study of key NIH Extramural Research Program positions while an assessment of newly instituted IRP methods is being accomplished. Additionally, NIH is currently co-chairing a Department-wide initiative to develop a leadership competency model and design competency based training and development opportunities for HHS leaders.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.		(FY01) NIH Workforce plan, June 2001		◆				
FY04	*Actual Performance:* (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.							
(Target 2) Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.		(FY02) Administrative Restructuring Advisory Committee		◆[e]				
FY04	*Actual Performance:* (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.							
(Target 1) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.		Practices related to recruitment, retention and succession planning			◆			
FY05	*Actual Performance:* (MET) Methods were implemented that addressed recruitment, retention and succession planning for key IRP positions.							
(Target 2) Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.		Practices related to recruitment, retention and succession planning			◆			
FY05	*Actual Performance:* (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.							
(Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.		(FY 05) Performance indicators that addresses recruitment, retention and succession planning established				◆		
FY06	*Actual Performance:* (MET) Recommendations developed for improving the effectiveness of recruitment, retention and succession planning for key ERP positions.							
(Target 2) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)		(FY 05) Performance indicators that addresses recruitment, retention and succession planning established				◆		
FY06	*Actual Performance:* (MET) Implemented leadership training for tenure-track and senior investigators and assessed the impact of utilizing adopted methods through surveys.							

(Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.)	(FY 04) Performance indicators to be determined from FY 2006 results					◇		
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
(Target 2) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program.	(FY 04) Performance indicators to be determined from FY 2006 results					◇		
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
(Target 3) Establish performance indicators with baselines related to recruitment, development and succession planning for the NIH Extramural Research Program.	Performance indicators to be determined from FY 2006 results					◇		
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
(Target 1) Evaluate and modify performance indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	Performance indicators to be determined from FY 2007 results						◇	
FY08	*Actual Performance:* Performance results will be reported in February 2009.							
(Target 2) Continue performance and report on performance indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	Performance indicators to be determined from FY 2007 results						◇	
FY08	*Actual Performance:* Performance results will be reported in February 2009.							
(Target 3) Assess the impact of utilizing newly adopted methods and processes for recruitment, development and succession planning for key scientific positions within the NIH Extramural Research Program. Report on performance indicators.	Performance indicators to be determined from FY 2007 results						◇	
FY08	*Actual Performance:* Performance results will be reported in February 2009.							

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

FY06 Target 1

The FY06 Target to develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program was MET. Office of Extramural Research (OER) leadership has begun designing the new Professional Designation and Pay Model to improve NIH's ability to attract, employ and retain the most accomplished scientists for key Extramural scientific positions. The model uses methods that include: (a) Providing a workable methodology for categorizing the majority of non-intramural positions; (b) Assessing all existing and incoming Extramural scientists to ensure all individuals hired under Title 42 are accurately categorized. The model will establish fundamental goals; define key Extramural scientific positions, responsibilities and oversight; provide a mechanism to move current employees to the new model; and establish national search requirements for recruiting purposes.

FY06 Target 2

The FY06 Target to assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program (OIR) was MET. OIR successfully implemented leadership training for tenure-track and senior investigators and utilized journal and website job opening advertisements in three scientific journals. Based on customer feedback surveys

conducted, the training was rated excellent by 80-90% of attendees. Recruitment of tenure-track investigators improved from 23 in 2005 to 32 in 2006, and 5 tenured senior investigators in 2005 to 13 tenured senior investigators in 2006.

Implementation Strategy Advances or Other Highlights

NIH has made significant progress with accomplishing key human capital studies during FY 2006 that provided updated strategic human capital management findings and recommendations for the Intramural and Extramural programs. NIH executive leadership will be examining the findings and recommendations, and taking next steps to continue progress in strategically managing human capital across the NIH.

The NIH Intramural Research Program post-doctoral training programs garnered recognition by The Scientist, which named the NIH as one of the best places to do a post-doctorate based on a nationwide survey of post-doctorates.

SMHC-4	**Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the agency's commercial inventory. (ongoing)**

BACKGROUND

Governed by OMB Circular A-76, the underlying goals of the competitive sourcing initiative are to:

- Increase competition, thereby generating savings and noticeable performance improvements.
- Promote innovation, efficiency, and greater effectiveness through competition.
- Provide an imperative for the public sector to focus on continuous improvement by focusing on desired results and outcomes and removing roadblocks to greater efficiency.

In support of the HHS objectives and the President's Management Agenda (PMA), NIH began identifying commercial activities for competitive sourcing reviews in FY 2002. By 2008, NIH will have performed cost comparisons on 100% of its commercial competitive activities; these will be completed according to the requirements provided in the future years.

The competitive sourcing program will ensure that commercial activities are subjected to the rigor and discipline of market competition. On completion of each comparison, NIH will select the source that can provide the necessary services and ensure that quality standards are met at the lowest possible price.

NIH will be using all tools at its disposal to retrain, counsel, and place affected employees within NIH, HHS, other federal agencies or alternate employers. Use of VERA and Voluntary Separation Incentive Payments should help reduce the number of affected employees who will need to be placed.

Rationale

The HHS views competitive sourcing as a method to "achieve excellence in management services and thereby improve overall Department management," (goal number 8 in the HHS strategic plan). Like consolidation and centralization, improved financial management, and electronic commerce, competitive sourcing aims to improve efficiency, in order that HHS may more effectively deliver health and human services. For this reason HHS has taken a highly strategic approach to institutionalizing competitive sourcing - one that carefully reflects the needs of the Department.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with the PMA, NIH plans to carry out annual competitive sourcing reviews. The bases for the reviews are the number of full time equivalent staff in particular functional areas as identified in the annual FAIR Act inventory process, supplemented by

annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. Subsets of the identified functional areas that are deemed appropriate for review are then reviewed. The A-76 requirement is met once the reviews are completed.

For FY 2004, the preplanning step identified 14 potential functional areas for review, and of these, eleven were deemed appropriate for review. All eleven have been completed.

As each review is completed, NIH develops transition plans to move to the new organizational structures and to fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards.

For FY 2004 the NIH delivered career transition services to employees impacted by the two FY 2003 competitive sourcing studies. In FY 2005, an evaluation of those services was performed; thereby, concluding the implementation of services. Consequently, this performance target will terminate in FY 2006.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Identify annually commercial activities for competitive sourcing comparison.		(FY02) Preplanning initiated for identifying functional areas	◆e	◆	◆	◆	◇	◇
FY03	*Actual Performance:* (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.							
FY04	*Actual Performance:* (MET) Nine streamlined and two standard studies conducted in FY 2004.							
FY05	*Actual Performance:* (MET) Thirteen streamlined and one standard studies conducted in FY 2005.							
FY06	*Actual Performance:* (MET) Identified 4 potential functional areas for review, all 4 were deemed appropriate for streamlined reviews.							
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
FY08	*Actual Performance:* Performance results will be reported in February 2009.							
(Target 2) Complete negotiated competitive sourcing reviews annually.		(FY02) Functional areas identified as appropriate for review	◆e	◆e	◆	◆	◇	◇
FY03	*Actual Performance:* (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.							
FY04	*Actual Performance:* (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.							
FY05	*Actual Performance:* (MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.							
FY06	*Actual Performance:* (MET)Four functional areas identified for reviews were announced for competition.							
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
FY08	*Actual Performance:* Performance results will be reported in February 2009.							
(Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.		(FY03) Transition plans developed for employees		◆	◆			
FY04	*Actual Performance:* (MET) Career transition services provided for out-placed staff as a result of competitive assessments/studies.							
FY05	*Actual Performance:* (MET) Career transition services were provided to employees displaced.							
(Target 4) Evaluate transition services provided to employees.		(FY03) Career transition services provided to employees impacted by one of the FY 2003 studies			◆			
FY05	*Actual Performance:* (MET) Evaluation conducted during FY 2005.							

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY06 target 'Identify annually commercial activities for competitive sourcing comparison' was MET. For FY 2006, the pre-planning step identified 4 potential functional areas for review, EEO administrative support, Clinical Center administrative support, IT network systems, and IT end user support & technical writers. All 4 were deemed appropriate for streamlined reviews each with a Most Efficient Organization (MEO).

Target 2

The FY06 target 'Complete negotiated competitive sourcing reviews annually' was MET. The 4 functional areas identified for reviews (see target 1 description above) were announced for competition in FY 2006.

For FY 2006, the preplanning step identified 4 potential functional areas for review, and all 4 were deemed appropriate for review. To date all 4 reviews have been announced and are due for completion by March 2007.

In addition, in FY 2006 NIH completed and won three reviews that were announced in FY 2005. These were: IT systems administration, Food services, and patient care unit clerks.

Implementation Strategy Advances or Other Highlights

In accordance with the PMA, NIH plans to carry out annual commercial sourcing reviews. The bases for the reviews are the number of full time equivalent staff in particular functional areas and the annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. Subsets of the identified functional areas are then deemed appropriate for review and then are reviewed. The A-76 requirement is met once the reviews are conducted and awards are made.

After each review is completed, NIH will develop transition plans to move to the new organizational structures and fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards.

SMHC-5	**Improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal. (ongoing)**

BACKGROUND

The NIH Portal is the next generation intranet for the NIH community. The NIH Portal serves as a launch pad for enterprise systems and access to information that pertains to the NIH mission. The NIH Portal has been integrated with a Single-Sign-On (SSO) solution so that NIH HR applications that are SSO-enabled can be launched from the NIH Portal. The Portal uses approximately 100 "portlets" to launch or interact with enterprise systems such as ITAS, HRIBS and the NIH Delegations database. The NIH Portal employs a document directory to organize documents, regardless of source, into a logical topic-based taxonomy. And finally, the community space on the Portal is available for different groups of employees such as the intramural research community or the travel community to collaborate and share information.

By presenting human resources information on the NIH Portal, we are providing HR content in a current and flexible design that can easily be repurposed for addressing specific audiences as well as being available to the NIH community for populating their own MyPage of content relevant to their individual needs. Instead of relying on static websites, we are providing interactive portlets, a launch pad to applications that are Single-Sign-On (SSO) enabled, and up-to-date content from reliable sources to our audience and presenting it to them in several formats. Making the HR Community of the NIH Portal available to the NIH community will give users one-one-stop shopping for relevant HR information, resources and systems.

Rationale

The HR community and other users of HR resources have often expressed frustration when trying to find current, relevant HR information. The Human Resources community and HR content on the NIH Portal is constantly drawing new content for a variety of sources and removing dead links and adding new content to the appropriate subject area. Additionally the portal technology will allow for the repurposing of content so that specific audiences can be addressed – NIH Employees, Administrative/Managerial community and HR Professionals. This allows those audiences to receive information tailored to their needs without becoming an oppressive content management burden.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Beginning in 2002, CIT worked with NIH focus groups to develop a logical taxonomy and identify documents and applications to be accessed through the NIH Portal. OHR helped identify human resources documents and applications that should be included on the NIH Portal. Dozens of HR and HR-related applications were made accessible through the NIH Portal and over 10,000 HR documents were reviewed from over 20 websites. Their relevance, currency and appropriate placement were considered in determining which ones would be accessible through the Portal. Duplicates and obsolete versions were discarded

and the remaining 4,000 to 5,000 documents were categorized in the document directory.

In 2003, OHR assumed management of its own content and committed to launching all new HR systems through the NIH Portal. In 2004, the Strategic Programs Division (SPD), OHR began maintaining these documents by 'crawlers,' which automatically check their target websites for new or revised information. If changes are detected, the new or revised document is automatically crawled to the Portal. The same is true for deleted documents. If a document has been deleted from its host website, the crawler will automatically remove it from the Portal. The SPD Web/Portal Team merely reviews new documents and approves them before they are published to the document directory. OHR has 112 crawlers that check their designated sites nightly.

NIH achieved Target 1 which was to develop an HR Community on the NIH Portal. This has become the primary site for NIH HR information, systems and resources. The target to identify HR critical elements and tools to monitor use and quality of the HR information was also realized. In FY 2005, SPD launched the HR Community area of the NIH Portal, trained users on accessing the Portal and the Community, marketed the Community's availability, and eliminated where feasible and appropriate, access to HR systems, information and resources through means other than the Portal.

Also in FY05, SPD established the HR critical elements and identified methods to measure them. For example, assuming usage of the HR Community site is one of the critical elements, SPD worked with CIT to determine methods to greater quantify and define usage as distinct hits on the HR Community site. SPD can subsequently demonstrate the increased usage (expressed as percentage of the NIH population) of the HR Community area by measuring the number of HR documents and systems available on the HR Community and the number of people accessing HR systems available only through the HR Community.

In FY06, SPD established baselines of the previously defined HR critical elements through the use of the Analytics Server which measure usage of the HR Community and HR tools and information on the NIH Portal. SPD also developed a corrective strategies plan to improve the usability and quality of HR information on the HR Community on the NIH Portal. As SPD begins to implement the plan in FY07, they can monitor the success of the plan compared to the established baselines.

This monitoring will be continued into FY08 as SPD continues to monitor satisfaction and usage of human resources content on the NIH Portal.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	(FY04) Multiple means of access to HR systems; multiple websites for HR information and resources.			◆			
FY05	*Actual Performance:* (MET) Developed HR Community on the NIH Portal as primary site for accessing HR information and resources						
(Target 2) Identify HR critical elements and tools to monitor use and quality of the HR information.	Inconsistent quality and currency of HR information.			◆			
FY05	*Actual Performance:* (MET) Worked with CIT to evaluate products for measuring usage of HR information on HR Community Portal.						
(Target 3) Establish baselines for the HR critical elements to monitor over time.	(FY05) HR critical elements and tools identified.				◆		
FY06	*Actual Performance:* (MET) The critical elements to be monitored are: freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools.						
(Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information.	(FY05) HR Community established.				◆		
FY06	*Actual Performance:* (MET) A Corrective Strategies Plan was developed to address improved usability and quality of HR information.						
(Target 5) Implement corrective strategies with subject matter experts and customers.	(FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 6) Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline.	Quality management plan established.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 3

The FY06 target to establish baselines for the HR critical elements to monitor over time was MET. The critical elements to be monitored are: freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools. We monitor freshness of content through a quarterly Content Stoplight Report that is provided to Content Managers in the Office of Human Resources. The administrators of the NIH Portal, the Center for Information Technology (CIT), purchased an Analytics Server that runs on the NIH Portal and provides usage statistics for the human resources information and resources on the Human Resources Community and HR documents and tools available on the NIH Portal.

Usage of the HR Community, including information on which pages on the HR Community are used most frequently, what search terms are used, and what documents are accessed most frequently is monitored with the Analytics Server tool. With this information we can continually make adjustments and improvements to lead users to the information they are requesting most frequently. We also work directly with our audience to determine their specific needs and requirements.

For example, Administrative Officers (AOs) at NIH are often the liaisons with the Office of Human Resources (OHR) and their Institutes and Centers. The AOs requested a better pipeline of human resources information, so the Admin/Managers page on the HR

Community was created to address this need. The Admin/Managers page serves up content that is directly relevant to that AOs as well as managers throughout the NIH. HR portlets and tools that populate the Admin/Manager page include: HR Systems Spotlight Newsletter; OHR News; HHS Careers; HR Resources for NIH Managers; Delegations of Authority; Compensation Links; HR Navigator; Recruitment and Staffing Information for Managers, Selecting Officials, and Administrative Officers; New HR Standard Operating Procedures (SOPs); Series in HHS Careers for Managers/AOs; Who Are My HR Contacts?; New Hires by Mission-Critical Category; NIH Population by Mission Critical Category: FY2000 through Present; NIH New Hires, Separations and FTE Usage.

Target 4

The FY06 target to develop plan for corrective strategies to improve usability and the quality of HR information was MET. A Corrective Strategies Plan was developed to address improved usability and quality of HR information. This plan was incorporated into the existing Web/Portal Project Plan that is used to monitor the HR Community on the NIH Portal as well as the public Office of Human Resources (OHR) websites. This plan includes the following strategies for improving quality and usability of HR information:

- Quarterly meetings with Content Managers from throughout the Office of Human Resources (OHR) to emphasize the need to continually monitor and update the information presented on the NIH Portal. Also to gather feedback from these Content Managers on how to improve the presentation and usability of this information.
- A "Community Leader" portlet on the HR Community gives contact information for users to send comments. SPD will continually monitor the questions/comments that are sent in to the HR Systems Support desk for any technically difficulties as well as suggestions for improvements to the community.
- Pilot/usability sessions for the HR Community. We will hold pilot sessions for NIH employees to review the HR resources and information available on the NIH Portal to gather feedback both on usability and content. SPD will specifically target the OHR and AO communities as well as potentially bringing in a sample of NIH employees.
- Pursue the purchase of a web Content Management System (CMS). SPD believes that a CMS will help improve both the quality and usability of HR information as well as helping to ensure that the HR content is accurate and timely.

Implementation Strategy Advances or Other Highlights

The SPD Web/Portal Team as well as HR Content Managers from throughout OHR continued to work on the goal of improving HR services by providing real-time access to tools via the NIH Portal. Some major accomplishments on the project for FY2006 include:

- Announced the creation of a new HR tool, the HR Navigator, to Administrative Officers (AOs) and Executive Officers (EOs) at NIH.
- Demonstrated a new HR tool, the HR Navigator, to Office of Human Resources (OHR) employees at an All-Hands meeting.
- Moved all HR Processing content from the public website into the NIH Portal.
- Prepared training materials and provided Portal training to new Office of Human

Resources (OHR) and Office of Strategic Management and Planning (OSMP).
- Provided an Advanced Portal Training session for OHR & OSMP staff.
- Marketed the HR Community on the NIH Portal to all NIH staff.
- The NIH Portal was upgraded to the 6.0 Version of the BEA Aqualogic Portal Software. SPD staff tested all HR content and resources after the upgrade.
- Held quarterly OHR Web/Portal Content Managers meetings.

- Developed and released a "New NIH Employees" page for the Human Resources community that provides information specifically for employees new to the NIH.
- Created three sub-communities to the main HR Community:
    - HR Systems Support – Provides information on receiving support for self-service HR tools.
    - WiTS – Provides access to workflow tracking tools used by OHR staff.
    - Staffing – Launch pad for all NIH staffing policy information and systems procedural resources.
- Developed and released new HR Portlets on the NIH Portal:
    - Alphabetical HR Search Index (as requested by OHR staff)
    - HR Systems Spotlight Newsletter portlet
    - OHR News Portlet
    - Recruitment and Staffing Information for Managers, Selecting Officials, and Administrative Officers
    - Series in HHS Careers for Managers/AOs
- Created an HR Self-Service Tools document highlighting HR Tools and Resources on the HR Community to be distributed to all new NIH employees at Orientation.
- Customized the banner for the HR Community with OHR branding.

PROGRAM OVERSIGHT AND IMPROVEMENT

NIH takes responsibility as a steward of Federal funds seriously. Exercising careful oversight is key to demonstrating good stewardship. In addition, NIH strives to continually improve oversight procedures, policies, and systems when needed or opportunity arises. Management systems must be repeatedly updated to keep pace with advances in public administration, and mechanisms to ensure proper stewardship must evolve with the development of new requirements and rising thresholds for accountability. Meeting these challenges has always been a priority for NIH, but the PMA and the 'One HHS' management objectives are focusing NIH's attention even more tightly on results-oriented management.

The philosophy/value of results-oriented management is beginning to permeate oversight practices for all types of NIH activities and at all levels of supervision. Examples include implementation of an Earned Value Analysis and Management System for oversight of construction projects, expansion of the use of performance-based contracting, and linkage of employee performance contracts with organizational objectives.

POI-1	**By 2007, ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an earned value analysis and management system (EVAMS).**

BACKGROUND

NIH is committed to efficient and effective management and oversight of its real property capital projects. An Earned Value Analysis and Management System (EVAMS) using a project data analysis framework that links cost and schedule estimates to actual results will provide a means to do this.

Earned Value Management (EVM) provides an early warning system for deviations from project plans and quantifies technical problems in cost and schedule terms, providing sound and objective basis for considering corrective actions. EVM helps flag and develop strategies to mitigate the risk of cost and schedule overruns while also providing a forecast of final cost and schedule outcomes. The EVAMS will provide NIH Project Managers with a management system, tools and the information needed to improve their ability to manage, track, and report on, project performance, and intervene when the risk to successful completion of a project increases.

Rationale

Earned Value Management (EVM) is an integrated project management system that will significantly improve NIH's ability to actively track capital project performance management.

This goal is consistent with the philosophy of the Federal Real Property Executive Order that recommends establishment of clear goals and objectives to improve agencies accountability for real property and with OMB Circular No.A-11, Part 7 that references EVM as a project management system required to support facility budget submissions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with OMB Circular No.A-11, Part 7, NIH implemented a project management review system based on EVAMS principles. This is being used to monitor and manage the performance of the design, acquisition, construction, and commissioning of capital facility projects. As a first step in the implementation of the EVAMS, NIH integrated existing project management data from Lab 33, and the Northwest Parking Garage, into a 'proof-of-concept' version of the NIH EVAMS. NIH is continuing use of the information generated by EVAMS data reports and analysis to evaluate and redesign work processes to improve the efficiency and effectiveness of its capital project delivery systems.

The NIH established preliminary EVMS policies and procedures in June 2003 as a management tool to improve the delivery of capital projects. Projects in design and proposed for construction were selected to pilot the system and be a source for collection of data to validate its effectiveness and flag areas needing enhancements.

Evaluation and assessment of existing project management systems and their integration into a proof-of-concept version of an EVAMS took 12 months. The first draft of the development of EVAMS policies and procedures began in late June 2003. Implementation of a revised project management system that incorporated lessons-learned from the proof of concept phase of the EVAMS development took place in FY06.

Further, NIH will continue review of its project management systems, benchmark with public and private sector organizations. A grant received under the NIH One Percent Evaluation Set Aside Program was utilized to assist in the evaluation, assessment, and validation of proposed EVAMS methodology.

Concurrent with this action, Office of Research Facilities (ORF) began initial implementation of its proposed EVAMS, beta tested the system using one (1) design and two (2) construction projects, and provided top management and Project Manager level training on the use of the EVM management system to enable better management and facilitation of on time, within scope, and within budget delivery of projects.

The NIH will continue data analysis and collection to enhance the EVMS. The services of a consultant, recognized as an EVAMS specialist, were obtained to review, analyze and further validate the proof of concept version. Data will be verified using information from the Office of Research Facilities Quality Management System and the earned-value analyses that are performed for pilot projects. The lessons-learned from the pilot test, the benchmark results and the observations of consultants was used to fully launch the NIH EVAMS in FY 2005.

At the end of FY 2006, Earned Value Analyses were conducted for NIH major capital acquisition projects using prior year information as a baseline. The lessons-learned will be reflected in revised Standard Operating Procedures (SOPs) now under development and in future year analyses.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Evaluate and assess existing project management systems and implement into a proof-of-concept version of the NIHs Earned Value Management System (EVAMS).	(FY03) Policies and procedures in place to identify data needed for evaluation		◆				
FY04	*Actual Performance:* (MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts.						
Implement a revised project management system that incorporates earned value analysis and management.	(FY03) EVAMS proof-of-concept version			◆			
FY05	*Actual Performance:* (MET) Project Management System was modified to reflect management and contracting procedures suitable for the project acquisition method used.						
Fully launch the Earned Value Management System (EVMS) and conduct Earned-Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio.	(FY05) Earned Value Management System (EVMS) is incorporated into the project management system				◆		
FY06	*Actual Performance:* (MET) EVAMS has been fully launched and was used to evaluate on time, on scope and on budget delivery of NIH major capital projects.						
Complete goal of ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an Earned Value Analysis and Management System (EVAMS).	FY06 results					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY2006 target to fully launch the Earned Value Management System (EVMS) and conduct Earned-Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio was MET. Monthly analyses are conducted to clearly understand the status of a project in terms of planned versus actual budget and schedule performance. The Office of Research Facilities used EVAMS to conduct Earned Value Analyses (EVA) for the major capital projects within the NIH facilities portfolio. The EVAs enabled better management and delivery of projects using the tracking and monitoring metrics to evaluate performance, control variances, and review business practices.

Implementation Strategy Advances or Other Highlights

The Earned Value Management System is one of the tools used to support evaluation of the within budget delivery of NIH facilities portfolio. The NIH continued use of lessons-learned from implementing the EVAMS to review business practices. An outcome of this was modifications to NIHs earned value policy to include commonly used fixed price contract practices.

PART

This goal was included in the FY 2007 PART of the Building & Facilities Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

POI-2 Utilize performance-based contracting (PBC). (ongoing)

BACKGROUND

One of the major challenges for Federal Government management and administration is improving the efficiency and effectiveness of contracting and procurement activities. Historically, Government policies, regulations, and attention have been directed at acquisition of supplies rather than services. A 1997 government-wide memorandum requires that all Federal agencies use Performance Based Contracting (PBC) methods, where practicable, and match acquisition and contract administration strategies with specific requirements.

PBC involves using performance requirements that define contracted work in measurable, mission-related terms, with performance standards of quality, quantity, and timeliness tied to those requirements. PBC also requires a quality assurance plan describing how contractor performance will be measured against performance standards. In cases where a contract is either mission critical or requires a large dollar amount, incentives are tied to the quality assurance plan measurements.

NIH is committed to increasing the amount of NIH contracts that are PBC. As new contract requirements and contract renewals arise, NIH will review each situation to determine whether using PBC is appropriate.

Rationale

As cited in the Procurement Executives Council's Strategic Plan, over the next five years, a majority of the service contracts offered throughout the federal government will be performance-based. In other words, rather than micromanaging the details of how contractors operate, the government must set the standards, set the results and give the contractor the freedom to achieve it in the best way. As a means of maximizing agencies' endorsement of PBC, annual targets were established.

The strong endorsement of PBC stems from the Government's emphasis on managing for results: by linking payments to results rather than to effort or process. PBC provides NIH with useful indicators of contactor performance and allows vendors to be innovative in responding to requirements for specific products and services.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH strategy to utilize PBC incorporates three basic elements: 1) promoting the value of PBC in acquisition and contract administration/management planning; 2) ensuring that PBC planning takes place on individual requirements and contracts; and 3) making certain that NIH acquisition staff is properly trained and aware of guidance on PBC.

Under the Office of Acquisition Management and Policy's (OAMP) leadership, the acquisition and project officer community have attended training sessions promoting PBC.

By fostering and facilitating these sessions as well as disseminating information about Government and industry sponsored events focused on PBC, the NIH has raised awareness and improved our ability to apply PBC methods to our requirements.

To ensure that PBC planning occurs, the OAMP/Division of Acquisition Policy and Evaluation (DAPE) stresses the implementation of PBC as required by the Federal Acquisition Regulation (FAR). Through publications such as the Seven Steps to Performance-Based Services Acquisition Guide, the acquisition community is reminded of the importance for considering PBC during the acquisition-planning phase. In addition, the Head of the Contracting Activity reviews solicitations submitted for Board of Contract Award reviews thereby providing the necessary oversight regarding the applicability of PBC.

As stated previously, PBC training opportunities continue to be offered to the acquisition and project officer community. In addition, consultant support has been identified to assist both contracting and project officers on their individual requirements. This effort has increased the familiarization of the community to PBC and eased the transition from traditional contracting methods to performance based contracting methods.

The monitoring of PBC activity is accomplished by the submission of monthly reports from the contracting offices and through reports of PBC funding activity from the Departmental Contract Information System. IC contracting offices are being reminded of the Government-wide move toward increased use of PBC and that PBC is an NIH GPRA target. Contracting staff will be continually reminded that the FAR requires that contracting officers include in their acquisition plans for service contracts or orders, a description of the strategies they will use for implementing performance-based contracting methods, or provide a rationale for not using these methods. The planned strategy for performance-based contracting is to meet the targets set annually.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	(FY02) $207 million projected for contracted work with requirements tied to performance	◆					
FY03	*Actual Performance:* (MET) Obligated $557 million of eligible service contracting dollars through performance-based contracting.						
Obligate 40% of eligible service contracting dollars through PBC.	Obligate 40% of eligible service contracting dollars through performance-based contracting		◆[e]	◆[e]			
FY04	*Actual Performance:* (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.						
FY05	*Actual Performance:* (MET) Obligated 44% of eligible service contracting dollars through performance-based contracting.						
Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	FY 2006 OMB/OFPP Goal				◆		
FY06	*Actual Performance:* (MET) Obligated 55% of the total eligible service contracting dollars through performance-based contracting.						
Obligate the FY 2007 OMB/OFPP goal of eligible service contracting dollars to PBC.	FY 2007 OMB/OFPP Goal					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
Obligate the FY 2008 OMB/OFPP goal of eligible service contracting dollars to PBC.	FY 2008 OMB/OFPP Goal						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target to obligate the eligible service contracting dollars through PBC was MET. Fifty-five percent of the total eligible service contracting dollars was obligated to PBC service contracts. The FY2006 goal was 40%. This information was reported in the Departmental Contract Information System (DCIS). These obligations were reported throughout the fiscal year as funds were committed to various contracts throughout NIH.

Implementation Strategy Advances or Other Highlights

PBC activity is tracked monthly through reports of funding activity obtained from the DCIS. Training opportunities continue to be offered to the acquisition and program community to ensure that they are properly trained in the use of PBC. Information about Government and industry sponsored events focused on PBC is regularly disseminated.

POI-5	**By FY 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems.**

BACKGROUND

Over the next several years NIH will continue its efforts to enhance its ability to demonstrate benefits resulting from extramural research investments. The specific steps contributing to the achievement of this goal involve capturing information electronically that will allow NIH to better track and characterize the scientific workforce and its research portfolio in order to better inform NIH's program planning process.

There are four related areas under this Goal:

- Permitting and collecting information on more than one Principal Investigator (PI) on a research grant by implementing policy and information systems that support multiple-PIs.
- Capturing standardized information digitally on electronically submitted grant applications using a new interagency grant application dataset, the Standard Form 424 [Research and Research Related (R&R)].
- Enhance public access to NIH-sponsored research findings through implementation of policy changes and electronic systems.
- Balancing workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications.

Rationale

On average, the NIH expects to receive and process more than 60,000 grant applications each year. It is important to understand the nature of the science being funded, how that science addresses the health-needs of the nation, the community that conducts that research, and the outcome of that research. An enterprise of this magnitude needs to develop automated ways to produce the data needed to make decisions and establish priorities on a global as well as by individual projects or programs. The policy changes NIH is making in this regard, in combination with the newly developed information technology, will support this goal.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

At this time, planned approaches involve the following activities.

Multiple Principal Investigators: The scale and complexity of biomedical research problems increasingly require collaborative teams of scientists that frequently combine the disciplines of the physical, biological and social sciences. This approach is specifically encouraged by the NIH Roadmap Initiative called Research Teams of the Future. A critical part of this involves the recognition of all key contributors on NIH projects. Accordingly, the NIH is completing an effort to permit more than one PI on an NIH funded research project. This change in policy will not only encourage the development of interdisciplinary

approaches, it will allow the NIH to recognize and acknowledge the contribution of all PIs. The White House Office of Science and Technology Policy issued a directive to all federal agencies on January 4, 2005 to begin planning to allow and recognize more than one PI. Under the NIH plan, it will be possible for more than one PI to share the responsibility for a research grant. Once fully implemented, grant applications will identify all PIs involved with a particular project. All the PIs will be listed on the notice of grant award and in reports related to that particular grant. Adapting to multiple PIs requires redesigning grant applications, the structure of the administrative database, and data entry modules used to process those applications and awards at all points in the grant cycle. NIH has successfully provided the opportunity for multi-PI designations in a number of grant opportunities and is now working towards full implementation of the policy change in FY07.

Research and Related Dataset: NIH is transitioning from paper submission of the PHS 398 grant application form to electronic submission of the SF424(R&R) data set through Grants.gov. The SF424 R&R dataset comprises application data elements and instructions that will be used by all Federal Agencies involved in Research and Related (R&R) grant funding. This common data set is intended to replace the data collection instruments (applications) currently maintained by each research agency, with the goal of creating a consistent application for research grant support to be used to apply for Federal research funding. Making this transition to a new application form and electronic submission requires NIH and the research community to reevaluate and make changes to policies and procedures involving the entire life cycle of the grant process, work closely with all Federal research agencies, establish aggressive communications campaigns, as well as undertake substantial information systems development. NIH has transitioned many of its research programs to require electronic submission on the new form set in FY 06, well ahead of its original schedule, and plans to complete transition of all research programs in FY08.

Public Access to Information on NIH-Sponsored Research: The NIH is using information technology systems within the NIH Commons and the National Library of Medicine's (NLM) PubMed Central (PMC), to archive publications resulting from NIH-funded research. This policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The policy is intended to: 1) create a stable archive of peer-reviewed research publications resulting from NIH-funded research to ensure the permanent preservation of these vital published research findings; 2) secure a searchable compendium of these peer-reviewed research publications that NIH and its awardees can use to manage more efficiently and to understand better their research portfolios, monitor scientific productivity, and ultimately, help set research priorities; and 3) make published results of NIH-funded research more readily accessible to the public, health care providers, educators, and scientists. The Public Access Policy will be implemented in 2005. NIH-funded investigators are requested to submit to the NIH NLM PMC an electronic version of the author's final manuscript using the NIH Manuscript Submission (NIHMS) system after it has been through the publication peer review process and accepted for publication.

By storing research publications from diverse sources in a searchable, electronic archive

with a common format, PMC facilitates greater integration with related resources in other NLM databases thus providing the opportunity to develop unprecedented scientific search and analysis capabilities for the benefit of science. This searchable archive will enable NIH program officials to manage their research portfolios more efficiently, monitor scientific productivity, and ultimately, help set research priorities. This strategy also will enable NIH to advance its goal of creating an end-to-end, paperless grants management process. Finally, it will make the publications of NIH-funded research more accessible to and searchable for the public, health care providers, educators, and scientists.

Changing Standard Application Receipt Dates: The transition to electronic application submission has heightened NIH's awareness of challenges posed by having very large numbers of incoming grant applications on any single day. NIH currently spreads the workload involved with receiving incoming grant applications through three annual council rounds that include multiple submission dates for each round. However, some of NIH's standing receipt dates currently allow up to eight thousand applications to come in for a single receipt date. This volume causes bottlenecks in a number of critical places: Grants.gov and eRA systems, where response time may slow under heavy volume; the Grants.gov and NIH help desks, which have to handle large spikes in call volume; the CSR Division of Receipt and Referral, which is responsible for referral of incoming applications in a timely way; and the research administration office at the applicant institution, which must now submit all applications. In addition, the principal investigator currently rushes to submit an application that sits waiting to get to the Scientific Review Administrator (SRA) while we process thousands of others. Spreading receipt dates to achieve a steady flow of applications rather than "boom and bust" cycles will allow many different groups to have a realistic approach to staffing that should minimize the need for either costly overtime or the use of less experienced part-time staff, while maximizing electronic system responsiveness. It also achieves another very important goal of providing additional time for less experienced researchers to work on their applications. Implementation of new standing receipt dates will be completed in FY08.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI. (FY08) Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	In FY 2004, all research grants had only one Principal Investigator			◆	◆	◇	◇
FY05	*Actual Performance:* (MET) Addressed signature and regulatory issues, and develop plans for application forms and data systems associated with multiple PIs.						
FY06	*Actual Performance:* (MET) The data structure of the system was modified to maintain data for multiple Principal Investigators (PIs) for a single application and grant in the spring of 2006. Both paper and electronic applications involving multiple PIs were received and processed by NIH.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) Mock Pilot 424-R&R forms using 'dead data' to assess utilization of common data sets. (FY06) Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements. (FY08) Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.	Paper grant applications currently received			◆	◆	◇	◇
FY05	*Actual Performance:* (MET) A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use.						
FY06	*Actual Performance:* (MET) NIH required electronic submission of applications through Grants.gov on the new form set for 19 research programs. Over 13,000 applications were accepted and processed electronically in FY06.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) ' Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) ' Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	(FY 04) No mechanism exists to receive manuscripts			◆	◆		
FY05	*Actual Performance:* (MET) NIH developed and launched the NIHMS system was May 2, 2005.						
FY06	*Actual Performance:* (MET) Receiving third party manuscript uploads met 12/05; Linking submissions met 2/06.						
(Target 4) Better balance workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications (FY 2008 accomplished) (FY08) – Implement changes to standing application receipt dates	(FY07) Peak receipt dates involving up to 8,000 applications.						◇
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY06 target to complete Modifications of forms and data systems to accommodate multiple PIs was MET. The data structure of the system was modified to maintain data for multiple Principal Investigators (PIs) for a single application and grant in the spring of 2006. The multiple-PI option was made available in pilot mode for paper applications submitted in response to a selected group of Requests for Applications (RFAs) and Program Announcements (PAs) with May-June 2006 receipt dates. The pilot was expanded to include electronically submitted applications for select Funding Opportunity Announcements towards the end of the fiscal year. Data systems are being modified to support reporting activities for multiple-PI grant applications and awards.

Target 2

The FY06 target 'Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements,' was MET. NIH required electronic submission of applications through Grants.gov on the new form set for the following 19 research types:

C 06 Research Facilities Construction Grants
R 03 Small Research Grants
R 13 Conferences
R 15 Academic Research Enhancement Awards (AREA)
R 18 Research Demonstration and Dissemination Projects
R 21 Exploratory/Developmental Grants
R 25 Education Projects
R 33 Exploratory/Developmental Grants Phase II
R 34 Clinical Trial Planning Grant
R 36 Dissertation Award
R 37 Method to Extend Research in Time (MERIT) Award
R 41 Small Business Technology Transfer (STTR) Grants - Phase I
R 42 Small Business Technology Transfer (STTR) Grants - Phase II
R 43 Small Business Innovation Research Grants (SBIR) - Phase I
R 44 Small Business Innovation Research Grants (SBIR) - Phase II
S 10 Biomedical Research Support Shared Instrumentation Grants
U C6 Construction Cooperative Agreement
U 18 Research Demonstration (Cooperative Agreements)
X 02 Interdisciplinary Research Consortiums (Roadmap)'

NIH accepted and processed over 13,000 applications electronically in FY06.

Target 3

The FY06 target to expand National Institutes of Health Manuscript submission system (NIHMS) capabilities by linking submission to PI Progress Report and receiving third part manuscript uploads to facilitate submission was MET. In December 2005, the National Library of Medicine developed two ways to facilitate third party manuscript submission. The

first method allows uploading of individual articles by librarians, project staff, and other research personnel including the PI. The second method is a Bulk Upload system where publishers or institutions can upload more than one manuscript at a time. Both processes include a system ensure author verification of all content prior to posting articles on PubMed Central. In February 2006, integration between the eRA system and the NIHMS system went live, allowing investigators to link manuscript submissions on NIHMS with their electronic progress reports.

Implementation Strategy Advances or Other Highlights

By the end of FY2006, both methods of third party submission are in routine use. In September 2006, Elsevier announced that bulk submission will become the default method to comply with the Public Access policy for all NIH funded articles.

POI-6	**Provide responsible stewardship over existing federally owned real property assets.**

BACKGROUND

Responsible stewardship over federally owned real property assets addresses the issue of deferred maintenance risks. Deferred maintenance compromises the life safety and health of the occupants in NIH facilities. It may prevent the facility from meeting all or part of its stated mission, impact the accreditation to conduct bio-medical research, and reduces the intrinsic and market value of a real estate asset.

Facility Condition Index (FCI) is an industry best practice for assessing and measuring the state of individual facilities and the portfolio of facilities by objectively quantifying deferred maintenance and non-compliance with recognized codes and applicable standards. Facility Condition Index (CI) is a mathematic way of expressing the relationship between the cost of deferred maintenance and the capital replacement value of a facility or portfolio of facilities.

FCI = (DM/RC) , where DM = deferred maintenance and RC = replacement cost in current dollars CI = 1 - (DM/RC)x100

Rationale

For NIH to assure its facilities are capable of supporting its biomedical research mission, NIH must have an objective way to measure the state of its real property assets and to plan for and to monitor the capital maintenance and repair program. The FCI is one of the required measures under the President's Management Agenda Real Property Asset Management initiative and is included under the "One Department, One Direction, One HHS" objectives of the Department of Health and Human Services.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In 2002, NIH adopted the facility condition assessment protocol to determine the condition of its real estate assets and to estimate deferred maintenance based on actual identified deficiencies. The baseline was completed in 2004 when the detailed evaluative survey that underpins the facility assessment program was completed for the Bethesda and Frederick campuses. Surveys of the other campuses were completed in 2003. To provide responsible stewardship, NIH must annually:

- Update the facility condition assessment data
- Modify the prior year's capital repair plan in light of actual funds appropriated
- Execute the funded plan
- Develop next year's annual capital repair plan based on the facility condition data, the work funded in prior years, and other criteria that optimizes the use of available capital repair funds in pursuit of the goal

Through this annual process, NIH will be able to maintain the condition of the portfolio so the average CI is 85 and not less than 95% of occupied facility gross square feet (GSF) has

a CI greater than 65, which are the criteria for optimum performance. By monitoring these measures annually, NIH can demonstrate good stewardship.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Maintain the condition of the portfolio so the average CIwa = 85*		(FY05) 54.0%		◆	◆[e]	◆	◇	◇
FY04	*Actual Performance:* (MET) The condition of the portfolio was maintained so that the average CI was 85.							
FY05	*Actual Performance:* (MET) The condition of the portfolio improved so that the average CI for 2005 was 87 which met and exceeded the 2005 target of 85.							
FY06	*Actual Performance:* (MET) The condition of the portfolio was maintained so that at least the average CI was 85.							
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
FY08	*Actual Performance:* Performance results will be reported in February 2009.							
(Target 2) By 2010, no less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%)		(FY05) 87.0%		◆	◆	◆[e]	◇	◇
FY04	*Actual Performance:* (MET) 86% of occupied GSF had a CI greater than 65.							
FY05	*Actual Performance:* (MET) 87% of the occupied space had a CI greater than 65.							
FY06	*Actual Performance:* (MET) The FY06 target of 88.5% occupied GSF was met and exceeded by 2.5%. 91% occupied space (GSF) had a CI greater than 65.							
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
FY08	*Actual Performance:* Performance results will be reported in February 2009.							

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY06 target to maintain the condition of the portfolio so the average CIwa =85 was MET. The condition of the portfolio was maintained so that at least the average CI was 85.

Target 2

The FY2006 target to ensure that not less than 88.5% of occupied gross square feet (GSF) will have a Condition Index (CI) greater than 65 was MET and exceeded by 2.5%. In FY06, The condition of NIH's facilities portfolio improved so that 91% occupied space (GSF) had a CI greater than 65. This higher percentage resulted from two new large facilities recently completed being added to the inventory. Repairs and improvements continued to focus on structural, architectural, mechanical, plumbing and electrical system to improve facility operations and reliability within resource constraints.

Implementation Strategy Advances or Other Highlights

NIH continued use of a Repair and Improvements Board (R&IB) consisting of cross-organization Subject Matter Experts to review and prioritize repair and improvements program requirements to help ensure maximum utilization of resources and the best possible return on investments to improve the condition of its facilities portfolio.

PART

This goal was included in the FY 2007 PART of the Building & Facilities Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

POI-7	**Manage design and construction of capital facility projects funded by the Building and Facilities Appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the approved budget. (Ongoing)**

BACKGROUND

The design and construction processes are complex, imprecise, and vulnerable to many outside influences including changing requirements, changing standards, weather, material shortages, and market forces. Thus, managing capital facilities design and construction so the planned scope of the project is completed within the approved budget and schedule is always an ambitious goal. Under current practice as defined by OMB A-11, federal construction projects are to be fully funded in advance. In this situation, it is critically important to manage each B&F project identified as a line item appropriation within appropriated amounts.

Two criteria for tracking capital project management performance are: (1) variance of the final project cost from the approved appropriated budget, (2) variance of the actual scope of the project from the scope identified in the approval documents. These criteria are tracked by the Department of Health and Human Services as part of the federal real property asset management initiative.

NIH actively manages its 'line item B&F' projects to deliver the scope within the budget. To accomplish this ambitious goal, NIH must annually manage funded projects to meet schedule and cost management targets. This involves development and execution of specific project management plans for each project that will include as a minimum:

- Formation of an Integrated Project Team that includes stakeholders
- Pre-project planning to manage potential project risks
- Development and approval of a program of requirements as a basis for design
- Design management to include peer reviews and approvals
- Acquisition planning
- Construction management and quality assurance programs
- Commissioning to validate that the facility is fully operational for the intended use

Criteria for optimal performance (to be assessed as annual targets):

- Manage all B&F line item projects so they are completed within 100% of the final approved total project cost.
- No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

This goal is to monitor and track on time, on scope and within budget delivery of facilities to be good stewards of the limited resources received to support the research mission of the NIH and to comply with OMB Circular A-11. Earned Value Management is one of the key tools that will be used to accomplish this objective.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 20 active projects (FY07) TBD active projects (FY08) TBD active projects *Previous Target:* (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) 24 active projects (FY07) TBD active projects (FY08) TBD active projects	(FY06) 20 active projects		◆	◆	◆	◇	◇
FY04	*Actual Performance:* (MET) All 19 projects were managed within the approved budget.						
FY05	*Actual Performance:* (MET) All twenty-one (21) projects were managed within the approved budget.						
FY06	*Actual Performance:* (MET) All twenty (20) active projects were managed within the approved budget.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 20 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD *Previous Target:* (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) 24 active projects / 10% ≤ 2 (FY07) TBD (FY08) TBD	(FY06) ≤ 2		◆	◆	◆	◇	◇
FY04	*Actual Performance:* (MET) No projects required scope adjustments.						
FY05	*Actual Performance:* (MET) All projects were managed within the approved scope.						
FY06	*Actual Performance:* (MET) All twenty (20) of the active projects were managed within the approved scope.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ **Active**	◆ **Met**	→ **Extended**	× **Not Met**

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1

The FY2006 target to manage all B&F line item projects so they are completed within 100% of the final approved total project cost was MET. The twenty (20) active projects in FY2006 were all managed within the approved budget. This included management of projects on the NIH Bethesda, North Carolina, Hamilton, Montana, and Frederick, Maryland campuses within the funding levels approved for those projects.

Target 2

The FY2006 target to manage facilities portfolio so that no more than 10% of the projects may incorporate plus or minus 10% adjustment of the approved scope was MET. All twenty (20) of the active projects were managed such that 100% of them were within the approved

scope. This included facilities on the NIH Bethesda, North Carolina, Hamilton, Montana and Frederick, Maryland campuses.

Implementation Strategy Advances or Other Highlights

The Office of Research Facilities (ORF) Earned Value Management System is one of the tools used to support evaluation of the within budget delivery of NIH facilities portfolio.

ORF continued use of its Earned Value Management System tool to support evaluation of the delivery of capital assets within the approved scope.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The number of active projects in FY2006 was reduced from 24 to 20 in Target 1 and 2. This reduction resulted from projects being dropped from the inventory.

PART

This goal was included in the FY 2007 PART of the Building & Facilities Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

POI-8	**By 2010, protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements.**

BACKGROUND

The National Institutes of Health's (NIH) extramural construction grant program supports construction and renovation projects that facilitate and enhance the conduct of PHS-supported biomedical and behavioral research. The extramural construction grant program supports the costs of designing, constructing and/or renovating non-Federal basic and clinical research facilities to meet the biomedical and behavioral research, research training, or research support needs of an institution or a research area at an institution.

Although there are ten NIH Institutes and Centers (IC), including the Office of AIDS Research, that have construction or modernization grant authority, in FY 2005 only two ICs had appropriated funds for extramural construction and have actively awarded construction grants over the past 5 years. The National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases (NIAID) actively support the program through the issuance of grants and/or cooperative agreements (hereafter referred to as grants).

The principal objective of NCRR's program is to facilitate and enhance the conduct of PHS-supported biomedical and behavioral research by supporting the costs of designing and constructing non-federal basic and clinical research facilities to meet the biomedical or behavioral research, research training, or research support needs of an institution or a research area at an institution.

The principal objective of NIAID's program is to support the construction of National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) at research institutions across the country. The NBLs will serve as a national and regional resource for research on biodefense and emerging infectious disease agents that require biosafety Level 2, 3 or 4 (BSL-2/3/4) biocontainment, while the RBLs will serve as a regional resource for research requiring BSL-2/3 biocontainment. The NBLs and RBLs will complement and support the research activities of NIAID's Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, and will be made available to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency.

Rationale

The administration of construction grants has unique controls in place to protect the interest of the Federal Government. Although there are many unique requirements applicable to the construction grant program, the focus here is on those requirements pertinent to the protection of the Federal Government's interest in grant-supported real property.

To protect the Federal interest in real property that has been constructed or has undergone major renovation using NIH grant funds, the NIH must ensure the awardee's compliance with additional requirements that are unique to the program.

When the grantee receives their award, the awardee must obtain NIH approval of all plans and specifications at each stage of design to ensure the grant-supported space is designed in accordance with NIH Design Policy and Guidelines and Good Laboratory Standards. The

proper design of the facility will ensure the safety of NIH grant-supported researchers who will occupy the completed facility. In addition, at the time construction begins the awardee is also required to file a Notice of Federal Interest (Notice) in the local land records in the jurisdiction in which the property is located. Filing of this Notice results in a lien on the property to ensure that the property will not be: used for any purpose inconsistent with that authorized by the grant program statute, mortgaged or otherwise used as collateral, or sold or transferred to another party without written permission of the NIH. The Notice ensures the Federal interest in the property will not subordinate to those of non-Federal parties unless a deviation is approved. The baseline for Target 1 is the number of projects under construction during the target year.

After construction is complete, the awardee must ensure that they are using the grant-supported space for its intended purpose throughout the usage obligation. The authorization and/or appropriation language for construction grant programs requires construction grant recipients to use the grant-supported space for the research purposes for which the space was built for a 20 year period after completion of construction. In order to ensure the awardee's compliance with the usage obligation and to protect the NIH's interest in grant-supported property, NIH monitors this usage in a variety of ways, including periodic facility use certifications or reports, site visits, or other appropriate means for the duration of the required usage period. The baseline for Target 2 is the number of projects completed in the 20 years prior to the end of the target year (e.g. FY05 baseline is number of projects completed during October 1, 1985 to September 30, 2005).

NIH staff also provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects.

NIH's grants compliance program works to ensure that the ICs adhere to NIH construction-specific grants oversight policies through a management controls initiative that examines IC policies and procedures, their compliance with NIH policy, and if IC staff follow the required procedures.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has collected data on IC compliance with certain policy requirements including monitoring the use of research space supported by NIH construction grants for the 20 year period specified in the Notice of Grant Award. Based on the findings of the data analysis, NIH staff will work closely with ICs to ensure that they have systems in place that meet policy requirements. NIH will reevaluate IC systems by re-administering a management controls questionnaire self assessment tool to validate continued compliance.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
(Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval. (FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	(FY05) 91 grantees (FY06) 50 grantees (FY07) 35 expected grantees (FY08) 21 expected grantees (FY09) TBD expected grantees	-	-	◆	×	◇	◇
FY05	*Actual Performance:* (MET) 100% of projects under construction have approved design and construction documents or are implementing corrective strategies, and 100% of projects ensured the Notice of Federal Interest has been recorded or are implementing corrective strategies.						
FY06	*Actual Performance:* (NOT MET) 66% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded. Corrective strategies have been taken to ensure that the remaining projects will meet the construction requirements.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						
(Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research. (FY05) 95% of 117 projects are in compliance (FY06) 95% of 123 projects are in compliance (FY07) 95% of 143 projects are in compliance (FY08) 95% of 164 projects are in compliance (FY09) 95% of 179 projects are in compliance (FY10) 95% of 196 projects are in compliance	No. of Projects occupied in past 20 years: (FY05) 117 prjs (FY06) 123 prjs (FY07) 143 prjs (FY08) 164 prjs (FY09) 179 prjs (FY10) 196 prjs	-	-	◆	◆	◇	◇
FY05	*Actual Performance:* (MET) 100% of projects monitored the use of grant-supported space or are implementing corrective strategies.						
FY06	*Actual Performance:* (MET) 97% of the extramural construction projects were in compliance with the post award 20 year usage requirement.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

Target 1:

The FY06 target was not met. During FY 2006, 100% of the grantees took the necessary actions to provide the construction designs documents, however, only 66% of the grantees took the necessary actions to provide the Notice of Federal Interest (NFI). The grantees with the outstanding NFIs have been contacted and corrective strategies are being taken to ensure that the construction requirements are met. Thus, 100% of projects either met the construction requirements or have taken corrective actions during FY 2006.

Target 2:

The FY06 target was MET. During FY 2006, 97% of the extramural construction projects were in compliance with the post award 20 year usage requirement to conduct research. NIH received one of the following from each grantee ensuring research was being conducted: a signed document, a publication, photos or other grant support verifying the 20 year usage requirement. For some projects, verification was attained through an NIH staff site visit to

the facility.

At the end of the 20 year monitoring period, a final acceptance letter is sent to the grantee with the encouragement to continue to use the space for the purpose(s) of the award.

PART

This goal was included in the FY 2008 PART of the Extramural Construction Program. NIH will continue to achieve this goal's annual requirements as indicted by the PART Improvement Plan.

POI-9	**By 2012, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors.**

BACKGROUND

The NIH is the steward of medical and behavioral research for the Nation whose mission is science in pursuit of fundamental biological knowledge and the application of that knowledge to improve public health. The Intramural Research Program at NIH conducts distinctive, high-risk, high impact laboratory, clinical and population-based research and trains new researchers to support this mission. There are 27 Institutes and Centers (ICs) at NIH and of those, 22 ICs have intramural research programs. The Intramural Research Programs have resources allocated to individual tenured and tenure-track investigators.

Rationale

Intramural research at NIH has been reviewed by committees of scientists from outside the NIH since 1956. The committees are called Board of Scientific Counselors (BSCs) and constituted to assist the Scientific Directors (SDs) of each IC in evaluating the quality of the intramural programs for which they are responsible. It is the policy of the NIH that all research conducted intramurally must be reviewed at regular intervals by highly qualified outside scientists. Every independent intramural scientist (Principal Investigator) on a tenured appointment must be reviewed and evaluated at a minimum of every four years. Although the principal purpose of these independent evaluations is to advise the SDs, the reports of the BSCs are distributed to the Director, National Institutes of Health (NIH), Deputy Director for Intramural Research (DDIR), the appropriate Institute or Center (IC) Director, and the Board of SDs. The BSC also reports annually to the National Advisory Council or Board of the IC. The composition of BSCs is based primarily on scientific qualification; members shall be international recognized as an authority in one of the fields of research under review. While the primary criterion for all appointments to the BSCs should be scientific excellence, each BSC should exhibit reasonable balance in membership in terms of points of view (scientific interests/disciplines) and with respect to gender, ethnicity, and geographical distribution of members' institutions.

BSC members serve for five-year terms, if possible, to allow them to be involved more than once in the regular quadrennial review of some programs. An effort should be made to have some BSC members (approximately one-third) who are not primarily funded by the IC on whose BSC they serve.

A BSC may make use of ad hoc reviewers when the Chair of the BSC, in consultation with the SD, deems it necessary. Such ad hoc reviewers should be selected by the BSC Chair, with the advice of the other BSC members, the SD, and the IC Director.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The review process used by BSCs will take into consideration the special nature of NIH intramural research made possible by stable funding, that high-risk research should be encouraged, and that the review process will emphasize past performance. The review will

address the accomplishments of individual scientists and the quality and productivity of their research. The BSCs make recommendations to the Scientific Director and IC Director regarding the allocation of resources. Recommendations regarding resources are explicit as possible, with a clear indication as to which resources (budget, space, and personnel) should remain the same, be increased, or decreased. The BSCs shall meet often enough (ordinarily two or three times each year) to assure that the work of each tenured and tenure-track intramural scientist and each Laboratory or Branch is reviewed at least once every four years. The BSC members meet face-to-face at the site visits and BSC review meetings to complete the Principal Investigators' review process.

The review cycle for each scientist is every four years indicating that 25% of the Principal Investigators will be reviewed each year. The BSCs will recommend the reallocation of resources at that time resulting in 25% reviewed resources being recommended for reallocation as a result of the reviews.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008
Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources.	BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.	◆	◆	◆	◆	◇	◇
FY03	*Actual Performance:* (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.						
FY04	*Actual Performance:* (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.						
FY05	*Actual Performance:* (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.						
FY06	*Actual Performance:* (MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
FY08	*Actual Performance:* Performance results will be reported in February 2009.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2006 PERFORMANCE RESULTS

Target

The FY 2006 target to Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources was MET. To assess quality of science, 25% of Principal Investigators were reviewed resulting in 25% of resources recommended to be reallocated. The NIH Manual Issuance 3005 – Review and Evaluation of Intramural Programs requires BSC reviews and recommendations in writing and distributed to the Deputy Director for Intramural Research (DDIR) and the Director, NIH. Members of the DDIR's Office of Intramural Research attend the BSC reviews monitoring specific reviews and resulting recommendations. The written reviews and recommendations are also provided annually to the ICs National Advisory Council.

Implementation Strategy Advances or Other Highlights

The annual meeting of the chairs of the Boards of Scientific Counselors met on May 12, 2006 to discuss issues relating to the BSC reviews. The discussions included intramural budgets, recruitment issues, trends in tenure and tenure-track appointments, clinical research

and specific issues from BSC chairs. The Director, NIH and DDIR, NIH attends the meeting and present current intramural issues.

The annual cost savings realized in FY 2005 was $31,043,271; this amount was reallocated within the Intramural Research Programs in FY 2005. Annual cost savings for FY 2006 will be available in 2007.

PART

This goal was included in the FY 2007 PART of the Intramural Research Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

CHANGES AND IMPROVEMENTS OVER PREVIOUS YEARS

The current Plan/Report contains 47 goals and 61 targets for the Initial FY 2008 Plan; 52 goals and 65 targets for the Final FY 2007 Plan; and 58 goals and 74 targets for the FY 2006 Report. Of these goals, the majority fall under the Scientific Research Outcome category. Goals in the remaining functional areas (Communication and Transfer of Results, Capacity Building and Research Resources, Strategic Management of Human Capital, Program Oversight and Improvement) address objectives described in the PMA and the management objectives in the One HHS Plan. These latter goals underscore NIH's commitment to responsible management of its research dollars.

In the SRO section, four goals were achieved in FY 2006, and one new goal was added to the plan. These changes are described in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
SRO-1.2	Goal achieved and will be dropped.		
SRO-1.2.3	Goal achieved and will be dropped.		
SRO-7.2	Goal achieved and will be dropped.		
SRO-7.8.3	Goal achieved and will be dropped.		
SRO-9.4	New goal added to the plan.		By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.
SRO-6.3	End date revised to reflect early termination of goal.	By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.
	Target revised to reflect new completion date.	(FY08) Sequence anchor all probe sets from public sequence-defined microarray platforms to respective genomes within CEBS, demonstrating chromosome/gene alignment of probe sets within a genome browser. Create extensive study and subject search capability such that the correspondence of gene expression profiles to specific study designs, subjects, and experimental outcomes may be determined. Enable a literature searching algorithm and user interface to identify and visualize relationships among known gene sets via query of PubMed.	(FY08) Complete goal of developing a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.
SRO-5.7	Target revised.	(FY07) Complete accrual in lung cancer therapy trial and perform final analysis of test-retest reproducibility of functional imaging scans.	(FY07) Perform additional analysis of test-retest repeatability data from 1st year of trial.
SRO-4.5.5	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-5.5	New Goal Identifier: SRO-4.5.5
SRO-5.6.2	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-6.2	New Goal Identifier: SRO-5.6.2
SRO-8.9.3	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-9.3	New Goal Identifier: SRO-8.9.3

For the non-scientific functional areas, three goals were achieved in FY 2006, and five new goals were added to the plan. The changes are summarized in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
CTR-2	Goal achieved and will be dropped.		
CTR-3	Goal achieved and will be dropped.		
CBRR-5	Goal achieved early and will be dropped.		
CBRR-3	End date revised to reflect completion of CRIS and movement into maintenance.	Streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS). (Ongoing)	By 2007, streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS).
CBRR-6	New goal added to the plan.		By 2010, build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.
CBRR-7	New goal added to the plan.		By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.
CBRR-8	New goal added to the plan.		By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.
CBRR-9	New goal added to the plan.		By 2010, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.
POI-9	New goal added to the plan.		By 2012, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors.
POI-5	New target added to the goal.		(Target 4) Better balance workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications (FY 2008 accomplished) (FY08) Implement changes to standing application receipt dates.
CBRR-1	Target revised due to PART measures.	(Target 1) Between 2004-2008, ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	(Target 1) Between 2006-2012, strive to ensure that the retention rate of former NRSA pre-doctoral trainees and fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of graduation) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12%

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
	Target revised due to PART measures.	(Target 2) Between 2004–2008, ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10% (FY08) N ≥ 10%	(Target 2) Between 2006-2012, strive to ensure that the retention rate of NRSA post-doctoral fellows (as indicated by applying for and receiving subsequent NIH support within 10 years of termination) is maintained relative to appropriate comparison groups. (FY06) N ≥ 12% (FY07) N ≥ 12% (FY08) N ≥ 12% (FY09) N ≥ 12% (FY10) N ≥ 12% (FY11) N ≥ 12% (FY12) N ≥ 12%
	Target deleted due to PART measures.	(Target 3) Between 2004-2007, ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments. (FY04) N ≥ 10% (FY05) N ≥ 10% (FY06) N ≥ 10% (FY07) N ≥ 10%	
	Target deleted due to PART measures.	(Target 4) By 2006, achieve 100% of the asymptotic (steady state) targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research. (FY04-FY06) Awards granted K23 120 K24 50 K30 50	
	Target deleted due to PART measures.	(Target 5) Between 2005–2008, provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity. (FY05) Estimate 1,500-2,000 positions (FY06) Estimate 1,500-2,000 positions (FY07) Estimate 1,500-2,000 positions (FY08) Estimate 1,500-2,000 positions	
	Target deleted due to PART measures.	(Target 6) Between 2004–2008, recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs. (FY04) 2,498 applications, 1,407 awards (56% success rate) (FY05) 3,290 applications, 1,600 awards (49% success rate) (FY06) Estimate 3,100-3,300 applications, 1,500-1,600 awards (FY07) Estimate 3,100-3,300 applications, 1,500-1,600 awards (FY08) Estimate 3,100-3,300 applications, 1,500-1,600 awards	

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
	Target deleted due to PART measures.	(Target 7) Between 2007-2011, build research capacity by providing more opportunities for new investigators to transition to independent research positions and subsequently apply for research project grant support. (FY07) Issue 150-200 new Pathway to Independence Awards (FY08) Issue 150-200 new Pathway to Independence Awards (FY09) Issue 150-200 new Pathway to Independence Awards • 75-80% of PI award recipients that complete the mentored phase of the award successfully transition to independent research positions. (FY10) Issue 150-200 new Pathway to Independence Awards • 75-80% of PI award recipients that complete the mentored phase of the award successfully transition to independent research positions • 65-70% of PI award recipients in independent research positions apply for research project grants. (FY11) Issue 150-200 new Pathway to Independence Awards • 75-80% of PI award recipients that complete the mentored phase of the award successfully transition to independent research positions • 65-70% of PI award recipients in independent research positions apply for research project grants.	
POI-8	Goal revised due to PART measures.	Protect NIH's interest in grant-supported real property supported under the extramural construction grant program, throughout each phase of the project. (Ongoing)	By 2010, protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements.
	Target deleted due to PART measures.	(Target 1) Between 2005-2008, meet 100% of pre-award requirements for construction grants or implement corrective strategies. -- Ensured the Availability of Matching Funds, when applicable -- Ensured Compliance with Public Policy Requirements -- Ensured Sufficient Title to Site	
	Target revised due to PART measures.	(Target 2) Between 2005-2008, for projects under construction, have met 100% of award requirements or implement corrective strategies. -- Approved Design and Construction Documents -- Ensured the Notice of Federal Interest has been Recorded	(Target 1) Through 2009, ensure that 100% of grantees have met all construction requirements, including NIH approved design and construction documents that ensures proposed research in the space is feasible, and ensures that grantees will take action to file or record a Notice of Federal Interest that ensures grantees cannot lease, sell or mortgage property without NIH approval.
	Target revised due to PART measures.	(Target 3) Between 2005-2008, meet 100% of post-award compliance measures, as defined by NIH Policies and Procedures, for completed construction grant projects or implement corrective strategies. -- Ensured Adequate Protection Against Physical Destruction -- Monitored the Use of Grant-supported Space	(Target 2) Through 2010, report on the percent of extramural construction projects that are in compliance with the post award 20 year usage requirement to conduct research.
SMHC-4	Target achieved and ended in 2005.	(Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	
	Target achieved and ended in 2005.	(Target 4) Evaluate transition services provided to employees.	

PROGRAM ASSESSMENT RATING TOOL (PART) SUMMARY

NIH has been PARTed in CY 2003, 2004, 2005, and 2006 with ratings above Moderately Effective achieving *Proud to Be* goals for the Research and Development Criteria under the President's Management Agenda. Each PARTed program has an approved efficiency measure. Below is a table showing the rating and improvement plan for each PARTed program.

YEAR	PROGRAM	RATING	PART IMPROVEMENT PLAN
FY 03	HIV/AIDS Research	Moderately Effective	• Initiating a Phase IIb trial of a promising vaccine candidate that may protect across viral clades (or subtypes). • Utilizing the enhanced ARIS database to track, monitor, and budget for trans-NIH AIDS research to more efficiently conduct portfolio analysis of 100% of expiring grants to reallocate resources.
FY 04	Extramural Research	Effective	• For at least one promising drug candidate for the treatment of AD, completing at least one of the four preclinical steps necessary for regulatory approval. • Reviewing and evaluating collectively, indicators of a diabetes clinical trial's progress to date to determine whether the science is progressing appropriately and whether the trial will be continued. • Using chemical libraries in high-throughput biological screens.
FY 05	Intramural Research	Effective	• Analyzing data from samples from additional populations to assess how well the genome-wide HapMap applies to additional diverse populations and how to choose HapMap SNPs to make them most useful. • Enabling a literature searching algorithm and user interface to identify and visualize relationships among known gene sets via query of PubMed. • Initiating preclinical studies on the nature of stem cell migration in adult tissue.
FY 05	Buildings & Facilities	Effective	• Ensuring that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an earned value analysis and management system. • Maintaining the condition of the existing infrastructure so that the average CI of all NIH facilities will be greater than or equal to 90 to comply with FRPC guidelines. • Managing all buildings and facilities projects so that they are completed within 100% of the final approved total project cost.
FY 06	Extramural Research Training and Research Career Development	Effective	• Ensuring that the proportion of post-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 12 percent within 10 years of termination. • Ensuring that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds the relevant comparison groups by 12% within 10 years of graduation. • Ensuring that 5% of trainee appointment forms are processed electronically, to enhance program management.
FY 06	Extramural Construction	Moderately Effective	• Ensuring that 100 percent of grantees meet all construction requirements. • Evaluating the self-certification process for monitoring the use of facilities for biomedical or behavioral research for at least twenty years after construction by the end of 2008. • Developing ways to achieve and improve the measurement of efficiency in the management of construction grants.

Program Assessment Rating Tool (PART) Summary Table CY 2002 - 2006

National Institutes of Health

CY 2002-2006

(Dollars in Millions)

Program	FY 2007 Continuing Resolution	FY 2008 Request	FY 2008 Request +/- FY 2007 CR	Narrative Rating
CY 2002 PARTs				
No programs PARTed				
CY 2003 PARTs				
HIV/AIDS Research	$2,903	$2,905	$2	Moderately Effective
CY 2004 PARTs				
Extramural Research	$21,220	$21,528	$308	Effective
CY 2005 PARTs				
Intramural Research	$2,867	$2,852	($15)	Effective
Buildings & Facilities	$178	$144	($35)	Effective
CY 2006 PARTs				
Extramural Research Training and Research Career Development	$1,345	$1,342	($3)	Effective
Extramural Construction	$25	$0	($25)	Moderately Effective

INDICES OF PERFORMANCE GOALS

The following tables provide a list of NIH's representative trans-NIH performance goals indexed by the disease or disorder category or topic and type of activity. The table lists the page numbers on which information related to this goal and or topic can be found.

Index by Functional Area and Goal Identifier

GPRA Goal	Disease/Disorder Categories or Topic	Types of Activity	Page Numbers
SRO-1.1	alcoholism	drug development animal models	19, 87
SRO-1.2	hearing impairment	device	19, 90
SRO-1.2.3	proteins, human genome informatics	research tool database genetics	21, 93
SRO-2.2	obesity	prevention, treatment	21, 97
SRO-2.3.2	antibiotic, biological pathogens	drug development	22, 101
SRO-2.3.4	HIV/AIDS	vaccine development	23, 105
SRO-2.4	symptom burden reduction	prevention, treatment	24, 110
SRO-3.1	Alzheimer's Disease	prevention, treatment	24, 113
SRO-3.2.1	transplantation, diabetes	treatment	25, 117
SRO-3.3	salivary	diagnostics	26, 121
SRO-3.5	substance abuse, psychiatric disorders	genetics	27, 124
SRO-3.6	stem cell mobility, cardiovascular	imaging technology	28, 127
SRO-4.5.1	HIV/AIDS	drug development	28, 131
SRO-4.5.4	molecules, nervous system diseases	diagnostics drug development	29, 136
SRO-4.5.5	drug abuse, community settings	treatment, clinical trials	30, 140
SRO-5.2	atherosclerosis, lupus, children	drug testing, treatment, clinical trials	31, 144
SRO-5.3	chemical libraries	basic research	32, 148
SRO-5.6	tobacco addiction	drug development	33, 151
SRO-5.6.2	cardiovascular, diabetes, kidney disease	treatment	33, 155
SRO-5.7	cancer	imaging technology	34, 160
SRO-5.8	hot flashes	diagnostic device	35, 164
SRO-5.9	health disparities	genetics	35, 167
SRO-6.1	macular degeneration, glaucoma	genetics	36, 172
SRO-6.3	chemical effects, toxicogenomics	research database	36, 175
SRO-6.4	asthma	prevention, treatment	37, 179
SRO-7.2	cancer, nanotechnology	diagnostics	38, 182
SRO-7.8.1	infectious disease	research resources	38, 185
SRO-7.8.3	genomic research informatics	research tool database genetics	40, 188
SRO-8.2	bone mass, skeletal system	animal models	41, 192

GPRA Goal	Disease/Disorder Categories or Topic	Types of Activity	Page Numbers
SRO-8.4	competitive investigators	impact assessment	42, 196
SRO-8.5	non-specific symptoms	research tool database impact assessment	42, 200
SRO-8.6	vision impairment	population-based research	43, 204
SRO-8.9.1	depression, comorbidity, years lost to disability	prevention, diagnostics, drug development, treatment	43, 207
SRO-8.9.2	stroke, minority health	prevention	44, 211
SRO-8.9.3	normal brain development, children	research tool database	45, 215
SRO-9.4	cytomegalovirus, hearing loss	diagnostics	45, 219
CTR-1	SIDS	prevention	47, 222
CTR-2	stroke	prevention	48, 226
CTR-3	technology transfer	technology	48, 231
CTR-4	SBIR/STTR	management	49, 236
CTR-5	knowledge management	technology	51, 240
CBRR-1	Training	impact assessment	52, 246
CBRR-2	NIH Business System	technology	56, 250
CBRR-3	Clinical Research Information System	bioinformatics	57, 255
CBRR-4	electronic Research Administration	database	58, 258
CBRR-5	informatics	training	59, 263
CBRR-6	extramural construction	management	60, 268
CBRR-7	HIV/AIDS	database	61, 271
CBRR-8	training	database	62, 275
CBRR-9	extramural construction	technology	62, 277
SMHC-3	human resources	management	64, 282
SMHC-4	competitive sourcing	management	65, 287
SMHC-5	human resources	technology	66, 290
POI-1	Building & Facilities	database	68, 296
POI-2	performance based contracting	management	68, 299
POI-5	extramural research	impact assessment	69, 302
POI-6	Building & Facilities	management	72, 308
POI-7	Building & Facilities	management	74, 311
POI-8	extramural construction	management	76, 314
POI-9	intramural research	management	78, 318

Index by IC and Goal Identifier

IC/Office	Goals	Page Number
NCI	SRO-5.7	34, 160
	SRO-7.2	38, 182
	SRO-2.2	21, 97
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-4.5.4	29, 136
	SRO-5.6	33, 151
	SRO-5.9	35, 167
	SRO-8.9.1	43, 207
	POI-8	80, 314
NEI	SRO-6.1	36, 172
	SRO-8.6	43, 204
	SRO-4.5.1	28, 131
	POI-8	76, 314
NHLBI	SRO-3.6	28, 127
	SRO-6.4	37, 179
	SRO-2.2	21, 97
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-5.6.2	33, 155
	SRO-5.9	35, 167
	SRO-8.9.2	44, 211
	POI-8	76, 314
NHGRI	SRO-5.9	35, 167
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-7.8.1	38, 185
NIA	SRO-3.1	24, 113
	SRO-4.5.4	29, 136
NIAAA	SRO-1.1	19, 87
	SRO-3.5	27, 124
	SRO-4.5.1	28, 131
	SRO-4.5.4	29, 136
	SRO-4.5.5	30, 140
	SRO-6.3	36, 175
	SRO-8.9.1	43, 207
NIAID	SRO-2.3.2	22, 101
	SRO-2.3.4	23, 105
	SRO-3.2.1	25, 117
	SRO-4.5.1	28, 131
	SRO-7.8.1	38, 185
	SRO-5.2	31, 144

IC/Office	Goals	Page Number
	SRO-6.4	37, 179
	CBRR-6	60, 268
	CBRR-9	62, 277
	POI-8	76, 314
NIAMS	SRO-5.2	31, 144
	SRO-8.2	41, 192
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-8.5	42, 200
NIBIB	SRO-3.1	24, 113
	SRO-3.2.1	25, 117
	SRO-4.5.1	28, 131
	SRO-4.5.4	29, 136
	SRO-5.3	32, 148
	SRO-5.7	34, 160
	SRO-7.2	38, 182
	CBRR-5	59, 263
NICHD	SRO-8.9.3	45, 215
	SRO-2.2	21, 97
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	CTR-1	47, 222
NIDA	SRO-4.5.5	30, 140
	SRO-5.6	33, 151
	SRO-1.1	19, 87
	SRO-2.3.4	23, 105
	SRO-3.5	27, 124
	SRO-4.5.1	28, 131
	SRO-4.5.4	29, 136
	POI-8	76, 314
NIDCD	SRO-1.2	19, 90
	SRO-9.4	45, 219
	SRO-2.3.4	23, 105
NIDCR	SRO-3.3	26, 121
	SRO-2.3.2	22, 101
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-7.8.1	38, 185
	SRO-8.2	41, 192
NIDDK	SRO-2.2	21, 97
	SRO-5.6.2	33, 155
	SRO-3.2.1	25, 117
	SRO-4.5.1	28, 131
	SRO-5.9	35, 167

IC/Office	Goals	Page Number
NIEHS	SRO-6.3	36, 175
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
NIGMS	SRO-5.3	32, 148
	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	CBRR-5	59, 263
NIMH	SRO-8.9.1	43, 207
	SRO-1.1	19, 87
	SRO-3.1	24, 113
	SRO-3.5	27, 124
	SRO-4.5.1	28, 131
	SRO-4.5.4	29, 136
	SRO-8.9.3	45, 215
NINDS	SRO-4.5.4	29, 136
	SRO-8.9.2	44, 211
	SRO-2.4	24, 110
	SRO-3.1	24, 113
	SRO-4.5.1	28, 131
	SRO-8.9.1	43, 207
	SRO-8.9.3	45, 215
	CTR-2	48, 226
NINR	SRO-2.4	24, 110
	SRO-4.5.1	28, 131
	SRO-8.9.2	44, 211
NLM	SRO-1.2.3	21, 93
	SRO-7.8.3	40, 188
	CBRR-5	59, 263
	CTR-1	47, 222
FIC	SRO-2.3.4	23, 105
	SRO-4.5.1	28, 131
	SRO-5.3	32, 148
NCCAM	SRO-5.8	35, 164
	SRO-4.5.1	28, 131
NCMHD		
NCRR	SRO-8.4	42, 196
	SRO-2.3.4	25, 105
	SRO-4.5.1	28, 131
	SRO-8.9.2	44, 211
	CBRR-6	60, 268
	CBRR-9	63, 277
	POI-8	76, 314
Roadmap	SRO-8.5	42, 200
	SRO-5.3	32, 148

Index by Disease/Disorder Categories or Topics

Disease/Disorder Categories or Topic	Types of Activity	GPRA Goal	Page Numbers
alcoholism	drug development animal models	SRO-1.1	19, 87
Alzheimer's Disease	prevention, treatment	SRO-3.1	24, 113
antibiotic	drug development	SRO-2.3.2	22, 101
asthma	prevention, treatment	SRO-6.4	37, 179
atherosclerosis	drug testing, treatment, clinical trials	SRO-5.2	31, 144
biological pathogens	drug development	SRO-2.3.2	22, 101
bone mass	animal models	SRO-8.2	41, 192
Building & Facilities	database	POI-1	68, 296
Building & Facilities	management	POI-6	72, 308
Building & Facilities	management	POI-7	74, 311
cancer	imaging technology	SRO-5.7	34, 160
cancer	diagnostics	SRO-7.2	38, 182
cardiovascular	treatment	SRO-5.6.2	33, 155
cardiovascular	imaging technology	SRO-3.6	28, 127
chemical effects	research database	SRO-6.3	36, 175
chemical libraries	basic research	SRO-5.3	32, 148
children	drug testing, treatment, clinical trials	SRO-5.2	31, 144
children	research tool database	SRO-8.9.3	45, 215
Clinical Research Information System	bioinformatics	CBRR-3	57, 255
community settings	treatment, clinical trials	SRO-4.5.5	30, 140
comorbidity	prevention, diagnostics, drug development, treatment	SRO-8.9.1	43, 207
competitive investigators	impact assessment	SRO-8.4	42, 196
competitive sourcing	management	SMHC-4	65, 287
cytomegalovirus	diagnostics	SRO-9.4	45, 219
depression	prevention, diagnostics, drug development, treatment	SRO-8.9.1	43, 207
diabetes	treatment	SRO-5.6.2	33, 155
diabetes	treatment	SRO-3.2.1	25, 117
drug abuse	treatment, clinical trials	SRO-4.5.5	30, 140
electronic Research Administration	database	CBRR-4	58, 258
extramural construction	management	CBRR-6	60, 268
extramural construction	technology	CBRR-9	62, 277

Disease/Disorder Categories or Topic	Types of Activity	GPRA Goal	Page Numbers
extramural construction	management	POI-8	76, 314
extramural research	impact assessment	POI-5	69, 302
genomic research	research tool database genetics	SRO-7.8.3	40, 188
glaucoma	genetics	SRO-6.1	36, 172
health disparities	genetics	SRO-5.9	35, 167
hearing impairment	device	SRO-1.2	19, 90
hearing loss	diagnostics	SRO-9.4	45, 219
HIV/AIDS	vaccine development	SRO-2.3.4	23, 105
HIV/AIDS	drug development	SRO-4.5.1	28, 131
HIV/AIDS	database	CBRR-7	61, 271
hot flashes	diagnostic device	SRO-5.8	35, 164
human genome	research tool database genetics	SRO-1.2.3	21, 93
human resources	management	SMHC-3	64, 282
human resources	technology	SMHC-5	66, 290
infectious disease	research resources	SRO-7.8.1	38, 185
informatics	research tool database genetics	SRO-7.8.3	40, 188
informatics	research tool database genetics	SRO-1.2.3	21, 93
informatics	training	CBRR-5	59, 263
intramural research	management	POI-9	78, 318
kidney disease	treatment	SRO-5.6.2	33, 155
knowledge management	technology	CTR-5	51, 240
lupus	drug testing, treatment, clinical trials	SRO-5.2	31, 144
macular degeneration	genetics	SRO-6.1	36, 172
minority health	prevention	SRO-8.9.2	44, 211
molecules	diagnostics drug development	SRO-4.5.4	29, 136
nanotechnology	diagnostics	SRO-7.2	38, 182
nervous system diseases	diagnostics drug development	SRO-4.5.4	29, 136
NIH Business System	technology	CBRR-2	56, 250
non-specific symptoms	research tool database impact assessment	SRO-8.5	42, 200
normal brain development	research tool database	SRO-8.9.3	45, 215
obesity	prevention, treatment	SRO-2.2	21, 97
performance based contracting	management	POI-2	68, 299
proteins	research tool database genetics	SRO-1.2.3	21, 93

Disease/Disorder Categories or Topic	Types of Activity	GPRA Goal	Page Numbers
psychiatric disorders	genetics	SRO-3.5	27, 124
salivary	diagnostics	SRO-3.3	26, 121
SBIR/STTR	management	CTR-4	49, 236
SIDS	prevention	CTR-1	47, 222
skeletal system	animal models	SRO-8.2	41, 192
stem cell mobility	imaging technology	SRO-3.6	28, 127
stroke	prevention	SRO-8.9.2	44, 211
stroke	prevention	CTR-2	48, 226
substance abuse	genetics	SRO-3.5	27, 124
symptom burden reduction	prevention, treatment	SRO-2.4	24, 110
technology transfer	technology	CTR-3	48, 231
tobacco addiction	drug development	SRO-5.6	33, 151
toxicogenomics	research database	SRO-6.3	36, 175
training	impact assessment	CBRR-1	52, 246
training	database	CBRR-8	62, 275
transplantation	treatment	SRO-3.2.1	25, 117
vision impairment	population-based research	SRO-8.6	43, 204
years lost to disability	prevention, diagnostics, drug development, treatment	SRO-8.9.1	43, 207

Index by Types of Activity

Types of Activity	Disease/Disorder Categories or Topic	GPRA Goal	Page Numbers
animal models	alcoholism	SRO-1.1	20, 87
animal models	bone mass, skeletal system	SRO-8.2	41, 192
basic research	chemical libraries	SRO-5.3	32, 148
bioinformatics	Clinical Research Information System	CBRR-3	57, 255
clinical trials	drug abuse, community settings	SRO-4.5.5	30, 140
clinical trials	atherosclerosis, lupus, children	SRO-5.2	31, 144
database	electronic Research Administration	CBRR-4	58, 258
database	HIV/AIDS	CBRR-7	61, 271
database	training	CBRR-8	62, 275
database	Building & Facilities	POI-1	68, 296
device	hearing impairment	SRO-1.2	19, 90
diagnostic device	hot flashes	SRO-5.8	35, 164
diagnostics	salivary	SRO-3.3	26, 121
diagnostics	molecules, nervous system diseases	SRO-4.5.4	29, 136
diagnostics	cancer, nanotechnology	SRO-7.2	38, 182
diagnostics	depression, comorbidity, years lost to disability	SRO-8.9.1	43, 207
diagnostics	cytomegalovirus, hearing loss	SRO-9.4	45, 219
drug development	alcoholism	SRO-1.1	19, 87
drug development	antibiotic, biological pathogens	SRO-2.3.2	22, 101
drug development	HIV/AIDS	SRO-4.5.1	28, 131
drug development	molecules, nervous system diseases	SRO-4.5.4	29, 136
drug development	tobacco addiction	SRO-5.6	33, 151
drug development	depression, comorbidity, years lost to disability	SRO-8.9.1	43, 207
drug testing	atherosclerosis, lupus, children	SRO-5.2	31, 144
genetics	proteins, human genome informatics	SRO-1.2.3	21, 93
genetics	substance abuse, psychiatric disorders	SRO-3.5	27, 124
genetics	health disparities	SRO-5.9	35, 167
genetics	macular degeneration, glaucoma	SRO-6.1	37, 172
genetics	genomic research informatics	SRO-7.8.3	40, 188

Types of Activity	Disease/Disorder Categories or Topic	GPRA Goal	Page Numbers
imaging technology	stem cell mobility, cardiovascular	SRO-3.6	28, 127
imaging technology	cancer	SRO-5.7	34, 160
impact assessment	competitive investigators	SRO-8.4	42, 196
impact assessment	non-specific symptoms	SRO-8.5	42, 200
impact assessment	Training	CBRR-1	52, 246
impact assessment	extramural research	POI-5	69, 302
management	SBIR/STTR	CTR-4	49, 236
management	extramural construction	CBRR-6	60, 268
management	human resources	SMHC-3	64, 282
management	competitive sourcing	SMHC-4	65, 287
management	performance based contracting	POI-2	68, 299
management	Building & Facilities	POI-6	72, 308
management	Building & Facilities	POI-7	74, 311
management	extramural construction	POI-8	76, 314
management	intramural research	POI-9	78, 318
population-based research	vision impairment	SRO-8.6	43, 204
prevention	obesity	SRO-2.2	21, 97
prevention	symptom burden reduction	SRO-2.4	24, 110
prevention	Alzheimer's Disease	SRO-3.1	24, 113
prevention	asthma	SRO-6.4	37, 179
prevention	depression, comorbidity, years lost to disability	SRO-8.9.1	43, 207
prevention	stroke, minority health	SRO-8.9.2	44, 211
prevention	SIDS	CTR-1	47, 222
prevention	stroke	CTR-2	48, 226
research database	chemical effects, toxicogenomics	SRO-6.3	37, 175
research resources	infectious disease	SRO-7.8.1	38, 185
research tool database	proteins, human genome informatics	SRO-1.2.3	21, 93
research tool database	genomic research informatics	SRO-7.8.3	40, 188
research tool database	non-specific symptoms	SRO-8.5	42, 200
research tool database	normal brain development, children	SRO-8.9.3	45, 215
technology	technology transfer	CTR-3	48, 231
technology	knowledge management	CTR-5	51, 240
technology	NIH Business System	CBRR-2	56, 250
technology	extramural construction	CBRR-9	62, 277
technology	human resources	SMHC-5	66, 290
training	informatics	CBRR-5	59, 263
treatment	obesity	SRO-2.2	21, 97

Types of Activity	Disease/Disorder Categories or Topic	GPRA Goal	Page Numbers
treatment	symptom burden reduction	SRO-2.4	24, 110
treatment	Alzheimer's Disease	SRO-3.1	24, 113
treatment	transplantation, diabetes	SRO-3.2.1	25, 117
treatment	drug abuse, community settings	SRO-4.5.5	30, 140
treatment	atherosclerosis, lupus, children	SRO-5.2	31, 144
treatment	cardiovascular, diabetes, kidney disease	SRO-5.6.2	33, 155
treatment	asthma	SRO-6.4	37, 179
treatment	depression, comorbidity, years lost to disability	SRO-8.9.1	43, 207
vaccine development	HIV/AIDS	SRO-2.3.4	23, 105