NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2009

Online Performance Appendix

NATIONAL INSTITUTES OF HEALTH
FY 2009 ONLINE PERFORMANCE APPENDIX

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INTRODUCTION

The Online Performance Appendix is one of several documents that fulfill the Department of Health and Human Services' (HHS') performance planning and reporting requirements. HHS achieves full compliance with the Government Performance and Results Act of 1993 and Office of Management and Budget Circulars A-11 and A-136 through HHS agencies' FY 2009 Congressional Justifications and Online Performance Appendices, the Agency Financial Report and the HHS Performance Highlights. These documents can be found at: http://www.hhs.gov/budget/docbudget.htm and http://www.hhs.gov/afr/.

The Performance Highlights briefly summarizes key past and planned performance and financial information. The Agency Financial Report provides fiscal and high-level performance results. The FY 2009 Department's Congressional Justifications fully integrate HHS' FY 2007 Annual Performance Report and FY 2009 Annual Performance Plan into its various volumes. The Congressional Justifications are supplemented by the Online Performance Appendices. Where the Justifications focus on key performance measures and summarize program results, the Appendices provide performance information that is more detailed for all HHS measures.

The National Institutes of Health Congressional Justification and Online Performance Appendix can be found at http://nihperformance.nih.gov/ and http://officeofbudget.od.nih.gov/.

OVERVIEW

The National Institutes of Health FY 2009 Online Performance Appendix contains the Performance Detail information for each of NIH's performance goals. It 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. It includes the Performance Goal Narratives which depicts the story of scientific discovery for each goal.

Functional Areas for NIH Activities

The NIH achieves its mission through a single overarching 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.

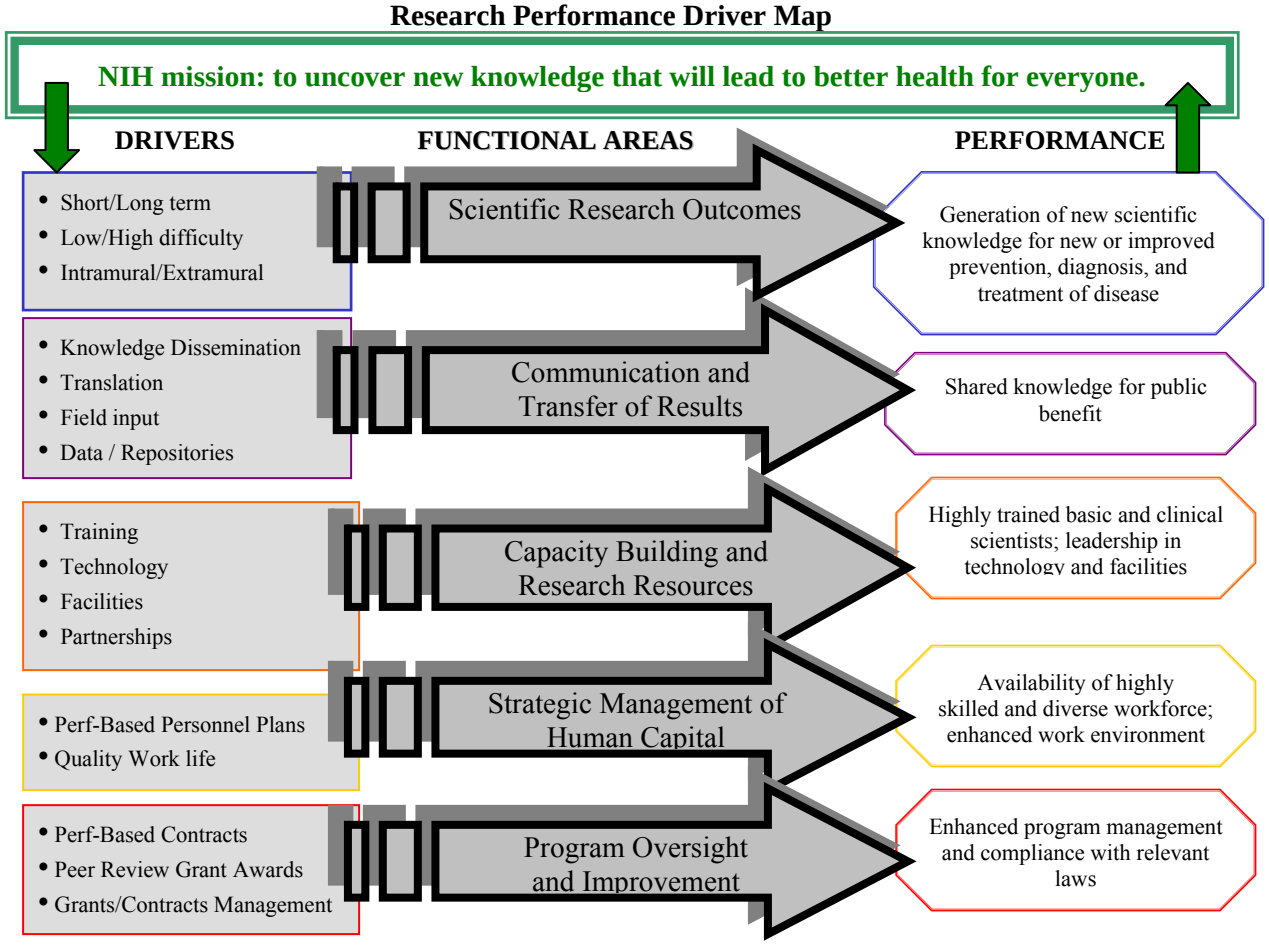
- *Capacity Building and Research Resources (CBRR).* The productivity of the research enterprise depends in large measure on the strength of the talent pool and on the technological and other research resources available for use in investigations. Support for pre-doctoral and

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.

PERFORMANCE GOALS BY FUNCTIONAL AREA SUMMARY TABLE						
FUNCTIONAL AREA	**PERFORMANCE GOALS**					
	FY04	**FY05**	**FY06**	**FY07**	**FY08**	**FY09**
Scientific Research Outcomes	28	36	35	36	44	47
Communication and Transfer of Results	4	5	5	4	5	4
Capacity Building and Research Resources	4	5	8	7	7	8
Strategic Management of Human Capital	2	3	3	3	3	5
Program Oversight and Improvement	3	7	7	7	6	6
Totals	41	56	58	57	65	70



This graphic is a logic model that depicts the inputs and outputs for each Functional Area. It is a representation of the Functional Areas described in the preceding paragraphs.

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. Each goal has a narrative that describes the impetus for the goal as well as the implementation plan to achieve the goal. The narrative contains the background/state-of-the-field, rationale for the goal, target context and conditions, an annual target table, 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. To simplify reporting, completion of the goal becomes the expected annual target for the end year of the goal.

The FY 2007 performance summary is provided with target achievements, associated budgets, and other advances. If a target is achieved efficiently, a short narrative description is provided. 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 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.

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. 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 36 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.

- *The Four Ps – Preemptive, Predictive, Personalized, Participatory.* The Scientific Research Outcomes represent the continuum of scientific discovery, which support the Four Ps of the NIH Core Strategic Vision, and promote the transformation to precision medicine:
  - Transform medicine and health from a Curative to a Preemptive paradigm (**P**reemptive)
  - Support basic research to identify the earliest molecular stages of disease in complex biological systems (**P**redictive)

- Accelerate translation of findings from the bench to the bedside to the community (**P**ersonalized)
- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system (**P**articipatory)

- *Target Adjustments.* The prospective target-based approach for science requires flexibility to reflect the discovery process. If an annual target is adjusted, it incorporates new knowledge and redirects performance towards achieving the best science of 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 and the establishment of new goals occurring as needed in order to achieve the intended outcome of the goal. Programs that perform well are sustained if funding is available and the research is continued to be deemed relevant. Poorly performing programs are corrected to overcome deficiencies or funding is shifted to higher priority projects.

SUMMARY OF NIH MEASURES AND TARGET RESULTS

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
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	57	71	76 (+2 FY05 & 3 FY06 extended)	107%	66	1	9	88%
2008	65	79			Performance results will be reported in February 2009.			
2009	70	77			Performance results will be reported in February 2010.			

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

PERFORMANCE DETAIL
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 32 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 difficulty (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

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
High	**1.1** By 2008, 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. **1.3** By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement. **1.4** By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders.	**2.1** By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials. **2.2** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2.4** 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. **2.5** By 2011, identify and evaluate 5 novel molecular-targeted interventions for cancer, and determine suitability for use in early phase clinical trials. **2.6** By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways. **2.7** By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others. **2.8** By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.	**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** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **3.3** By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. **3.4** By 2010, develop an HIV/AIDS vaccine. **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. **3.7** By 2019, develop at least two novel therapies for immune-mediated disease. **3.8** By 2016, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment.
Medium	**4.3** By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults. **4.4** By 2011, identify or study additional genes involved in communication disorders in humans and animal models. **4.5** By 2011, identify genetic and environmental factors which predispose to three complex diseases.	**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. **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. **5.4** By 2007, identify 20 small molecules that are	**6.1** By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. **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. **6.3** By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach. **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

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
		active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools. **5.5** By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings. **5.6** By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction. **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 2012, 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. **5.10** By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures. **5.11** By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes. **5.12** By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders.	treating asthma exacerbations. **6.5** By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks. **6.6** By 2015, provide at least one new or significantly improved minimally-invasive treatment for clinical use in patients using image-guided interventions.
Low	**7.4** By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis. **7.5** By 2009, determine the feasibility of applying at least 2 tailored interventions designed to prevent dental caries in one or more underserved populations. **7.7** By 2011, assess community-based methods for facilitating cancer research and	**8.1** By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases. **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	**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). **9.2** By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities. **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

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
	providing patients access to optimal cancer care.	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). **8.7** By 2012, identify three (3) effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice. **8.8** By 2012, identify at least one candidate intervention that extends median lifespan in an animal model.	database of MRI and clinical/behavioral data and analytical software. **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. **9.5** By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.

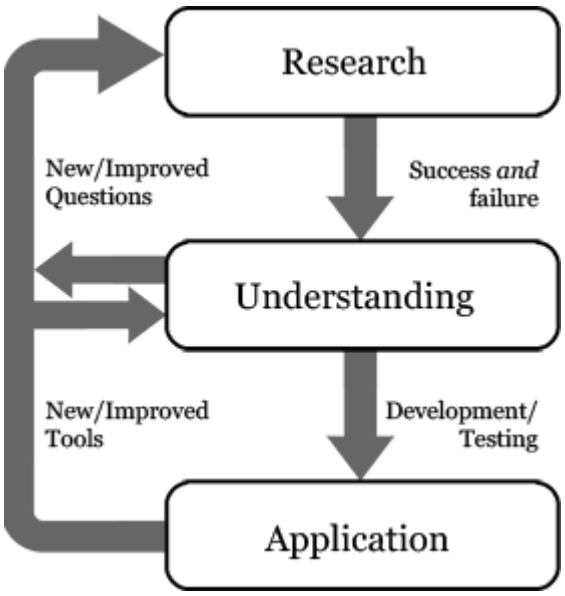
The matrix of goals selected by NIH reflects the challenges of complex biological systems. They range across a continuum of low to medium to high difficulty, and they have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes high-difficulty 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-difficulty goal in the early stages cannot be guaranteed. In contrast, NIH low-difficulty goals usually have a long history associated with the scientific effort, and the knowledge base has known parameters. With low-difficulty 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-difficulty/ambitious goals as well as low-difficulty/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 uncertainty 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 may not 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. The trend has been that time lags occur 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. 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. NIH is committed to a well-honed system of peer review that NIH can maintain its focus on supporting research of the highest possible quality. On June 8, 2007, NIH Director, Dr. Elias Zerhouni, called upon leaders from across the scientific community and NIH to join a trans-NIH effort to examine the two-level NIH peer review system with the goal of optimizing its efficiency and effectiveness, and to ensure that the NIH will be able to continue to meet the needs of the research community and public-at-large. The effort involves both external and internal working groups. In parallel, the Center for Scientific Review (CSR) has launched several peer review pilots and initiatives, which will help inform the ongoing effort. Once the diagnostic phase is complete, analyses and summaries of the various inputs, data collected and breadth of ideas will be provided to NIH leadership to determine next steps, including piloting and associated evaluations.

SRO-1.1	**By 2008, 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. Nearly 18 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

Target Context and Conditions

Three strategies have been identified. First, NIH prepared a clinical protocol to test rimonabant for its ability to reduce alcohol drinking and a phase I/II clinical study of rimonabant was recently completed. 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 was completed in 2007. Third, NIH designed a protocol to be used for testing antalarmin in alcoholics for relapse prevention and reduced alcohol drinking. This step is ambitious because of the normal risks associated with any medications development program.

Baseline: 2007

- (FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking
- (FY06) Toxicology studies of antalarmin have been performed in monkeys and a phase IIa clinical trial of rimonabant has been conducted.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) A toxicologic evaluation on antalarmin has been completed.	(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.	(MET) Toxicology studies of antalarmin in non-human primates were conducted as required by FDA.	(Target 1) Test antalarmin for relapse prevention in alcoholics. (Target 2) 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.	(MET) Rat models failed to move to clinical trials. Therefore non-human primates were used to test antalarmin. (EXT) A Phase I/II clinical trial of rimonabant was conducted. For the drug antalarmin, the FDA must approve the IND application before a Phase I clinical trial can be conducted.	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.	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$2,300	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target, extended from FY05, was MET. The results of the initial toxicology studies of antalarmin indicated further evaluation of the compound was warranted, so testing in humans was deferred until its toxicological effects could be evaluated further in monkeys as required by the FDA. The use of non-human primates was expected to provide a more accurate prediction of how humans would respond to antalarmin. In this study a range of doses were evaluated and an exposure level that produced no significant adverse effects in non-human primates was established; therefore, antalarmin is ready to be evaluated in a Phase I clinical trial.

The FY07 target to begin Phase I and II trials of two potential treatments will be EXTENDED to FY2008. While one of the drugs, Rimonabant, completed Phase I/II trials, the other drug awaits FDA approval of an IND application. Rimonabant, a drug approved for clinical testing in other diseases, was tested for its effectiveness in reducing alcohol consumption and craving in heavy social drinkers. A Phase I/II clinical trial was completed in 2007 and in this study rimonabant showed no statistically significant effect on reducing alcohol consumption. However, there was a trend toward reduction of the number of drinks consumed. Considering the well documented ability of rimonabant to reduce alcohol drinking in animal models, further testing of rimonabant for the treatment of alcoholism appears to be justified. Although rimonabant was not effective under the experimental conditions tested, the results will be used to improve the experimental design of future studies.

The second drug, antalarmin, has not yet begun its Phase I/II trials, but is expected to in the next year. In order for the trial to be conducted, an Investigational New Drug (IND) application to the FDA must be approved. An IND application for antalarmin is being prepared by the NIH and is expected to be submitted to the FDA by January/February 2008. If approved, a Phase I clinical trial to test the efficacy of antalarmin in preventing relapse in alcoholic patients could begin in 2008. Therefore, achievement of this goal is dependent on the approval of the IND by the Food and Drug Administration.

Advances or Other Highlights

In support of this goal in medications development, other compounds have been validated in animal models and advanced to the next stage of development in humans. In October 2007, a drug that acts in the same pathway as antalarmin by blocking the CRH1 receptor entered a Phase I clinical trial.

SRO-1.3	**By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement.**

BACKGROUND

Often times, individuals who suffer and survive a stroke, survive with hemiparesis (muscular weakness or partial paralysis on one side of the body). Recent studies have shown that rehabilitation therapy that involves practicing a functional arm movement repeatedly can enhance recovery of arm function for certain stroke survivors. In an effort to speed the rehabilitation process to enable individuals to regain function of the arm, NIH-supported researchers are developing upper extremity exoskeleton robots—a device that patients can wear around the arm, like a brace. Such a device would help the patient move the affected arm when practicing repetitive motions. Existing robots are expensive, powered by large power sources, and are too complex for clinical or home use. Recently, researchers began making strides in overcoming the challenge of reducing the sheer size of the robot by designing devices that can be powered with compressed air (pneumatics). Further development that leads to low-cost robotic exoskeletons holds the promise of providing therapeutic activities at the clinic or at home for a range of stroke patients.

Prevalence/Incidence

Stroke is a leading cause of serious, long-term disability in the United States. The American Heart Association notes that each year about 700,000 people have a new or recurrent stroke.

Disease Burden

The American Heart Association estimates that the direct and indirect cost of stroke in the United States for 2007 is $62.7 billion.

Rationale

Rehabilitation therapy is beneficial but requires much time and energy, not only from the individual seeking to regain function in the arm, but also from the skilled physical therapists who spend many hours helping patients repeatedly move the arm. To improve this rehabilitation process, the NIH is developing robotic devices that would enable patients to practice functional arm movements on their own. By enabling patients to practice rehabilitation exercises that have been programmed in a robotic device, not only may the patient regain function of the arm more quickly than with conventional physical therapy sessions, but the costs of physical therapy for the patient could also decrease.

While there are preliminary research findings that suggest the robotic devices would be useful, the challenge is to develop a device in such a way so that patients will have access to it, for example at a clinic. NIH-supported researchers are now tackling this challenge by developing a portable robotic device that can be programmed to deliver aid to a patient undergoing a rehabilitative therapy program.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH is developing robotic exoskeletons for clinical rehabilitation of upper extremity movement. Currently, the robotic devices can be programmed for repetitive exercises. The next steps involve engineering the device to respond to the patient's progress so that the device provides more aid and support in the beginning of the rehabilitation process and less aid as the patient regains arm function. Researchers are also developing feedback programs that will enable the device to sense the intent of the patient. For instance, when reaching for an item or when eating, the device will enable the patient to complete that particular task.

The immediate short-term and high risk goal will involve developing a device that will accommodate and control a broad range of naturalistic arm movements to enable the patient to practice functional movements needed in daily living activities. A suite of control and assessment software will be developed to allow treatment planning and evaluation, such as assessing a patient's current level of function, and to provide feedback to patients. Researchers will also refine the device design using feedback from periodic clinician/patient focus groups. These steps will lead to the development of a device to the point where researchers can execute a preliminary study to demonstrate the effectiveness of the device in retraining arm movement after chronic stroke in the clinic.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Develop a suite of control and assessment software to allow treatment planning and evaluation.	Refine the device design and software using feedback from periodic clinician/patient focus groups.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$1,537	$547

SRO-1.4	**By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders.**

BACKGROUND

Alcohol-induced disorders, including organ damage and addiction, reflect both the genetic make-up and the cumulative responses to alcohol exposure and environmental perturbations over time (epigenetic), with each individual factor, whether genetic or environmental, generally contributing only a small fraction to the overall symptoms or phenotypes. Alcohol exerts its effects at the DNA, RNA and protein levels as well as the systems level where alterations in multiple biochemical, metabolic, or signaling pathways result in the dysfunction of many different cells and tissues. This high degree of complexity in alcohol-induced disorders limits the utility of traditional gene-by-gene studies that provide only a fragmented view of a complex picture. Thus, global approaches such as gene expression profiling are essential to capture the full complexity of alcohol-induced disorders. Gene expression profiling surveys the whole genome and has the potential to capture alterations in expression patterns of a broad range of genes associated with susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. Identifying variations in gene expression patterns will advance the understanding of the etiology of these disorders and, more importantly, will provide new avenues for diagnosis, prognosis, and therapeutic intervention of these disorders, and ultimately, lead to personalized medicine.

Prevalence/Incidence

Alcohol use disorders (AUDs) encompass alcohol abuse and alcohol dependence, and arise from drinking too much, too fast and/or too often. In 2003, the worldwide prevalence of AUDs was estimated at 1.7%, accounting for 1.4% of the total world disease burden in developed countries. In the United States, 18 million Americans (8.5% of the population age 18 and older) suffer from AUDs. Only 7.1% of these individuals received any treatment for their AUD in the past year. In addition, the prevalence of drinking, especially binge drinking (i.e., drinking five or more drinks on one occasion), puts adolescents at risk for developing AUDs. For example, almost 30% of 9th to 12th graders report binge drinking at least one day of the previous month.

In addition to the adverse health effects that result directly from excessive alcohol consumption, AUDs often co-occur in individuals who abuse other drugs, in people with psychiatric disorders, and in people who smoke tobacco. An estimated 90% of cocaine addicts have alcohol problems and as many as 60% of patients at community mental health centers have co-morbid alcohol and other drug abuse disorders. Individuals diagnosed with severe mental illness are more likely to experience a co-occurring substance abuse disorder. For example, women with bipolar disorder are 7 times more likely to be alcohol dependent than women without psychiatric diagnoses. Research on individuals who smoke and drink shows an estimated 50% to 90% of alcohol dependent individuals are heavy smokers who become more addicted to nicotine and are less successful at quitting smoking than other smokers. This puts them at a high risk for certain cancers and cardiovascular diseases that develop more readily in the presence of both alcohol and nicotine.

Disease Burden

Excessive alcohol consumption often leads to adverse health effects and medical conditions, resulting in significant economic and public health burdens to our society. These medical conditions include addiction as well as alcohol-induced organ damage such as liver disease (hepatosteatosis, inflammatory disease, alcoholic hepatitis and cirrhosis), pancreatitis, cardiomyopathy (disease of the heart muscle), fetal abnormalities, and brain damage. Excessive alcohol use is also associated with an increased risk for some types of cancer. According to the Centers for Disease Control and Prevention, excessive alcohol consumption is the number-three cause of preventable death in the U.S., after tobacco and diet/activity patterns. The World Health Organization also ranks alcohol third among preventable risk factors for premature death in developed nations, after tobacco and hypertension. Problems related to the excessive consumption of alcohol cost U.S. society an estimated $185 billion annually due to lost productivity, medical costs and other factors.

Rationale

Characterization of variations in gene expression patterns will provide information about how alcohol alters gene expression and will improve the understanding of the mechanisms that underlie alcohol-induced disorders. The aim of this goal is to identify signature gene expression patterns that are associated with alcohol-induced disorders using peripheral tissues from individuals with and without AUDs. The rationale is three-fold. (1) Gene expression profiling is a global approach that can capture the complexity of AUDs and provide signature gene expression patterns associated with the susceptibility, initiation, progression, and pathogenesis of these disorders. (2) A critical barrier for the translational research of alcohol-induced disorders is the unavailability of diseased tissues, such as brain samples from living human subjects with AUDs. The proposed studies on peripheral tissues or cell lines derived from lymphoblastoid cells (a type of immortalized white blood cells) from individuals with AUDs provide unlimited resources for a wide range of studies and offer the ease of experimental standardization and manipulation. Currently, there are over 145,000 immortalized lymphoblastoid cell lines available from NIH-funded repositories, including cell lines derived from individuals with AUDs, and a large amount of clinical, behavioral, and genetic data is available. (3) Immortalized lymphoblastoid cell lines and peripheral tissues have been increasingly utilized successfully to identify gene expression signatures associated with complex diseases, such as autism, schizophrenia, drug dependence, and obesity, especially for those research areas where diseased tissue from patients is not available.

PERFORMANCE ANALYSIS

Target Context and Conditions

NIH plans to use immortalized lymphoblastoid cells and/or peripheral tissues of human subjects to identify gene expression signatures that are associated with the susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. This goal will be achieved through a strategy implemented in four stages. In the planning stage, a workshop titled “Gene expression in immortalized cell lines: toward standardizing methodologies for GxE interaction studies” will address various technical issues, including experimental standardization and manipulations of immortalized cell lines. Based on the outcome of the workshop and further input from the alcohol research community and extramural staff, a

Request for Applications will be developed and issued. In the second stage of this project, funded laboratories will coordinate efforts to standardize cell culture procedures and some aspects of experimentation and data analysis. In the third stage, signatures will be obtained in immortalized lymphoblastoid cells for one alcohol-induced disorder. These signatures will be then validated using different groups of human subjects. In the last stage of this project, the signatures will be obtained for additional alcohol-induced disorders, and then validated in different groups of people.

SRO-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

Target Context and Conditions

NIH will initiate several Phase II and III trials on a variety of interventions to accomplish the goal of evaluating the feasibility of islet transplantation with immune modulating therapies for the treatment of type 1 diabetes. 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 and immunologic studies as well as formal quality of life assessments. In 2005, the end date for this goal was extended from 2013 to 2015 as these studies are anticipated to take 7 to 10 years from the development of a clinical protocol to the publication of the trial results. These trials will be conducted through the Clinical Islet Transplantation (CIT) Consortium, 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. Current manufacturing, validation, and characterization processes have been developed in order to improve procedures for the preparation of islets and ensure consistency and quality across multiple CIT clinical trial sites. These processes are expected to be useful in the production of islets for use in clinical protocols conducted outside of the CIT Consortium as well as form the basis for licensure of an islet product.

In FY 2006, the islet production "batch record" describing the common protocol for islet manufacture was completed and accepted by the Food and Drug Administration for implementation. In early FY 2006, collagenase, a critical ingredient used in islet manufacturing, was discovered to be unsuitable for use in a licensed cellular product. In addition, the manufacturer of another critical component of the manufacturing procedure, the isolation and purification media, notified the CIT that they would be unable to supply media for the Islet Consortium. The need to identify new sources for these materials, and then to test them for incorporation into the batch record, led to substantial unanticipated delays in FY07. It is anticipated that the remaining details of islet manufacture, including the completion of agreements with sources of raw materials such as enzymes, will be achieved in FY 2008. This will lead to the planned FY 2008 and FY 2009 performance targets to begin accruing research subjects into Phase II and III clinical trials.

The Phase III trial is designed to demonstrate sufficient efficacy and safety to allow sites to apply for licensure of the islet product using a consensus "state of the art" immunosuppressive regimen and the standardized manufacturing process. Each Phase II trial will test a different innovative approach to improve islet engraftment, using the same standardized manufacturing process as in the Phase III trial. The Phase II trials will set the stage for further incremental improvements in islet transplantion outcomes once the islet product is licensed and will be conducted concurrently with the Phase III trial. The target enrollment is 20 subjects for the Phase II trials and 48 subjects for each of the Phase III trials over an approximate recruitment period of 2 years. The rate of enrollment will be determined in large part by the availability of donor pancreata for all three trials. Other conditions and events that could alter the current timeline include: changes in the availability of reagents used in the manufacturing process, and/or investigational agents or licensed therapeutics specified in the clinical protocols; or staffing changes at participating manufacturing sites.

Baseline: 2007

- (FY06) Clinical protocols under development.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(MET) Uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers was developed.	Develop 2 clinical protocols.	(MET) Seven clinical protocols were developed.	Initiate enrollment of individuals who have type 1 diabetes and who have severe hypoglycemic episodes and hypoglycemia unawareness into two Phase II clinical trials and one Phase III clinical trial to evaluate the effectiveness of islet transplantation.	Continue enrollment into all three trials, to reach target enrollments.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$6,565	$11,400	$7,530

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET and EXCEEDED as evidenced by the development five additional clinical protocols for a total of seven protocols. The CIT Consortium continued its two pivotal licensure clinical trials and proceeded forward with more innovative clinical trials after successfully developing the process to manufacture, validate and characterize to improve islet transplantation. The seven clinical protocols have been reviewed and approved by NIH. Initiation of each trial is on schedule, with expected start dates in FY 2008.

• "Peritransplant Deoxyspergualin in Islet Transplantation in Type 1 Diabetes" is a Phase II clinical trial. The purpose of this study is to assess the safety and efficacy of deoxyspergualin, an immunosuppressant drug, on post-transplant islet function in people with Type 1 diabetes who have not responded to intensive insulin therapy.

• "LEA29Y (Belatacept) Emory Edmonton Protocol (LEEP)" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.

• "Islet Transplantation in Type 1 Diabetes" is a Phase III clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.

• "B-Lymphocyte Immunotherapy in Islet Transplantation" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with the immunosuppressive medications and medications to support islet survival for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.

• "Efficacy of Islet After Kidney Transplantation" is a Phase III clinical trial. The purpose of this study is to compare the safety and effectiveness of islet transplantation versus intensive insulin treatment (ITT) for treating Type 1 diabetes in patients who have received kidney transplants.

• "Strategies To Improve Islet Survival" is a Phase II clinical trial. The purpose of this study is to determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications and medications to support islet survival, for treating Type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.

• The seventh clinical trial, entitled "Open Randomized Multicenter Study to Evaluate Safety and Efficacy of Low-Molecular Weight Sulfated Dextran in Islet Transplantation," is in the

process of being submitted to Clinical Trials.gov. The primary purpose of this study is to evaluate the safety and efficacy of Low Molecular Weight Dextran Sulfate to enhance engraftment and prevent Instant Blood Mediated Inflammatory Reaction in islet transplantation to Type 1 diabetic subjects.

Advances or Other Highlights

In the past year, CIT investigators in Sweden completed a Phase I clinical trial of the agent Low Molecular Weight Sulfated Dextran. The data from this study is the basis for the safety and dosing parameters in the seventh clinical trial described above. More information on the CIT trials and recruitment of study subjects can be found at http://www.CITisletstudy.org.

Efficiency

The Consortium continues its two pivotal licensure clinical trials. Having successfully developed the process to manufacture, validate and characterize islets for transplantation, the Consortium has also developed additional innovative clinical trials in the interest of moving forward the field of islet transplantation.

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 achievement of the goal of obesity prevention may be benefitted 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

Target Context and Conditions

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 is exploring five or more lifestyle-based approaches to obesity prevention, including behavioral or environmental interventions, in settings such as schools, communities, and homes; in addition, seven studies are evaluating the effects on weight control of worksite interventions that include environmental components; and at least three studies are evaluating 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 is investigating 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 is comparing 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 is 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. In addition, pharmacotherapeutic strategies are being evaluated for their ability to enhance weight maintenance and/or to reverse the physiological compensatory mechanisms in response to weight loss that may contribute to weight re-gain.

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 has fully recruited two clinical studies to investigate the effects of two different pharmacologic agents, 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.

Baseline: 2007

- (FY05) Few obesity intervention programs targeting children have been designed and tested to establish their effectiveness outside of small clinical settings.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) More than two studies to test the effects of worksite interventions on weight control were developed and launched.	(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.	(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.	(MET) Four new clinical trials were developed and launched to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children.	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.	Complete goal of evaluating the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$26,576	$12,395	$10,270

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET and exceeded. Four new clinical trials were developed and launched to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children. Among the studies, researchers are examining the barriers to using body mass index as a quick initial assessment of obesity in children at primary care practices. Another project is designed to test the effectiveness of a program that targets parents to help treat and/or prevent obesity in their children. Other researchers are testing a six-month family-centered intervention to increase physical activity and to improve eating patterns in both parents and obese children. Researchers will also test an intervention designed to address the different developmental stages of teenage girls with the goal of promoting behavioral changes.

Advances or Other Highlights

NIH scientists recently completed a trial and are now analyzing the data collected to

determine the efficacy of metformin for weight control in severely overweight children with hyperinsulinemia.

A computer based behavioral intervention has been developed to encourage healthy eating and exercise in an attempt to prevent/delay childhood obesity and diabetes. This interactive DVD for teenagers has won awards for innovation (e.g., Best in Class in 2006 from the Interactive Media Council, Gold Award Winner for Flash in 2007 from Horizon Interactive Awards).

Data collection for the Weight Loss Maintenance clinical trial was completed in June 2007.

Efficiency

In addition to the three clinical trials that the NIH expected to launch, an additional trial was funded, totaling four projects that may lead to new interventions that can be implemented in primary care settings to prevent and/or reduce obesity in children.

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

Target Context and Conditions

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.

Baseline: 2007

- (FY04) Two (2) IRB approved clinical research protocols addressing cancer treatment-related oral complications and associated pain are open to accrual.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(MET) Two studies on the evaluation of interventions to reduce pain and other symptoms in patients undergoing treatment for cancer were completed.	Evaluate two interventions for reducing pain, fatigue, psychological distress, or other symptoms in patients undergoing treatment for cancer or other illness/chronic disease.	Complete the goal of developing and testing multidiscilinary 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.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$115	$115	$15

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. Researchers completed two studies on the evaluation of interventions to reduce pain and other symptoms in patients undergoing treatment for cancer. One study focused on graft-versus-host disease (GVHD) and one on stomatitis. GVHD is a condition that occurs in patients who have received bone marrow transplants, often for the purpose of treating certain forms of cancer. It can cause pain, fever, or other adverse symptoms in response to immune cells in the donated marrow attacking the patient's own cells. In this study, researchers explored the relationship between the severity of GVHD

symptoms and levels of salivary protein messengers known as cytokines. The study was performed with patients being treated with immunosuppressive agents and pain relievers. It found significant associations between symptoms such as oral dryness, oral pain, and erythema (redness of skin) with levels of certain cytokines. Researchers concluded that lower levels of oral pain could be related to appropriate symptom management, and that cytokine levels could be useful as objective measurements of disease severity in clinical evaluations. In a related study, scientists developed standardized criteria for evaluating symptoms and therapeutic response in clinical trials with chronic GVHD patients. Standardized evaluation criteria will allow researchers to better assess the effectiveness of GVHD therapies in reducing adverse symptoms and improving patient quality of life.

Another study focused on stomatitis, an inflammation of the mouth that can occur as a result of chemotherapy in cancer patients. This condition often causes oral pain and reduced quality of life. Researchers assessed oral pain intensity, as well as cytokine levels, in patients undergoing chemotherapy. Higher cytokine levels correlated with increased pain intensity. Patients also received treatment with opioids. However, despite the opioid treatment, some patients continued to experience pain. These results again pointed to the usefulness of certain cytokines as measures of symptom intensity, but highlighted the need for additional research into therapeutic strategies to manage adverse symptoms. Taken together, this research suggests additional avenues of inquiry into effective therapy for treatment-related pain in cancer patients. It also demonstrates the potential of using certain biological markers as indicators of pain intensity, which could facilitate improved, objective analyses in future clinical research projects.

In 2007, research addressing cancer-related oral complications remains ongoing. Future research may lead to more effective treatments for managing and treating symptoms associated with cancer therapy, including stomatitis and GVHD, as well as symptoms associated with other chronic illnesses.

SRO-2.5	By 2011, identify and evaluate 5 novel molecular-targeted interventions for cancer, and determine suitability for use in early phase clinical trials.

BACKGROUND

Prevalence/Incidence

Cancer is the second leading cause of death in the United States and the economic cost of cancer in 2005 has been estimated at over $200 billion. Although significant progress has been made toward reducing the burden of cancer in America, one of every four deaths is due to cancer. It is estimated that in 2007 there will be about 1,444,920 new diagnoses of invasive cancer and 564,830 Americans will die of cancer.

Recent advances in the molecular pathogenesis of cancer offer unprecedented opportunities to discover and develop novel, molecularly targeted therapeutic and preventive strategies and agents. The challenge is the definitive validation of human cancer-pertinent molecular targets. The NIH is identifying and characterizing new molecular targets important in cancer processes, diagnostics, and therapeutics. The NIH is facilitating moving novel discoveries through the development process to develop new cancer therapies by supporting the pre-clinical development of promising molecularly targeted lead compounds.

Rationale

Discovering new molecular targets through a strong basic science program will accelerate the selection and development of new treatment regimens for further validation in *in vitro* studies, preclinical models, and early phase clinical trials. By targeting specific genetic alterations that occur in cancer cells, more effective therapies can be developed to attack tumor cells while normal cells remain unharmed. This will lead to the management of cancer as a chronic condition and enhance the quality of life of cancer patients.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH plans to identify 5 novel molecular-targeted interventions for cancer. Once the interventions have been identified, a number of approaches will be taken to assess the suitability of these agents for early phase clinical trials.

The agents will be evaluated using *in vitro* assays well in advance of early phase clinical trials. These assays aim to develop an understanding of the biochemical and physiological effects of a drug and how it affects cancer cell growth and division in culture.

Following *in vitro* testing, the agents will be tested in animal models molecularly engineered to mimic human cancers. Such tests will validate the targets and demonstrate drug target effect in preclinical models and in human tissue prior to initiating the clinical trial.

A molecular toxicology profile of novel agents will be developed. The NIH will develop and authenticate a variety of tests well in advance of human studies, so they can be used in

early phase trials to provide information about the safety and efficacy of the agents being tested.

Using the science-based evidence collected in the previous steps, the suitability of these agents for evaluation in early phase clinical trials will be determined.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Identify two novel targeted cancer interventions.	Evaluate two targeted interventions using preclinical testing.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$20,422	$19,359

SRO-2.6	**By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways.**

BACKGROUND

Substantive evidence exists to support the concept that common human diseases, such as asthma, cardiovascular disease, and cancer, arise from a complex interplay between genes and environmental factors, including chemical toxicants and biological toxins. It follows that to understand important gene-environment interactions in these diseases, it is necessary to understand both the genetic component and the environmental component. With the human genome project, the ability to link the genetic component of human health and disease is rapidly progressing. The environmental component, however, is lagging, due in large measure to an inability to accurately measure exposures and to define the early biological consequences of those exposures.

There are currently two ways by which exposures are measured or tracked:

- Measures of what is in the environment as revealed by toxic waste reporting, air monitoring, or water assessments. These measures, however, cannot show what actual amounts of an environmental component are being taken into an individual's body.
- Individual exposure (body burden) data, such as those provided by the National Health and Nutrition Examination Survey. These data, however, have limitations for large studies both because it requires expensive blood work and because the measurement is but a single "snap shot" in time; whereas real-world exposures and the consequences of these exposures play out over a long period of time.

To move the field forward in a way that links gene-environment interactions with human health outcomes, improvements are needed in exposure assessment technology. These improvements would involve:

- Personalized exposure monitoring systems;
- Nano-scale sensing technologies that monitor personal exposures over time;
- Molecular profiling technologies that would assess important underlying biological responses to exposure such as changes in gene expression, protein levels, or metabolite formation.

The Genes, Environment and Health Initiative (GEI) aims to accelerate the understanding of genetic and environmental contributions to health and disease. It has two components: the genetic component which focuses on identifying major genetic susceptibility factors and the environmental component which focuses on development of innovative techniques to measure environmental exposures, diet, physical activity, psychosocial stress, and addictive substances that may contribute to development of disease. This goal addresses the second effort, the Exposure Biology Program (EBP), which will create new ways to assess exposures that may be used in studies which capture information about susceptibility across the entire

genome. Optimally, using new bioengineering approaches, exposures that an individual comes in contact with will be measured more accurately during critical time points. This program will also develop ways to measure an individual's response to these exposures using new molecular technologies. It is envisioned that these methods will provide measures of personal exposure that are quantitative, precise, reliable, reproducible, and that can be scaled up to implement in large population studies in the near future.

Rationale

The Exposure Biology Program (EBP) arose from the recognition that current methodologies for detection and measurement of the actual exposure sustained by a human or other organism are often limited in the number of analytes detected and the temporal, spatial, and quantitative resolution of the measurements. This is in contrast to the robust tools employed in the fields of genetics and genomics. In order to advance understanding of the gene-environment interactions underlying the majority of human disease, scientists must have personalized measures of environmental exposures and stressors that are equivalent in precision to current technology for measuring genetic variability. Fortunately, the increasing sophistication of research tools for understanding the biological pathways involved in host response to a given exposure provides new knowledge that can be applied to the development of improved methods for detecting and measuring environmental exposures and stressors. Ultimately, the information and tools generated by the EBP will be used to generate a better understanding of gene-environment interactions in disease etiology that can translate into improved health care and early, more effective, interventions.

PERFORMANCE ANALYSIS

Target Context and Conditions

The goals of the 3-year reporting period are to refine or enhance current technologies to improve detection or analysis of environmental exposures, and to identify and characterize pathways of response for important environmental exposures. This involves a continual effort by the investigators over the reporting period. To overcome the known limitations of current technologies, enhancement and then validation are critical. In FY08 and FY09 the effort will verify sensor devices and biomarker profiles in laboratory and clinical settings, which will set the stage for validation in larger populations. Verification and feasibility testing of new technology, devices or assays often allows for future validation studies in larger populations. The funding mechanisms for these initiatives are cooperative agreement mechanisms, which are assistance mechanisms that allow for substantial NIH programmatic involvement. Applicants were required to submit milestones for development of the proposed technology or biomarkers that can be used to judge the success of the proposed research in each project. In addition, investigators will participate in Steering Committee meetings to discuss their research progress. It is expected that the milestones will be adjusted annually at the award anniversary dates to incorporate the group's scientific accomplishments and progress and to reflect any recommendations of the Steering and Advisory Committees. As with other grant mechanisms, grantees will submit annual progress reports to their program administrator.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Refine current technologies to demonstrate analyte specificity and sensitivity in benchtop assays, and identify pathways of response for important environmental exposures	Enhance current technologies to allow detection of multiple analytes, and use novel technologies to characterize the response in biological pathways to environmental exposures

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$19,500	$19,500

SRO-2.7	**By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others.**

BACKGROUND

The World Trade Center and anthrax attacks of 2001 exposed the vulnerability of the U.S. civilian population to terrorist groups armed with unconventional weapons. Chemicals are attractive terrorist weapons in that they are relatively easy to obtain and have the potential to cause mass casualties. A terrorist group could illegally obtain or manufacture traditional chemical warfare agents (i.e., nerve agents, pulmonary agents, or blistering agents). Terrorists could also sabotage manufacturing plants, storage sites, or transport vehicles to release any number of toxic industrial chemicals (e.g., cyanide). According to a 2003 report published by the General Accounting Office (GAO), the Environmental Protection Agency (EPA) has identified 123 chemical plants in the U.S. where a terrorist attack or accident could potentially expose more than 1 million people to a cloud of toxic gas.

Rationale

The U.S. military has developed some countermeasures to protect military personnel from a chemical attack, but many of these are ill-suited for chemical terrorism scenarios. Protective clothing, gas masks, and prophylactic drugs used by the military can be effective with advanced preparation, but a terrorist chemical attack against civilians is likely to come without warning. In order to respond to a chemical terrorist attack, medical personnel will require rapid and effective diagnostic technologies, as well as safe and effective post-exposure treatments appropriate for a diverse population. Currently, diagnosis is limited to observation of clinical signs and symptoms, which can be similar for chemicals that require very different treatment regimens. Available treatments for chemicals that affect cellular respiration (e.g., cyanide) or the nervous system (e.g., nerve agents) have dangerous side effects and a short therapeutic window. Post-exposure treatments for chemicals that affect the respiratory system, skin, and eyes are largely limited to supportive therapy and alleviation of symptoms.

In 2007, the NIH developed the "NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats" for the development of improved medical countermeasures that could be used in the case of chemical terrorist attack or accident, at the request of the U. S. Department of Health and Human Services (HHS). The plan focuses on therapeutics and diagnostics for chemicals that affect the nervous system; respiratory tract; skin, eyes, and mucous membranes; and cellular respiration.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH established the Countermeasures Against Chemical Threats (CounterACT) Research Network in FY 2006 to develop new and improved diagnostic technologies and therapies for conditions caused by chemicals that could be used in a terrorist attack or released by accident. The Network includes research projects, research centers, small business grants, and contracts. All of the research activities are milestone-driven, and

progress is reviewed annually.

The CounterACT Network has launched several diagnostic development projects. Several teams are designing portable devices that can be used in an emergency setting to detect chemically induced seizures that may be masked by paralysis. Others are developing "biosensors" that can rapidly detect signs of chemical exposure in blood or saliva samples. Each CounterACT diagnostic development project includes milestones for prototype development and clinical validation.

The majority of CounterACT research is directed toward therapy development. Researchers are dissecting and manipulating the biological pathways affected by various chemicals to identify promising therapeutic targets. Several potential targets have been identified and are undergoing further characterization. These include at least two classes of receptor molecules associated with chemically induced seizures, a signaling molecule involved in inflammation, and a family of sensory proteins that appear to activate nerve endings in response to chlorine and other toxic industrial compounds.

CounterACT researchers are also conducting preclinical safety and efficacy studies on promising new lead therapeutic compounds. These include a new treatment for cyanide exposure, a compound to prevent chemically-induced neurodegeneration, a treatment for chemically induced skin injuries, and a protein-based "bioscavenger" that captures and deactivates nerve agent molecules.

One especially promising chemical countermeasure has already entered clinical trials under the CounterACT program. Department of Defense (DoD) researchers discovered that midazolam, a Food and Drug Administration (FDA)-approved intravenous sedative and anesthetic, stops seizures in animals exposed to nerve agent. The CounterACT program includes a clinical trial to test the efficacy of intramuscular midazolam in epilepsy patients. Clinical efficacy data from this trial will support a NIH/DoD joint effort to obtain FDA approval for use of midazolam against nerve agent-induced seizures. The NIH is also collaborating with the DoD to complete the animal studies necessary for FDA approval of midazolam as a nerve agent treatment.

Scientific research, by its nature, is also unpredictable; while this goal allows some flexibility, unanticipated technical challenges or experimental results could require modifications to the research strategy or timeline.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Determine whether three molecules associated with chemical injury show promise as new therapeutic targets	Develop a prototype technology to diagnose chemical exposure in an emergency setting

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$53,731	$53,731

SRO-2.8	By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.

BACKGROUND

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. There are many different forms of muscular dystrophy, which differ in their mode of inheritance, age of onset, severity, and pattern of muscles affected. Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy, which is caused by mutations in the dystrophin gene, resulting in an absence or deficiency of this protein. DMD usually becomes clinically evident when a child begins walking, and patients die in their late teens or early 20s. Becker muscular dystrophy is also caused by mutations in the dystrophin gene, but results in production of a truncated form of the protein and a less severe course of disease progression. An animal model, the mdx mouse, is extensively used to study these disorders, and large animal models (e.g., dog) also exist. The most common adult form of muscular dystrophy is myotonic dystrophy. It is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. Myotonic dystrophy type 1 and type 2 are caused by nucleotide repeat expansions (repeated sequences of DNA components) in different genes. Recent studies have uncovered important underlying genetic and molecular mechanisms and developed animal models appropriate for testing new therapeutics. Other forms of muscular dystrophy include facioscapulohumeral muscular dystrophy (FSHD), the limb-girdle muscular dystrophies (LGMDs), and the congenital muscular dystrophies. There are varying levels of knowledge about the mechanisms underlying these different forms; this allows disease mechanism-targeted therapeutic development to proceed for some types of muscular dystrophy while further basic studies are required before targeted therapies can be developed for other types.

Prevalence/Incidence

Duchenne and Becker muscular dystrophies together affect 1 in 3,500 to 5,000 male births. Between 400 and 600 boys in the United States are born with these conditions each year. Females are typically carriers of the genetic mutations and are rarely affected by these forms of muscular dystrophy. Myotonic dystrophy affects about 1 in 8,000 people worldwide. Type 1 is the most common form of the condition, accounting for about 98 percent of all cases. The remaining 2 percent of cases are myotonic dystrophy, type 2. The prevalence of the two types of myotonic dystrophy varies among different ethnic populations. For other forms of muscular dystrophy, it is difficult to estimate incidence, due to variability among different forms of the disease and/or lack of precise diagnostic methods.

Rationale

There is currently no treatment that can stop or reverse the progression of any form of muscular dystrophy. However, advances in the understanding of disease mechanisms (particularly for DMD), diagnostics, and research technologies make this an opportune time to emphasize therapeutic development. In addition, the MD-CARE Act required the Muscular Dystrophy Coordinating Committee (which includes NIH and other federal agencies) to develop a plan for conducting and supporting research and education on muscular dystrophy. The resulting Action Plan for the Muscular Dystrophies identified a series of promising therapy development goals. A recent workshop convened by NIH

reviewed the status of therapy development for the muscular dystrophies and also concluded that a number of therapeutic strategies are showing promise and have a strong likelihood of leading to clinical trials in the next few years.

PERFORMANCE ANALYSIS

Target Context and Conditions

Based on a better understanding of the disease mechanisms at play in the muscular dystrophies, there are now multiple potential pathways to therapeutic development, including: drug-based therapies to maintain muscle mass; strategies to enhance the normal regenerative process of muscle; cell-based muscle therapeutic strategies; strategies for gene replacement; and genetic modification therapies to bypass inherited mutations.

Many NIH activities have enhanced research utilizing a number of these approaches. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which have been designed to accelerate the translation of fundamental scientific advances to the clinic through close interaction between basic researchers and clinicians. Translational research projects at the Wellstone Centers are focused on optimizing gene therapy and stem-cell-based therapeutic approaches as well as identifying therapeutic strategies to enhance muscle regeneration. NIH has also funded numerous grants through the program announcement, "Muscular Dystrophy: Pathogenesis and Therapies," and broader solicitations for preclinical therapy development projects for neurological conditions. The NIH specialized program announcement, "Translational Research in Muscular Dystrophy," released in late 2005, has already resulted in a dramatic increase in the number of applications received and funded by NIH for development of novel therapies for muscular dystrophy. Successful applications have focused on both DMD and myotonic dystrophy, and use a range of strategies. While NIH is rigorously pursuing all pathways to therapeutic development, a few approaches are showing significant promise.

Genetic modification strategies using synthetic oligonucleotides (short sequences of DNA or RNA) to either bypass or correct the genetic mutations responsible for muscular dystrophy are showing promise in animal models. This strategy is particularly relevant to DMD, where mutations in the dystrophin gene prevent the dystrophin protein from being produced. NIH currently funds studies employing synthetic oligonucleotides to correct the mutations in the dystrophin gene or to alter the translation of the mutated dystrophin gene into protein such that the mutations are bypassed ("read-through") resulting in the restored production of dystrophin protein. Although clinical trials using synthetic oligonucleotides have been initiated in Europe, these are early-stage, single muscle tests, and the development of a therapeutically significant treatment requires more research on oligonucleotide chemistry and systemic delivery.

Gene replacement therapy (replacing the defective gene or increasing the expression of functionally equivalent genes) is also showing promise in the mdx mouse and other animal models. However, one of the major hurdles of this approach is determining ways to deliver the gene systemically, allowing delivery of the gene to all muscles of the body. Research currently funded by NIH is developing ways to address this problem. One project is utilizing pharmacological agents to permeabilize the blood vessel walls to allow for better access of the vector (delivery vehicle) to muscle and testing this approach in a canine model

of DMD. Another NIH-funded investigator is pursuing the use of stem cell technologies for DMD gene therapy by developing vectors that can be used to integrate the corrected genes into muscle stem cells, which can then be transplanted into diseased animals. Plus, investigators who recently received an NIH grant are working to develop the optimal vector for vascular delivery of genes. The optimal vector would be one that does not elicit a strong immune response and would enable the human body to accept the therapy.

Small molecule drugs represent another promising therapeutic approach. NIH recently funded a large-scale project to develop new small molecule drugs for the treatment of DMD and potentially other forms of muscular dystrophy as well. The project will pursue a number of strategies for therapy development, including stimulating muscle growth by modulating growth factor pathways, and upregulating proteins that may structurally and functionally substitute for dystrophin or contribute to the dystrophin protein complex in normal muscle cells. The researchers have already completed a high-throughput screening process on each of these strategies in order to identify small molecules that are candidate therapies. The project will focus on improving the properties of these small molecules as drug candidates and carry out research that will help support further clinical studies using these compounds. One exciting aspect of this project is the fact that a patient voluntary organization as well as a biopharmaceutical company is contributing funds to this project, thereby creating a public-private partnership to leverage funds for this project.

Scientific research, by its nature, is also unpredictable; while this goal allows some flexibility, unanticipated technical challenges or experimental results could require modifications to the research strategy or timeline.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Test a new strategy to improve the efficacy of an oligonucleotide-based therapy in animal or cell models	Test a new strategy for systemic delivery of a therapeutic gene in a large animal model

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$26,327	$27,655

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. 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 other potential interventions.

PERFORMANCE ANALYSIS

Target Context and Conditions

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). Early results suggest that 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, including through the Alzheimer's Disease Cooperative Studies initiative; 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.

Baseline: 2007

- (FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) NIH continued a preclinical toxicology program and expanded a program for pre-clinical drug discovery and development.	(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.	(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.	(MET) NIH-supported research has helped to identify and characterize two particularly promising target molecules for AD treatment and development: beta-amyloid production and p38 alpha MAPK.	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.	Start at least one pilot clinical trial on promising interventions based on results of previous trials and new leads for drug discovery.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$263,679	$263,224	$262,835

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. The identification and characterization of molecular targets for treatment or prevention of Alzheimer's disease (AD) is a major component of the NIH Neuroscience portfolio; at present, some ten molecular targets are under study. Two particularly promising target molecules whose identification and/or characterization have received significant NIH research support in recent years are:

-- Beta-amyloid. Beta-amyloid protein forms the characteristic plaques found in the brains of AD patients. Our increased understanding of this protein, gained through NIH-supported research over the past several years, has led to the development of novel treatment strategies, including immunotherapies. For example, intravenous immunoglobin (IVIg), a form of passive immunization, contains naturally-occurring antibodies against beta-amyloid, and preliminary studies have shown that IVIg promotes clearance of beta-amyloid from the cerebrospinal fluid, as well as improved cognition in AD. An NIH-supported clinical trial scheduled to begin in early 2008 will demonstrate whether IVIg is useful clinically for

treating AD.

-- p38 alpha MAPK. NIH-supported investigators have found that a molecule called p38 alpha MAPK, already an established target for drug discovery in peripheral tissue disorders, is also implicated in brain inflammation associated with AD, and that brain p38 alpha MAPK is a viable molecular target for development of potential AD treatments.

Advances or Other Highlights

Grants supported under three program announcements, “Alzheimer’s Disease Drug Development Program” (PAR-05-148) and “Grants for Alzheimer’s Disease Drug Discovery” (PAs-05-022 and its successor, PAS-06-261), build on NIH-supported discoveries related to molecular targets to facilitate the discovery, development, and preclinical testing of novel compounds for the prevention and treatment of the cognitive and behavioral symptoms associated with AD. There are currently 24 projects funded under these three Program Announcements, exploring a wide array of approaches, including agents that inhibit the development of AD's characteristic amyloid plaques and neurofibrillary tangles, immunotherapies, antioxidant drugs, and neuroprotective agents. It is anticipated that additional meritorious projects will be funded across the life of these PAs.

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	**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

Target Context and Conditions

To accomplish the goal of developing one universal or broad-spectrum antibiotic/antimicrobial/anti-infective that is effective against multiple classes of biological pathogens, NIH is stimulating research toward the development of broad-spectrum antimicrobials through targeted solicitations and is continuing to expand the availability of critical research resources to the community. Examples of research resources that are being expanded include development of screening assays and screening capacity to support discovery of novel antimicrobials and broad-spectrum activity, increased capacity for medicinal and combinatorial chemistry, and enhanced library and database resources. New methodologies, chemical libraries, and software tools are expanding 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 re-emerging 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-spectrum 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.

Baseline: 2007

- (FY05) Resources provided to the scientific community for development of medicinal and combinatorial chemistry capacity and assay optimization.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(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.	(MET) NIH optimized several compounds for antimicrobial activity through medicinal and combinatorial chemistry approaches.	Begin determining safety and pharmacology profiles (e.g. bioavailability) of at least 1 candidate compound that has shown broad spectrum activity in vitro.	Conduct IND enabling toxicology and preclinical animal studies on at least 1 candidate compound that has shown broad spectrum activity in vitro.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$849,858	$853,000	$800,000

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. NIH optimized several compounds for antimicrobial activity using medicinal and/or combinatorial chemistry:

NIH-supported scientists designed a potently bactericidal, cationic dodecapeptide, SC4, in 2004, which is similar to the antimicrobial peptides that are part of the innate immune systems of many organisms. Cationic peptides, like SC4, act by disintegrating bacterial membranes. This gives cationic peptides general, broad-spectrum antibiotic activity. In 2007, this group of scientists used medicinal chemistry approaches to optimize the broad-spectrum activity of SC4 and enhance its properties as a drug. SC4 has shown activity against Gram-positive bacteria strains [Staphylococcus aureus (staph), Streptococcus pyogenes, and Bacillus anthracis (anthrax)], including S. aureus strains resistant to conventional antibiotics, as well as against Gram-negative bacteria such as Yersinia pestis (plague). In vitro and in

vivo studies are ongoing.

Acute respiratory distress syndrome (ARDS) is a major cause of morbidity and mortality resulting from pulmonary infection. NIH has supported the preclinical development of a compound that targets ARDS pathogenesis mechanisms that occur in the host, which gives the compound potentially broad-spectrum activity against diseases caused by a variety of respiratory pathogens. This compound, developed by the Japanese company Accuthera Inc. in collaboration with Colorado State University and the University of Utah, inhibits the activity of two host enzymes, human neutrophil elastase (HNE) and PR3 protease, thus relieving the extracellular matrix breakdown that occurs in ARDS. Promising derivatives of the lead compound are being tested in vitro and studies are beginning in vivo.

NIH grantees conducted a screen for Type III secretion system inhibitor compounds with activity against Salmonella. One still-confidential compound was identified as having the desired activity without toxicity to the host or other unwanted side effects. In FY 2007, the researchers used medicinal chemistry to design a library of compounds related to the confidential compound that can be tested for: ability to inhibit Salmonella's Type III secretion mechanisms; broad-spectrum activity against other Gram-negative bacteria such as Y. pestis and Francisella tularensis (tularemia); and possession of other desirable physiochemical properties. Ongoing studies will further characterize the mechanism of action of this family of compounds and compare target proteins in different Gram-negative bacterial species.

Under the "Cooperative Research into Therapeutics and Diagnostics for Category B Bacteria, Viruses, and Parasites" program, NIH awarded a cooperative agreement to develop a broad-spectrum antiparasitic drug for use against the anaerobic protists Giardia lamblia and Entamoeba histolytica. Both cause debilitating diarrhea in normal adults and are classified as enteric Category B pathogens. G. lamblia and E. histolytica infect more than a billion people worldwide and can readily be added to water supplies, thus presenting a credible bioterrorism threat. In FY 2007, NIH grantees used medicinal chemistry to synthesize new derivatives of metronidazole (Mz), which is the current drug of choice for these infections, but is increasingly ineffective because of the emergence of drug-resistant strains of these pathogens. Medicinal chemistry was used to create candidate drugs with increased activity against diverse Mz-sensitive and Mz-resistant Giardia. A future objective of the project is to extend these findings to drugs for treating Entamoeba infections.

Optimization of compounds is a critical step in drug development that allows an opportunity to identify derivatives of the original compound that may be more amenable to use as a drug (e.g., less toxicity, better solubility, etc.) than the original form. Once a compound is optimized, it is ready for preclinical testing and, if successful, may proceed through subsequent stages of the drug development process. If the compound/experimental drug fails any of these steps, the process may need to return to an earlier stage to try to address the problem. Or if the problem cannot be solved, the process ends and efforts are shifted to other candidates. If a compound that was taken through early phase development by NIH (i.e., preclinical testing) is successful, NIH or partners (e.g, drug companies or public private partnerships) may move the candidate into clinical testing and final stages of development

toward licensure. With the need for new antimicrobial drugs to treat a wide variety of infectious diseases—especially in light of the growing problem of drug resistance—any new antimicrobial drugs that are developed with the support of NIH and other critical partners will provide new and much-needed options for the treatment of infectious diseases.

Advances or Other Highlights

In FY 2007, NIH supported the evaluation of 3,700 compounds for activity against NIAID biodefense Category A, B, and C viruses through the "In Vitro Antiviral Screening Program." Through this contract and another entitled "Animal Models of Human Viral Infection for Evaluation of Experimental Therapies," NIH has supported identification of a therapeutic with broad-spectrum potential to treat orthopoxvirus and herpesvirus infections. N-Methanocarbathymidine [(N)-MCT] is a novel nucleoside analog that is active against some herpesviruses and orthopoxviruses in vitro. The compound is non-toxic in vivo and effectively reduces the mortality of mice infected with orthopoxviruses, as well as those infected with herpes simplex virus type 1 when treatment is initiated within 24 hours after infection. These results indicate that (N)-MCT is active in vitro and in vivo, and its mechanism of action suggests that the molecule may be an effective therapeutic for orthopoxvirus and herpesvirus infections, thus warranting further development.

In FY 2007, NIH-supported researchers found that a new influenza antiviral drug, T-705, whose preclinical development was supported by NIH, also may have potential as a broad-spectrum antiviral to treat arenavirus and bunyavirus infections. The drug, which entered drug company-sponsored clinical trials in the United States and Japan for influenza in FY 2007, was tested by NIH contractors in in vitro and animal models of bunyaviruses and arenaviruses. In general, T-705 was found to be more active than ribavirin in cell-based assays and in vivo, as reflected by substantially greater therapeutic indexes. The results suggest that T-705 may be a viable alternative for the treatment of life-threatening bunyaviral and arenaviral infections.

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

Target Context and Conditions

The salivary diagnostics projects are breaking new ground in making new diagnostic tools a reality. Compared with existing diagnostic systems, the ability to screen and discover multiple biomarkers simultaneously may provide a more valid clinical diagnosis and may be more useful to recognize molecular patterns predictive for disease development. In the next five years of the project, known as Phase II, grantees will develop an easy-to-use diagnostic prototype with wireless communication systems that has the potential to attract commercial development. Specifically, the fabricated platforms will be integrated with existing front-end technologies to create a fully functional hand held salivary diagnostic test that can be used in different settings, from the hospital to the home.

The Human Salivary Proteome program, which complements the Salivary-Based Diagnostic Technologies program, continues to make substantial progress towards deciphering the entire spectrum of salivary proteins. Intense efforts are now ongoing towards the comprehensive identification of all proteins in parotid and submandibular/sublingual saliva. The human salivary proteome will present for the first time, a complete "alphabet" for the translational and clinical utility of saliva as a diagnostic fluid. This toolbox will contain the entire "alphabet" necessary for scientists to harness from saliva the proteomic elements that will mark clinical diseases, local and systemic, such as caries, Sjögren's syndrome, oral cancer and systemic diseases.

Baseline: 2007

- (FY05) Three groups of researchers are currently working to catalog the salivary proteome.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Three research projects implemented to identify and catalog salivary proteomes.	(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.	(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.	(MET) A common proteome database has been established that includes data from 3 subject groups. 1166 proteins have been identified, comprising 84 percent of the human salivary proteome.	Complete the design of bioinformatics management systems for storing, searching, and disseminating salivary proteomics data.	Complete integration of the individual components of the handheld device and establish the limit of detection, accuracy, precision and specificity for the device in detecting anaytes associated with both oral and systemic diseases.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$9,496	$6,563	$6,460

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET and EXCEEDED. The Human Salivary Proteome program, which complements the Salivary-Based Diagnostic Technologies program, has made substantial progress towards deciphering the entire spectrum of salivary proteins. Using state-of-the-art identification methods, about 1,166 saliva proteins were identified, comprising approximately 84% of the human salivary proteome. Comprehensive identification and characterization of all proteins in parotid and submandibular/sublingual saliva is well under way at three research institutions across the country. Fifty-seven percent of proteins were found in both parotid and submandibular/sublingual (SM/SL) saliva, whereas 27% were unique to the gland(s) of origin. The human saliva proteome data is stored for further analysis at a common web site which will become available to all saliva researchers after the paper in published.

Compilation of the salivary proteome is the first step in identifying aberrations in the protein and/or peptide composition of saliva that identifies both oral and systemic disease processes. These aberrations are potential diagnostic or prognostic markers that could be used to guide

the saliva-based diagnostic program. Moreover, a comparison of the saliva proteome to those of tears and blood plasma will identify common protein aberrations found in various body fluids during disease states and further improve the use of these body fluids as diagnostic media.

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.

Efficiency

Initial targets that specified two study groups identifying 80% of the salivary proteome have been exceeded. Currently 84% of the salivary proteome has been identified by three study groups. Having three study groups increases the efficacy of the research as a greater variety of the population is included in the sample. This wider sample ensures a more complete representation of the human salivary proteome, helping the NIH identify more salivary proteins and increasing the potential of using this methodology to identify systemic diseases.

SRO-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 28 million people, surpassing tuberculosis and malaria as the leading cause of death from infectious disease worldwide. In 2006, an estimated 39.5 million of the world's population, including 2.3 million children younger than 15 years of age were living with HIV/AIDS. In addition, almost 3 million people died from AIDS in 2006, and more than 4 million people were newly infected with HIV, of which 530,000 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 newly diagnosed infections have remained relatively stable at approximately 40,000 per year, the proportion of new HIV infections that occur among adults over 50 years of age and some racial and ethnic groups continues to rise.

Disease Burden

The impact of the AIDS pandemic is profound. Although global availability of resources to combat HIV/AIDs has increased since 2001, the populations most affected by HIV are still at greater risk of poverty, hunger and childhood mortality than those less affected by the pandemic. In some parts of southern Africa, adult prevalence of HIV infection is 25 percent or greater and prevalence amongst pregnant women who attend antenatal clinics can be more than 40 percent. The AIDS pandemic continues to destroy families and communities and thereby to weaken and threaten the social stability and national security of developing nations. There is evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States and some European countries and of similar hidden epidemics in Latin America and Asia.

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

Target Context and Conditions

As of March 2007, the NIH has supported 99 HIV vaccine trials involving 55 different products, 22 adjuvants, and over 26,000 volunteers. At present, there are 20 ongoing vaccine trials (13 Phase I, 4 Phase II, 2 Phase IIb, and 1 Phase III).

In the past year, through the NIAID-funded HIV Vaccine Trials Network (HVTN), the NIH continued to advance two promising T-cell based vaccines—the Merck Adenovirus and NIAID Vaccine Research Center's (VRC) DNA prime followed by an Adenovirus boost—towards preventive vaccine efficacy studies. Additional, separate trials are expected to begin within a year to further evaluate the efficacy of these two vaccine approaches. These will include testing in populations outside of the United States. The evaluation of these products will be critical to meeting the planned targets and in formulating plans for future studies. Importantly, the HVTN study evaluating the safety and immunogenicity of the VRC vaccine composed of a DNA prime dose and adenovirus-booster dose is being coordinated with two other studies, one conducted by the U.S. Military HIV Research Program (USMHRP) and one by the International AIDS Vaccine Initiative (IAVI). The successful implementation of these three studies is a major step in the development and design of the first collaborative Phase IIb test-of-concept study, which will evaluate the potential of the VRC combination product to prevent HIV infection across multiple viral clades (or subtypes) and/or to decrease plasma viremia. This high-priority study is anticipated to be a collaborative effort by NIAID, HVTN, IAVI, USMHRP, and the Centers for Disease Control and Prevention and to be conducted in the United States, several countries in Africa, and possibly elsewhere in the Americas/Caribbean.

A Phase III trial being conducted in Thailand is evaluating a second-generation vaccine and has enrolled 16,402 participants who were all vaccinated after enrollment. The study has been reviewed by the Data and Safety Monitoring Board (DSMB), which did not find any safety concerns; it will continue to be monitored by the DSMB, which will review operational and statistical criteria at each meeting. The study has taken steps to improve visit compliance, overall retention and community engagement in efforts to ensure its continuation.

The Center for HIV/AIDS Vaccine Immunology (CHAVI) will also continue to play a vital role in accelerating the development of a safe and effective prevention vaccine. To date, CHAVI has established collaborations with 11 clinical trial sites, developed or began to develop 12 clinical research protocols, initiated its first study, is now implementing additional projects, and has established an HIV Transmitted Virus Sequence Database. These efforts will help support efforts to identify promising vaccine candidates.

In June 2006, the NIH announced the Leadership Groups of the newly restructured HIV/AIDS Clinical Trials Networks. The HVTN, an international collaboration of scientists and educators searching for an effective and safe HIV vaccine, was among the six networks funded, under leadership at the University of Washington. Awards for the Clinical Trials Units and Clinical Research Sites affiliated with HVTN were announced in March 2007, although some international awards are still pending. A total of 29 clinical research sites was funded in affiliation with the HVTN. Together, they have the capacity to conduct all phases of clinical trials, from evaluating experimental vaccines for safety, to testing the vaccine's ability to stimulate immune responses, and to confer protective immunity against HIV.

When a vaccine is available, the NIH will also be poised to test the vaccine through the Adolescent Trials Network for HIV/AIDS (ATN). Researchers are creating a national clinical research infrastructure that addresses the particular challenges and unique clinical management needs of HIV-positive pre-adolescents, adolescents and young adults, and those youth at risk of infection.

NIH's ability to develop a preventive HIV vaccine by 2010 will be contingent on the results of ongoing research; data from ongoing trials will be a foundation to help guide future research.

Baseline: 2007

- (FY05) NIH is conducting Phase I trials of a second third generation candidate (6 plasmid DNA plus Adv boost).

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	(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.	(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.	(MET) NIH initiated a Phase II/IIb trial to evaluate the safety and efficacy of Merck's clade B–based Adenovirus HIV-2 gag/pol/nef vaccine in South Africa.	Initiate a Phase IIb trial of a promising vaccine candidate that may protect across viral clades (or subtypes).	Begin analyzing final data from a phase III trial of a second generation vaccine.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$596,775	$592,634	$597,955

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. During FY 2007, NIH initiated a Phase IIb study (known as HVTN 503 or the Phambili trial) to evaluate the safety and efficacy of a three-dose regimen of Merck's recombinant adenovirus (rAd5) HIV-1 gag/pol/nef vaccine candidate. The study was designed to enroll 3,000 adults in South Africa, where clade C HIV-1 infection is

prevalent. The trial would have provided important information regarding cross-clade efficacy of this clade B-based vaccine in a clade C endemic area. The trial was designed to assess whether the vaccine candidate could reduce the proportion of volunteers who acquire HIV infection, and/or decrease the HIV-1 viral load set-point in volunteers who acquire HIV-1 infection relative to those study volunteers who had received a placebo. In addition, the trial was designed to examine immune responses to determine if this clade B candidate vaccine would elicit cellular immune responses to clade C HIV-1 antigens.

In September 2007, the NIH, the pharmaceutical company Merck & Co. Inc., and the NIH-funded HIV Vaccine Trials Network (HVTN) announced that immunizations in the HIV vaccine clinical trial known as the STEP study—also referred to as HVTN 502—would be discontinued. The decision was based on recommendations made by an independent Data and Safety Monitoring Board (DSMB), which concluded that the vaccine candidate could not prevent HIV infection or reduce the amount of virus in those who became infected with HIV. The STEP study was designed to evaluate the safety and begin evaluating the efficacy of the same Merck rAd5 HIV-1 gag/pol/nef vaccine candidate used in the HVTN 503/Phambli study. As a result of those findings, immunizations and enrollment in the HVTN 503/Phambili trial were paused to allow for further analysis of the STEP findings. In early October 2007, a separate, independent DSMB for the Phambili trial concluded that there was no basis for anticipating more favorable results in the South African clinical trial. Consequently the HVTN 503 study sponsors have permanently suspended immunizations and enrollment in the Phambili trial.

Advances or Other Highlights

During FY 2007, the NIH initiated six new vaccine clinical trials, including:

• A Phase I clinical trial (HVTN 064) testing, separately and together, two Pharmexa-Epimmune vaccine candidates, EP-1043 and the DNA vaccine candidate EP HIV-1090. The study is being conducted in healthy, uninfected adult volunteers in the United States.
• A Phase I clinical trial (HVTN 069) comparing three regimens of three DNA prime doses and one rAd5 booster dose, with 30 healthy, uninfected volunteers in each regimen.
• A Phase Ib open-label clinical trial (HVTN 071) in healthy, uninfected adult volunteers designed to characterize the immune response (particularly the CD4 T-cell response) to a three-dose regimen of the Merck adenovirus-based HIV gag/pol/nef vaccine candidate. Immunizations in this trial recently have been paused.
• A Phase Ib clinical trial (HVTN 072) to assess the NIH VRC rAd35 vaccine in combination with a VRC DNA or a VRC rAd5 vaccine candidate in healthy, uninfected adult volunteers at sites in Switzerland and in the United States.
• A Phase I clinical trial (VRC 012) to examine the safety and tolerability of rAd35-envA and rAd5-envA vaccines in healthy, uninfected adult volunteers.
• A Phase I clinical trial to evaluate the safety and immunogenicity of a multiclade HIV rAd5 vaccine. This study is being conducted in collaboration with the U.S. Military HIV Research Program (USMHRP) in healthy, uninfected adults in Uganda.

The vaccine DSMB also met during FY 2007 to review interim data from the RV 144 trial, a Phase III trial of a live recombinant HIV vaccine candidate with a VaxGen gp120 B/E boost in healthy, uninfected Thai adults. Based on the interim analysis, the DSMB recommended

that the study continue as planned.

In FY 2007, the NIH also continued supporting eight ongoing HIV vaccine trials conducted by the HVTN, two in collaboration with the USMHRP, and five through the VRC. Volunteer visits were completed in seven other studies (three studies conducted by the HVTN, one study conducted in collaboration with USMHRP, and in three studies conducted by the VRC). Finally, another study conducted in collaboration with the International AIDS Vaccine Initiative (IAVI) was completed.

In the past year, data from several studies have been published that have helped direct vaccine research:

• A study of the safety and immunogenicity of a gag-pol candidate DNA vaccine showed it was safe, but its immunogenicity was poor. Based on these results, a new multiclade DNA candidate vaccine is being developed.
• Three vaccine candidates have proved safe and immunogenic in Phase I trials. This includes a multiclade HIV-1 DNA vaccine, an rAd5-vectored gag-pol clade B vaccine, and a six-plasmid (envA/envB/env/gagB/polB/nefB) DNA vaccine administered with a needle-free device. While the last gag-pol candidate was safe and well tolerated, its immunogenicity was poor; however, this initial product led to development of the 4-plasmid multiclade VRC DNA candidate vaccine.
• NIH-funded researchers also published data from a phase II study of an HIV-1 canarypox vaccine (vCP1452), which did not elicit an immune response strong enough to be considered for a phase III study.
• A study of the first comprehensive characterization of HIV-specific T-cell immunity in vaccine study participants. It compared HIV-specific T-cell immunity in vaccine study participants who acquired HIV after being vaccinated to non-vaccinated subjects with primary HIV-1 infection. The trial has provided important knowledge about the impact of HIV vaccines on the immunologic response to HIV-1 infection in previously vaccinated people.

The NIH also funds the Center for HIV/AIDS Vaccine Immunology (CHAVI) to support intensive and highly collaborative projects addressing key immunological roadblocks to the discovery and development of a safe and effective HIV vaccine. CHAVI is a virtual center that consists of 95 collaborating investigators in 36 institutions in 8 countries in North America, Africa, and Europe. Among its activities, CHAVI has formed several discovery teams to investigate different topics related to HIV vaccine research.

Finally, the NIH is supporting the Adolescent Trials Network for HIV/AIDS Interventions (ATN) to enable future vaccine trial research infrastructure for adolescents and young adults at domestic U.S. sites. As a part of the ATN's Connect-to-Protect program (C2P) being conducted at all network sites, the community mobilization intervention phase of C2P has continued efforts in preparing communities for HIV vaccine trials in youth, and in effecting structural changes aimed at reducing HIV incidence; it also has included the implementation of one of two CDC programs (MPowerment and PROMISE) at each of those ATN locations. In addition, the ATN and C2P staff formed community partnerships at two new ATN sites to

focus on HIV prevention and HIV vaccine trial preparedness. 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 domestic U.S. 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-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 nucleotide 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. Nearly 18 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. Of individuals diagnosed with major depression, 25% 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

Target Context and Conditions

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. Variation in the identified genes will be examined through the use of knockout and transgenic mice, as well as through human pharmacogenetic studies, to understand differences in addiction vulnerability across 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.

Baseline: 2007

- (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
		Validate or replicate previously identified chromosome regions in different	(MET) Replicated the genetic associations of GABRA2, ADH4, and	Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek	(MET) Fine mapping studies were conducted to identify specific haplotypes of genes that influence risk for	Identify potential functional differences from fine mapping studies of specific haplotypes.	Validate the functional differences identified from previous fine mapping studies.

		sample sources by one or more groups to identify genes.	CHRM2 to alcohol dependence in different sample sources in multiple groups.	potential functional differences coming from these haplotypes.	alcohol dependence. Functional differences of various haplotypes were identified.		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$96,615	$91,845	$85,047

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. Research performed through the Collaborative Study on the Genetics of Alcoholism (COGA), a large family-based study, has made great strides in identifying genes that are associated with an elevated risk for alcohol dependence and related disorders. At the finer sequence level, NIH-supported investigators have identified sequence variations within certain genes, called single nucleotide polymorphisms (SNPs), and sets of closely linked SNPs, called haplotypes, that are specifically associated with an elevated risk for alcohol dependence in special population studies. For example, sequence variations in a haplotype unit in the GABRA2 gene on chromosome 4 were discovered to influence risk for alcohol dependence in European American, African American, Chinese, Thai and Hmong populations. In a separate study, a haplotype of GABRA2 was linked to alcohol dependence, and to symptoms of alcohol withdrawal that also correlate to severity of alcohol dependence.

Research indicates a relationship between genetically controlled personality traits and risk for substance dependence, including alcohol dependence. In a recent study of European Americans and African Americans, variations in personality traits were shown to be associated with haplotypes of CHRM2 (chromosome 7) and ADH4 (chromosome 4) in the same DNA regions that previously had been associated with substance dependence. These results suggest that personality and substance dependence may have a common genetic basis.

These results do not necessarily suggest the sample populations are at increased risk for alcoholism but rather individuals possessing these genetic variants may be more vulnerable to developing alcohol dependence. The sequence variants may be used in the future as markers to predict risk of developing alcohol dependence and related disorders.

Advances or Other Highlights

A genetic association between chromosome 1 and alcohol dependence was identified using samples from the COGA study. Findings from the COGA study also revealed an association of specific types of electrical brain currents and genes that increase vulnerability to alcohol dependence, e.g. GABRA2 and CHRM2. Brain electrical currents are quantitative phenotypes that are being used to identify genes that increase risk for alcohol dependence. Such quantitative measures are helpful considering the complexity and heterogeneity of alcohol dependence.

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 arterial 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 not for reversing damage to the myocardium or generating new blood vessels. Moreover, preclinical data gathered by NIH researchers over the past few years suggest that the differentiation (the process by which an unspecialized cell, such as a stem or progenitor cell, becomes specialized into one of the many cells that make up the body, such as a heart, liver, or muscle cell that performs specific functions) of stem cells is not properly controlled during injection of stem cells into animal or human subjects. For the stem or progenitor cells to be effective at stimulating repair and/or regeneration, the cells need to differentiate into the specific types of cell needed to promote repair and regeneration. Therefore, the inability to control the differentiation of the cells limits their therapeutic potential. NIH-funded researchers have begun to focus on improving understanding of stem cell differentiation in order to develop methods to direct the differentiation or development of stem cells along specific cell lineages to yield replacement cells for clinical use.

Other recent 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. Researchers continue efforts to develop noninvasive imaging techniques for monitoring cell-based therapy because cell therapy remains an important potential strategy for delivering secreted factors, such as cytokines, to patients. For example, NIH extramural researchers currently are developing methods to protect and track stem cells using a cell encapsulation strategy designed to be used with X-ray CT imaging. The ultimate goal of the research is to develop a cell-based therapy for peripheral arterial disease (PAD), a form of CVD in which plaque builds up inside the walls of the arteries blocking the flow of blood from the heart to the head, internal organs, and/or limbs.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH intramural program has undertaken a multimodality imaging effort 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 using 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.

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

The NIH extramural program is supporting efforts to develop and test a new imaging tool to promote stem cell engraftment and allow stem cell tracking in vivo. Efforts in the extramural program entail:

- Development of a method to prevent rapid destruction of stem cells in vivo. One of the major barriers to the development of allogenic cell-based therapy is the rapid destruction of allogenic cells in vivo. Extramural researchers are developing a cell encapsulation agent to protect and enable tracking of mesenchymal stem cells.
- Evaluation of the use of the cell encapsulation agent to allow stem cell imaging and tracking using X-ray CT imaging.

Baseline: 2007

- (FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.	Complete optical imaging probe development.	(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.	(NOT MET) Due to changes in the scientific field and a new direction for this goal, this step to initiate and validate toxicology studies was not needed at this time.	Formulate a biocompatible cell encapsulation agent designed to protect and track mesenchymal stem cells for administration to patients to promote cell survival and engraftment.	Demonstrate that encapsulated cells can be tracked non-invasively by X-ray computed tomography.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$900	$800	$699

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The initial pre-clinical targets for stem cell imaging for the goal have been completed successfully. However, the FY 2007 target 'to initiate and validation and toxicology studies' in preparation for clinical studies in humans is not needed at this point since clinical studies would not be undertaken until further work could be done to improve understanding of the control of stem cell differentiation. Based on recent findings in the field, researchers have realized the critical importance of control of stem cell differentiation to the success of stem cell-based therapy. Therefore, although the NIH will continue to pursue GPRA Goal SRO-3.6 by supporting efforts to develop and enable tracking the mobility of stem cells in cardiovascular tissues, NIH-funded researchers will also focus on improving understanding of stem cell differentiation in order to develop methods to direct the differentiation or development of stem cells along specific cell lineages to yield replacement cells for clinical use.

After determining validation and toxicology studies were not needed at this time, the FY 2007 activity shifted to initiating preclinical studies of the nature of stem cell migration in adult tissues, which was the previous FY 2008 target. The intramural program has undertaken studies of the nature of stem cell migration in adult tissues including a preclinical study in a rat model. Intramural researchers conducted preclinical MRI imaging studies using multipotent adult progenitor cells (MDPCs) in a rat hindlimb model of ischemia (inadequate blood supply/circulation to a local area due to blockage of the blood vessels to the area). The studies found that computerized imaging methods showed promise for assessing the effects of MDPCs on the restoration of blood flow to the ischemic hindlimb.

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-3.7 By 2019, develop at least two novel therapies for immune-mediated disease.

BACKGROUND

This goal is one of several new trans-NIH initiatives created within the Office of Intramural Research and focuses on the translation of advances in basic immunology research to the care of patients. The ultimate objective of this goal is to facilitate information sharing among clinicians, between clinical and basic investigators, and to develop new therapies for diseases involving the immune system. As a component of the goal, the NIH also plans to create a new center within the NIH intramural research program to foster collaborations that attempt to rigorously characterize similarities and differences in pathophysiologies, with a major objective being the determination of possible common mechanisms of inflammation or immunologically-based disease that could be treated with common therapies. Other objectives include the development of high-risk projects, less conventional areas; NIH investigator-initiated intra- and extramural clinical collaborations to better utilize the vast resources of the Clinical Research Center; establishment of specific core facilities, as examples, generating valuable reagents and to facilitate the development and execution of clinical protocols and novel drug development, and broader sharing of existing core facilities in tetramer biology, flow cytometry, cytokine measurements and other specific immunologic assays, and nucleotide sequencing; and expansion of current training programs.

Rationale

NIH is in a unique position to foster increased interaction among different clinical specialties and to create trans-disciplinary translational and clinical programs at the research and training levels. This effort would help to achieve horizontal and vertical integration of advances from a wide range of medical sub-specialties and between basic and clinical sciences. The program could be paradigmatic for research at NIH, allowing the more rapid development and testing of novel therapies to directly benefit patients; creating a new perspective for interdisciplinary training; and ultimately providing a model for focused trans-NIH research that is intended to be synergistic in its creation of opportunities without being directive and diminishing the valued role of the individual principal investigator. The NIH intramural research program is in the best position to attempt these types of integrated translational, clinical, or educational approaches because of its concentration of expertise and technical resources.

PERFORMANCE ANALYSIS

Target Context and Conditions

This initiative promotes research that can result in improved translational research for immune-mediated diseases and can directly result in improved therapies important and often unique biologic information from the study of humans. The spectrum of diseases that a trans-NIH initiative in autoimmunity and immunology could include is large and diverse. The broad scope of current disease research in the different Institutes should provide the required resources, communication, and cross-fertilization among the different disciplines that are at the heart of this initiative and justify the uniqueness of NIH in attempting this type of endeavor.

NIH investigators, in collaboration with extramural academic investigators, have launched two clinical projects to address the failure of interferon-based therapy in patients with late-stage chronic hepatitis C and to gain insight into the mechanism of non-response to interferon-based therapy and develop new strategies to improve the treatment response rate. Complementing these areas of investigation will be research to establish the role of early cellular immune responses in the outcome of acute hepatitis C virus.

Antithymocyte globulins (ATG), biological agents with complex immunosuppressive and immunomodulatory effects are widely used and effective in immune-mediated human diseases, including for the treatment of graft-versus-host disease in stem cell transplantation, to prevent and treat graft rejection in solid organ transplantation, and in a variety of autoimmune hematologic diseases. ATGs from horse and rabbit sources are often used interchangeably, but laboratory data suggest that they are not identical, and their mechanisms of action are imperfectly understood. The relative efficacy of horse and rabbit ATGs in aplastic anemia needs to be tested with concomitant laboratory studies of lymphocyte phenotype and function. NIH anticipates developing a protocol, including ancillary assays of immunologic function, to improve administration of the immunosuppressive biologic anti-thymocyte globulin from horse and/ or rabbit in the treatment of an autoimmune disorder.

With advances in high-throughput technology, researchers engaged in large-scale genome-wide association studies are now able to examine genetic variations in a shorter time frame and at a much lower cost. Sample collection is underway for a genome-wide association study of Behcet's disease, a complex disorder of inflammation affecting skin, eyes, gastrointestinal tract, lungs, vasculature, and joints. NIH researchers have obtained new technology to examine these data in order to identify susceptibility genes that could be used to develop targeted treatment strategies.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							Develop a protocol, including ancillary assays of immunologic function, to improve administration of the immunosuppressive biologic anti-thymocyte globulin (from horse and/ or rabbit) in the treatment of an autoimmune disorder.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SRO-3.8	**By 2016, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment.**

BACKGROUND

Breast cancer is the most frequently diagnosed cancer in women, with an estimated 178,480 new cases of invasive breast cancer expected in the United States in 2007. Over one-half of these women will have estrogen receptor positive, lymph node negative breast cancer. For 80 percent to 85 percent of those women, the current standard treatment practice is surgical excision of the tumor, followed by radiation and hormonal therapy. Chemotherapy is also recommended for most women, but the proportion of women who actually benefit substantially from chemotherapy is fairly small.

Rationale

The majority of women with early-stage breast cancer are advised to receive chemotherapy in addition to radiation and hormonal therapy, yet research has not demonstrated that chemotherapy benefits all of them equally. Because chemotherapy can cause serious side effects such as nausea, hair loss and fatigue, doctors want to find ways to identify patients who will benefit from chemotherapy and those who may be able to avoid it because of little added benefit. For women with node-negative, estrogen receptor-positive breast cancer, the benefit of adding chemotherapy to hormone therapy is small. The use of a molecular profiling test (a technique that examines many genes of the tumor simultaneously) in clinical decision making may more precisely estimate a woman's risk of cancer recurrence than standard characteristics normally used to assess recurrence risk (tumor size, tumor grade, etc.). This may spare women unnecessary treatment if chemotherapy is not likely to be of substantial benefit.

The Trial Assigning IndividuaLized Options for Treatment (Rx), or TAILORx, was launched to examine whether the level of expression in the tumor of genes that are frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment. Women recently diagnosed with estrogen receptor and/or progesterone receptor positive, Her2/neu negative breast cancer, which has not yet spread to the lymph nodes, are eligible for the study. This trial is one of the first to examine a methodology for personalizing cancer treatment, and it aims to change the way breast cancer is treated. It should improve the quality of patient's lives by identifying women who are likely to benefit from chemotherapy and those who are not. TAILORx seeks to individualize cancer treatment by using, evaluating, and improving the latest diagnostic tests.

PERFORMANCE ANALYSIS

Target Context and Conditions

TAILORx is sponsored by the National Institutes of Health (NIH), and is coordinated by the Eastern Cooperative Oncology Group (ECOG). Numerous clinical trials groups that perform breast cancer research studies have collaborated in the trial's development and are

participating in this study. The study will enroll over 10,000 women at 900 sites in the United States and Canada. Women will be studied for 10 years, with an additional follow-up of up to 20 years after initial therapies.

Molecular profiling with the Oncotype DX™ test will be used to analyze a specific set of genes within the breast tumor to determine a recurrence score. The recurrence score is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis. Based on their recurrence score, women will be assigned to three different treatment groups in the TAILORx study:

• Women with a recurrence score higher than 25 will receive chemotherapy plus hormonal therapy (the standard of care)
• Women with a recurrence score lower than 11 will receive hormonal therapy alone
• Women with a recurrence score of 11 to 25 will be randomly assigned to receive adjuvant hormonal therapy, with or without chemotherapy.

TAILORx is designed primarily to evaluate the effect of chemotherapy on those with a recurrence score of 11 to 25. The trial will require 4,390 women to be randomly assigned to ensure a statistically valid assessment of the effect of chemotherapy. Because the degree of benefit of chemotherapy for women with recurrence scores between 11 and 25 is uncertain, TAILORx seeks to determine if a validated diagnostic test (Oncotype DX™) will be helpful in future treatment planning for this group.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Accrue two-thirds of the TAILORx trial participants.	Complete accrual for the TAILORx trial.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$6,700	$7,500

SRO-4.3	By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults.

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver disease in the U.S. In the initial stage of the disease, fat accumulation in hepatocytes leads to the development of fatty liver (steatosis) that is characterized by excessive triglyceride deposition. NAFLD is often associated with elements of the metabolic syndrome, a clinical constellation of obesity, hypertension, insulin resistance, glucose intolerance, and hyperlipidemia, and encompasses a spectrum of liver disorders from simple hepatic steatosis to the more ominous condition known as NASH. NAFLD can eventually lead to severe fibrosis (cirrhosis), and in some patients hepatocellular carcinoma—all in the absence of alcohol consumption in amounts considered detrimental to the liver. NASH, the most severe form of NAFLD, is a progressive liver disease characterized by inflammation. Patients with NASH frequently have other co-morbid conditions such as obesity, diabetes, and hyperlipidemia (excess fatty materials in the blood)—components of the "metabolic syndrome," with insulin resistance emanating as the most significant and consistent underlying abnormality. NASH occurs most often in adults over the age of 40 who are overweight or have diabetes, insulin resistance (pre-diabetes), or hyperlipidemia. Approximately 5% of liver transplants are due to end-stage NASH.

Prevalence/Incidence

Although the true prevalence of NAFLD is unknown because it is unethical to perform liver biopsies on unselected asymptomatic patients from the general population, it is estimated to affect approximately 20-30% of the U.S. adult population. NAFLD occurs in all age groups, including children, and its prevalence increases with increasing body mass index. NASH is associated strongly with obesity and type 2 diabetes, conditions that have been increasing markedly in the U.S. population in the previous two decades. NASH accounts for about 10 percent of newly diagnosed cases of chronic liver disease, and ranks as one of the leading causes of cirrhosis in the United States.

Rationale

Given the rising prevalence of obesity in the general population, NASH is likely to become a significant future cause of liver-related morbidity and mortality. No approved treatments exist for NASH or NAFLD. An effective treatment for NASH—targeting the inflammatory component—would greatly impact morbidity/mortality and health care utilization associated with NASH.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH has initiated a randomized clinical trial to evaluate the safety and efficacy of pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with NASH (PIVENS). The target patient recruitment of 240 will be randomized into three arms, treated for 96 weeks and outcome measured by liver biopsy. The trial has significant industry sponsorship through a Cooperative Research and Development Agreement (CRADA).

Baseline: 2007

- (FY06) 176 participants of proposed 240 enrolled (73%)

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Complete total enrollment of 240 participants in PIVENS randomized clinical trial to evaluate the safety and efficacy of two new treatments for NASH in adults.	(MET) NIH completed enrollment of 247 participants by January 2007.	Retain/collect outcome data from greater than 85% of the participants in PIVENS to assess liver function.	Complete goal of evaluating the safety and efficacy of two novel treatments for NASH in adults

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$1,764	$1,600	$1600

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. NIH completed enrollment of 247 participants in the PIVENS randomized clinical trial by January 2007 exceeding the target of 240 participants. Seven additional participants were enrolled beyond the target because they were already in the screening process. Clinical trials screen more individuals than are needed because sometimes participants are determined to be ineligible during screening. It isn't ethical to screen and not randomize if the participant still wants to join the trial.

SRO-4.4	**By 2011, identify or study additional genes involved in communication disorders in humans and animal models.**

BACKGROUND

The NIH conducts and supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. These processes of sensing, interpreting, and responding are fundamental to the way the world is perceived and the ability to communicate effectively and efficiently.

The NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. NIH-supported scientists are actively working to understand the genes responsible for human communication disorders. NIH currently supports a broad portfolio of scientists working towards this goal, with the hope of using their knowledge to diagnose, treat, or cure communication disorders.

Below are highlights of the compelling needs of individuals who have communication disorders and the extraordinary research opportunities at the NIH that address these needs.

Prevalence/Incidence

Birth and Early Childhood

- Each year, approximately two to three out of 1,000 babies born in the United States have a detectable hearing loss, which can affect their speech, language, social, and cognitive development.
- About eight percent of American children in kindergarten have a disorder called specific language impairment (SLI). These children have difficulty developing and using language. These difficulties affect not only speaking but also reading and writing tasks.
- Middle ear infections (otitis media) are the most frequent reason that a sick child visits the doctor. The estimated total cost of otitis media in the United States is $5 billion per year. Children with otitis media can suffer temporary hearing loss during the infection as well as during treatment, and some may suffer permanent hearing loss.
- Approximately one out of every 200 American children is diagnosed with autism, a disease that interferes with normal language and social development. Boys are four times more likely than girls to be born with autism. Girls with the disorder, however, tend to have more severe symptoms and greater cognitive impairment.
- Roughly one million American children stutter. Stuttering affects individuals of all ages, but occurs most often in young children who are beginning to develop language skills. Boys are three times more likely to stutter than girls.
- Approximately five percent of American children entering first grade have noticeable speech (phonological) disorders, ranging from a few substituted and missing sounds

to serious impairments that make their speech difficult to understand. These speech disorders are about 1.5 times more prevalent in boys than girls. The majority of these speech disorders have no known cause.

- Flavor is the primary determinant of whether children under the age of two eat certain foods. Based on taste alone, about one-fourth of American infants and toddlers between seven and 24 months consume no vegetables and about one-fourth consume no fruits on a given day, which has important nutritional consequences.

Adulthood

- Approximately 15 percent (32.5 million) of American adults report some degree of hearing loss.
- There is a strong relationship between age and reported hearing loss: 18 percent of American adults 45-64 years old, 30 percent of adults 65-74 years old, and 47 percent of adults 75 years old or older have a hearing impairment. At all ages, more men (18.6 percent) than women (12.6 percent) report problems with their hearing.
- Approximately 10 percent (22 million) of American adults between 20 and 69 years old have suffered permanent damage to their hearing from exposure to loud sounds or noise at work or in leisure activities. Noise-induced hearing loss is more prevalent in men than in women.
- Nearly one million American adults have aphasia, a language disorder that results from damage to the language centers of the brain, and that can occur after a stroke or other brain injury.
- More than six million adults over the age of 60 have swallowing problems. Some swallowing disorders, such as from stroke, can put people at risk for aspiration pneumonia.
- Each year, 55,000 Americans develop cancer of the head and neck. Treatment for these cancers and other types of cancer may subsequently result in a loss of hearing, balance, or the ability to speak and swallow.
- Approximately four percent (almost eight million) of American adults report a chronic problem (lasting three months or longer) with balance, while an additional 1.1 percent (2.4 million) of American adults report a chronic problem with dizziness alone. Overall, the cost of medical care for patients with balance disorders exceeds $1 billion per year in the United States.
- Balance disorders are a major cause of falls by American older adults, and are the most common reason individuals over the age of 75 visit their primary care physician. Patient care costs for these falls are more than $8 billion per year.
- An estimated 24.5 percent (approximately 15 million) of Americans 55 years old or older suffer olfactory impairment, which increases with age. Approximately 30 percent of Americans between the ages of 70 and 80 and 62.5 percent over age 80 experience problems with their sense of smell. Impairment in olfaction can have serious consequences, such as the inability to detect the foul smelling odorants that are added to natural gas as a warning sign of leaks.

PERFORMANCE ANALYSIS

Target Context and Conditions

NIH-supported scientists are capitalizing on the wealth of knowledge available from the Human Genome Project. The scientists strive to identify and/or describe inherited genetic mutations that cause communication disorders or play a role in susceptibility to conditions that impair communication. Some areas of active investigation include hereditary hearing loss, gene variants that predispose an individual to develop age-related hearing loss or noise-induced hearing loss, genetic mutations that cause syndromes that include hearing loss, balance disorders, loss of the sense of smell and/or taste, or other communication disorders, genes inherited by individuals who stutter, and identification of genes that permit detection of tastants (sweet, sour, salty, bitter) and odors.

To use deafness genes as an example, NIH-supported scientists are examining target populations (for example, inbred families that carry deafness genes) to identify regions of DNA that may carry the mutation that causes deafness. Once a putative mutation-carrying region is identified, NIH-funded scientists compare as much DNA as possible from different families carrying deafness genes to published human DNA sequences found in databases. This helps them identify with more precision which region on the chromosome carries a mutation. The scientists must then sequence the mutated gene from the target population. In this way, they are identifying new genes responsible for hearing and for the maintenance of our ability to hear. When these important hearing genes are mutated, they disrupt hearing and result in hearing loss. By comparing normal and mutated hearing genes, NIH-funded scientists are able to describe how the protein produced by that gene functions in the normal and mutated states.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							Identify or describe one or more genes involved with human communication disorders.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$54,797

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SRO-4.5	By 2011, identify genetic and environmental factors which predispose to three complex diseases.

BACKGROUND

With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers now have a set of research tools that make it possible to find the genetic contributions to common diseases. The tools include databases that contain the human genome sequence, the HapMap, a map of human genetic variation and a set of new technologies that can quickly and accurately analyze whole-genome samples for genetic variations that contribute to the onset of a disease.

Recently made possible by the completion of the HapMap, a Genome-Wide Association (GWA) study is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat and prevent the disease.

Researchers already have reported considerable success using this new strategy. For example, in 2005, three independent studies found that a common form of blindness is associated with variation in the gene for complement factor H, which produces a protein involved in regulating inflammation. Few previously thought that inflammation might contribute so significantly to this type of blindness, which is called age-related macular degeneration.

Similar successes have been reported using GWA studies to identify genetic variations that contribute to risk of type 2 diabetes, Parkinson's disease, heart disorders, obesity, Crohn's disease and prostate cancer, as well as genetic variations that influence response to anti-depressant medications.

Although genetic variation can contribute to the onset of disease, a person's environment also influences disease susceptibility. Environmental factors such as diet, activity level, and stress, have been linked to common diseases such as cardiovascular disease and diabetes.

Rationale

Recent increases in the incidence of chronic diseases such as type 2 diabetes, childhood asthma, obesity, or autism are unlikely to be due to major shifts in the human genome, and are then most likely to be a result of changes in environments, diets, and activity levels.

Both an individual's genes and environment can increase disease risk, but these risks seldom operate independently. Subtle variations in a person's genetic code may have little effect on their risk of disease unless they are exposed to a specific environmental trigger; conversely, low level environmental exposures most common in this country may have little impact on disease risk unless the person exposed is genetically susceptible. To better understand the processes by which gene-environment interactions cause common chronic diseases, the HHS

Secretary proposed the Genes and Environment and Health Initiative (GEI), which will examine these interactions at the level of the individual.

The GEI will have two main components: (1) The Genetics Program, a pipeline for analyzing genetic variation in groups of patients with specific illnesses using a GWA study; and (2) The Exposure Biology Program, an environmental technology development program to produce and validate new methods for monitoring environmental exposures that interact with a genetic variation to result in human diseases. All data from this initiative will be placed in NIH databases and can be accessed by NIH-approved users.

Ultimately, the information and tools generated will be used to generate a better understanding of gene-environment interactions. In disease etiology that can translate into improved health care and early, more effective interventions.

PERFORMANCE ANALYSIS

Target Context and Conditions

The GEI initiative was created to identify genetic and environmental factors which predispose complex disease, and to investigate the interplay between the two.

An initial step towards understanding the interaction of genetic and environmental factors which lead to common complex diseases is to perform GWA studies for diseases of interest. That is to say diseases for which environmental factors have been implicated.

The 2009 target - "complete genome-wide genotyping for three complex diseases, such as type 2 diabetes or cardiovascular disease" - will generate the genetic information that will be investigated in concert with environmental studies.

As of 2007, only a handful GWA studies have been completed, and many have not been replicated, an essential step in order to validate the results of the study.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							Complete genome-wide genotyping for three complex diseases, such as Type 2 diabetes or cardiovascular disease.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$67,494

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SRO-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 28 million people, surpassing tuberculosis and malaria as the leading cause of death from infectious disease worldwide. In 2006, an estimated 39.5 million of the world's population, including 2.3 million children younger than 15 years of age were living with HIV/AIDS. In addition, almost 3 million people died from AIDS in 2006, and more than 4 million people were newly infected with HIV, of which 530,000 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 newly diagnosed infections have remained relatively stable at approximately 40,000 per year, the proportion of new HIV infections that occur among adults over 50 years of age and some racial and ethnic groups continues to rise.

Disease Burden

The impact of the AIDS pandemic is profound. Although global availability of resources to combat HIV/AIDS has increased since 2001, the populations most affected by HIV are still at greater risk of poverty, hunger and childhood mortality than those less affected by the pandemic. In some parts of southern Africa, adult prevalence of HIV infection is 25 percent or greater and prevalence amongst pregnant women who attend antenatal clinics can be more than 40 percent. The AIDS pandemic continues to destroy families and communities and to thereby weaken and threaten the social stability and national security of developing nations. There is evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States and some European countries and of similar hidden epidemics in Latin America and Asia.

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 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

Target Context and Conditions

NIH-supported clinical trial networks, with more than 100 U.S. and international sites at major medical centers, academic institutions, and community-based clinics, conducted Phase I through Phase IV therapeutic clinical studies between FY 2002 and FY 2007 that were designed to evaluate the safety and efficacy of drug regimens to treat and control HIV disease, and to prevent and treat the various complications and co-infections associated with HIV/AIDS among adults, adolescents, and children. In addition, the networks conducted studies designed to identify strategies for preventing mother-to-child transmission of HIV. The standards of care for the treatment of HIV infection and its associated illnesses in the United States and Western Europe continue to be based, in part, on important clinical findings from many of these NIH-sponsored therapeutics clinical trials.

In FY 2006, the HIV/AIDS clinical trials networks funded by the NIH were restructured. Awards for the Leadership Groups for HIV/AIDS Clinical Trials Networks were made in FY 2006, while the vast majority of awards for affiliated Clinical Trials Units (CTU) and Clinical Research Sites (CRS) were made in FY 2007. As a result of the restructuring, six networks were funded, expanding NIH's clinical research capacity and better integrating global HIV prevention, vaccine, and therapeutic research activities. Each network focuses on one or more of NIH's highest HIV/AIDS research priorities, which are: developing a safe and effective HIV vaccine; conducting translational research for new drug development; optimizing clinical management of HIV/AIDS, including co-infections and other HIV-related conditions; developing microbicides to prevent HIV acquisition and transmission; creating strategies to prevent mother-to-child HIV transmission; and developing new methods of HIV prevention.

Two of the funded networks—the AIDS Clinical Trials Group (ACTG) and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) —are pursuing research on 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; and improved adherence. The ACTG also has a translational research portfolio to move new therapeutic approaches (e.g. new agents and immunomodulators) into the clinical setting. A third network, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), was funded to conduct research in the areas of prevention of mother-to-child transmission, optimization of treatment for HIV and co-morbidities in children, adolescents, and pregnant women; evaluation of vaccines for the prevention of mother-to-child transmission, sexual transmission of HIV among adolescents, and therapeutic use; and translational research and drug development of pediatric

formulations and antiretrovirals for use in pregnant women. In addition, the NIH funds the International and Domestic Pediatric and Maternal HIV Clinical Trials Network and the Adolescent Trials Network, which work collaboratively to develop and conduct studies with the NIH-funded HIV/AIDS clinical trials networks as well as with other international networks such as the Pediatric 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, primarily through collaboration with other NIH partners and agencies.

Baseline: 2007

- FY 2003 to FY 2006 results

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(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.	(MET) NIH achieved and exceeded this goal by completing 2 studies (one in children and one in adults) that compared the effectiveness of different treatment approaches and 2 trials in adults that evaluated combinations of agents against the current standard of care.		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$724,742	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target and overall GPRA goal were MET and exceeded. In the past two years alone, the NIH completed four Phase III/IV studies that achieved this goal: one study evaluated when to initiate antiretroviral therapy in HIV-infected infants; one compared two different treatment approaches for HIV-infected adults, namely, continuous versus episodic use of antiretroviral therapy; and two studies evaluated some of the most common first-line treatment regimens for HIV-infected adults.

The results of the first two studies—one to determine the optimal time to begin antiretroviral therapy (ART) for HIV-infected infants under three months of age, and one to address the clinical management of HIV-infected adults—are highlighted below.

• Children with HIV Early Antiretroviral Therapy (CHER). This study evaluated whether early antiretroviral therapy (ART) given over a limited period of time to HIV-infected infants would delay progression of disease compared to those treated only when their immune

system began to decline. The current standard of HIV care in many parts of the world is to treat infants with ART, but only after they show signs of illness or a weakened immune system. The CHER study enrolled infants infected with HIV into one of three groups: one group received immediate ART for 40 weeks; a second group received immediate ART for 96 weeks; and a control group, whose treatment was initiated only after doctors observed signs of clinical or immunological progression toward the development of AIDS. During an interim analysis, data from the CHER study showed that there was a significant increase in survival among infants who received immediate ART (96 percent) compared to infants who received therapy later (84 percent), based on declining immune function linked to a defined CD4 T cell count and/or clinical progression. The study demonstrated that early diagnosis of HIV infection and initiation of ART resulted in a 75 percent reduction in early mortality in HIV-infected infants in the resource-limited settings in which it was conducted. These findings are significant because they show that deaths may be prevented by treating infants as soon as they are found to be HIV-infected instead of waiting until they show signs of HIV disease. It also highlights the need for early and improved testing of infants so that those who are HIV-infected can be identified quickly. These results could have a significant impact on global health, and lead to changes in the standards of care for the clinical management of HIV-infected infants.

• Strategies for Management of Antiretroviral Therapy (SMART study). The use of ART is associated with multiple risks, including metabolic and cardiovascular complications, waning adherence, and HIV resistance. This study compared the clinical outcomes associated with two ART strategies: continuous drug therapy, designed to suppress viral load as much as possible; or episodic ART, where ART was used only when the CD4 T cell count was below a certain threshold. The results demonstrated that continuous ART was superior to episodic ART. Episodic ART was associated with increased risk of death and disease progression, compared to continuous ART. Contrary to predictions, physical functioning, general health perception, and energy scores—all measures of quality of life (QOL)—actually worsened among patients in the group that received ART intermittently compared to those who received it continuously. These data demonstrate that interrupting ART, even when CD4 T cell counts are high, places patients at risk, and may not improve QOL.

The two studies that compared regimens against the current standard of care [Efavirenz (EFV) plus two nucleoside reverse transcriptase inhibitors (NRTIs)] are highlighted below.

• Activity of EFV-based regimens in treatment-naïve patients across a range of pre-treatment HIV-1 RNA levels and CD4 cell counts: ACTG 5095. The use of two NRTIs plus EFV (which is a non-nucleoside reverse transcriptase inhibitor, or NNRTI) is widely used as the initial treatment regimen for HIV-infected individuals worldwide, but concern remains about its potency in patients with high viral loads or low CD4 T cell counts. This study compared three treatment regimens (EFV plus two NRTIs, EFV plus three NRTIs, and three NRTIs alone) in HIV-infected individuals with a wide range of viral loads and no previous treatment. Early results showed that regimens containing EFV were superior, and the third arm of the study was stopped. The final comparison of two regimens containing EFV showed no significant treatment differences in HIV-1 RNA or CD4 responses. This study is significant because EFV is one of most common treatment regimens for HIV-infected

individuals in the United States who have not received prior therapy for HIV infection. This study debunked the long-held belief among many clinical practitioners that EFV-based regimens do not work as well in people with lower CD4 T cell counts or higher viral loads. This study also showed that using an additional NRTI in an already-potent EFV-based regimen did not improve outcome.

• A prospective, randomized Phase III trial of NRTI-, protease inhibitor (PI)-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection: ACTG 5142. This study compared three drug-sparing regimens for HIV-infected individuals who had not received prior treatment for HIV. The three regimens compared were EFV plus two NRTIs, Lopinavir/ritonavir (LPV) plus two NRTIs, and a combination of LPV plus EFV. This was the first study to do a head-to-head comparison of the two first-line U.S. regimens (the NNRTI-based EFV plus two NRTI, and the PI-based LPV plus two NRTIs). It was also the first randomized comparison of standard-of-care regimens with the nucleoside-sparing regimen of including LPV and EFV. The study was designed to detect differences between the two regimens in terms of: 1) their ability to reduce the amount of virus in the blood, and 2) patient adherence. The results of this study suggest that EFV may offer better virologic suppression than LPV when combined with two NRTIs, and that the NRTI-sparing regimens including LPV and EFV may be equivalent to the often-prescribed antiretroviral regimen that includes both EFV and two NRTIs.

Over the past five years, NIH has met the annual performance targets that were designed to support various aspects of HIV treatment research. In meeting these targets, NIH addressed the need for building capacity in resource-limited settings, pursued research for treating complications and co-infections of HIV, conducted clinical trials of new drug and multidrug regimens, and evaluated both strategies for prevention of mother-to-child transmission of HIV and the impact of these interventions on future treatment options for women.

• In 2003, NIH increased capacity and training at sites located in resource-poor settings that were affiliated with the AIDS Clinical Trials Group (ACTG), the Pediatric AIDS Clinical Trials Group (PACTG), the International and Domestic Pediatric and Perinatal HIV Clinical Trials Network, and the Comprehensive International Program of Research on AIDS (CIPRA).

• In 2004, NIH supported studies for HIV-infected individuals who were co-infected with hepatitis C virus (HCV) or a fungus that causes cryptococcal meningitis (CM). HCV is a major cause of co-morbidity in HIV-infected individuals, and NIH-supported research showed that the combination of peginterferon and ribavirin was superior to the combination of interferon and ribavirin. Mortality from CM is high in the absence of appropriate therapy. NIH-supported scientists used animal models to determine that the combination of amphotericin B plus fluconazole had better antifungal potential compared to amphotericin B alone. This contributed to the design of an international clinical trial that will further determine the effectiveness of this treatment approach. The NIH also conducted studies evaluating treatment interventions for co-infected adolescents, including studies aimed at optimizing immune responses to vaccines for hepatitis B, influenza, and measles. The NIH also assessed the impact of improved penetration of antivirals into the central nervous system

compartment in individuals with HIV-associated neurologic disease.

• In 2005, the NIH initiated a clinical trial of a new anti-HIV drug (an orally administered viral entry inhibitor) and four trials of multidrug regimens. These trials were conducted through the ACTG and CIPRA.

• In 2006, NIH completed one study of viral resistance, two studies of antiretroviral dosing regimens in pregnant women, and one perinatal intervention study through the PACTG and the International and Domestic Pediatric and Perinatal HIV Clinical Trials Network. Three studies were also initiated through the ACTG and PACTG to examine treatment options for women and children who had previously been exposed to antiviral drugs to prevent mother-to-child transmission.

Advances or Other Highlights

NIH continues to acquire data on potential drugs for HIV and opportunistic infections (OI). Advances in web technology for reporting chemical information have permitted access by the public to non-confidential portions of an internal master database (339,000 compounds) through a web format (http://chemdb.niaid.nih.gov/struct_search/default.html). The NIH HIV/OI/TB Therapeutics Database also includes information about compounds and testing data for potential inhibitors of HIV, associated OIs, and selected viruses of medical importance, including those in the area of biodefense. Whenever possible, compounds in the database link to scientific papers or to chemical databases in other areas of the NIH, including PubMed, PubChem, National Library of Medicine (NLM)'s ChemID Plus, and the National Institute of Standards and Technology's HIV Structural Database (HIVSD).

Construction of a database to catalogue the cellular proteins known to interact with HIV-1 proteins during virus gene expression and replication was completed this year. Over 100,000 journal abstracts were screened and 1,448 human proteins that interact with HIV-1 were cataloged. A total of 2,589 unique interactions between HIV-1 proteins and human host proteins were identified. The database is now available to the public via the website of the National Center for Biotechnology Information of the NLM at: http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/.

The regulatory proteins of HIV-1 represent targets of high priority for the development of new drugs to combat AIDS. NIH contractors developed and validated cell-based assays capable of identifying inhibitors of interactions of the HIV regulatory proteins Rev, Tat, and Vif. During the past year, 675 compounds were screened in the Tat and Rev inhibition assays, and 68 inhibitors were identified. A 15,000-compound library was screened in the Vif interaction assay, and 14 compounds were identified as potential inhibitors. Compounds scoring positively in the described assays are undergoing confirmatory testing.

In 2007, the NIH also completed two studies related to the treatment of HIV co-infections. One examined the effect of concomitantly administered rifampin, a tuberculosis treatment, on the pharmacokinetics and safety of atazanavir, a protease inhibitor used for the treatment of HIV. Atazanavir, administered at twice the current recommended dose, did not maintain adequate blood levels when administered with rifampin. This is important because atazanavir is used frequently due to once-daily dosing and low risk of metabolic complications. If used

in patients receiving rifampin for the treatment of tuberculosis, the anti-HIV effects of atazanavir may be diminished. A second study focused on the concurrent treatment of HCV and HIV. Ribavirin is critical for treating HIV/HCV co-infection because it is the only approved small-molecule antiviral drug for HCV. However, some co-infected individuals may require the addition of an NRTI, such as zidovudine, for their treatment. This second study found that zidovudine remained efficacious when used in combination with ribavirin.

Also in the area of HIV therapeutics, the NIH reported the results of several other studies. One showed that the drug vicriviroc, designed to prevent the virus from entering human cells via the CCR5 co-receptor, has a potent antiviral effect when given to individuals who had prior treatment. Another study examined when to switch antiviral medication based on levels of HIV RNA. The latter study showed that delaying a change in ART may be a reasonable short-term strategy for individuals with very limited treatment options because they can no longer tolerate or respond to commonly used antivirals.

Additional analyses of data from the SMART study of individuals who received episodic versus continuous ART were published in FY 2007 comparing the rate of AIDS-related and AIDS-unrelated malignancies in the two groups. Malignancies traditionally thought to be unrelated to HIV infection are now more common than are HIV-related malignancies in treated populations. The analysis revealed that the rates of all malignancies were higher among those who were received intermittent ART. This result provides further evidence against the use of ART based on CD4 T cell count. To confirm this finding, data from this study were analyzed to determine the long-term clinical impact of structured treatment interruption in patients with multidrug-resistant HIV. The study showed that for individuals who experienced treatment failure due to multidrug resistance, an interruption in treatment before starting a new regimen does not have a benefit over an immediate switch to a new regimen.

NIH also funded a study that evaluated the response to nevirapine-based therapy in women with and without prior exposure to single-dose nevirapine for prevention of mother-to-child transmission. This important study demonstrated that if women started nevirapine-based therapy less than six months after single-dose nevirapine exposure, their virologic response was suboptimal compared to women who did not have single-dose nevirapine exposure. However, if women started nevirapine-based therapy more than six months following single-dose nevirapine exposure, the virologic response was similar in women with and without single-dose nevirapine exposure. These data have important implications for treatment of women following exposure to regimens for prevention of mother-to-child transmission.

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-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

Target Context and Conditions

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. Clinical sites send weekly reports to the Clinical Trials Manager and monthly calls are conducted to coordinate efforts between the sites. The coordinating center generates monthly data reports, which are shared with the site coordinators and investigators during the monthly calls. Strategies to encourage data timeliness are discussed during these calls. Follow up with individual coordinators is conducted, as needed.

Enrollment was completed in November 2006, and participants continue to be followed. Strategies to retain participants in the study include holiday cards, newsletters and a compensation plan. The plan was distributed among sites to encourage participant

compliance and long-term retention. Additionally, it promotes positive reinforcement of preventive care concepts related to cardiovascular health and lupus. Retention efforts and plans continue to be discussed during the monthly calls. Therefore, the NIH funding components participating in this goal are fully committed to supporting efforts toward its completion as outlined in the contract and consistent with current NIH fiscal year policies in effect at the time of funding.

Baseline: 2007

- (FY06) Number of Clinical Sites: 20

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) There are currently 16 sites actively recruiting patients into the study.	(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.	(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.	(MET) The sites exceeded their overall average recruitment goal of 3 new patients per month, by enrolling an average of 4.2 new patients per month. This rate increased steadily from September, 2003 to November, 2006, to an average of 13.5 new patients per month at the end of the enrollment period.	Implement two strategies to attain study medication compliance rate of at least 80 percent.	Complete goal of determining the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$726	$363	$363

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 performance target was MET. Twenty-one sites enrolled a total of 221 patients in the study between September, 2003 and November, 2006. The recruitment ended November 10, 2006, and patient follow-up is expected to be completed in December, 2009. The sites exceeded their overall average recruitment goal of 3 new patients per month. By the end of the enrollment period, the average enrollment rate was 13.5 new patients per month.

Advances or Other Highlights

The formation of two committees, comprised of the study's site investigators, has been proposed. These committees would facilitate the use of resources acquired from the APPLE trial, and would establish guidelines for future studies conducted by the Childhood Arthritis and Rheumatology Research Alliance network (CARRA), in which all investigators for the APPLE trial participate.

1) The Data and Biologic Specimen Committee would develop guidelines for the use of data and specimens collected by the investigators that are not needed for the primary or secondary outcomes.

2) The Publication Committee would provide oversight for all publications reporting results of the APPLE trial and related studies.

Efficiency

An enrollment improvement plan was implemented which created a significant increase in the monthly enrollment rate, exceeding the FY 2007 target. The plan included site visits by the principal investigator (PI) and NIAMS staff, to solve enrollment problems on a site-by-site basis. Increased personal contact with the site investigators raised the study's visibility among other physicians at the sites that were seeing lupus patients. Additionally, monthly teleconferences with the site investigators were implemented. The FY 06 target was to enlist 20 enrollment sites. Due to the low incidence of SLE in children, more sites were recruited in order to enhance the ability to achieve recruitment goals on time. Sites that were delayed in starting the trial due to logistical issues were dropped, resulting in a final 21 enrollment sites. These efficiency strategies have enhanced recruitment goals.

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

Target Context and Conditions

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.

Baseline: 2007

- (FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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).	(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.	(MET) Supported the development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds.	Use chemical libraries in high-throughput biological screens.	Complete goal of expanding the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medicines. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$68,332	$65,542	$73,196

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The 2007 target was MET by awarding 10 grants to investigators, 5 in 2005 and a second group of 5 awards in 2006 that are developing models and detection systems to measure and describe the absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) of bioactive compounds. In fact, an initial zebrafish model has been developed to detect cardiac arrhythmias of chemical compounds and is now undergoing testing to determine how accurate it is or if it needs further improvement. In addition,these grant awards will validate metabolic approaches to detect and identify metabolites by NMR and GC-MS methods in the urine or serum of rats, which have been treated with drugs that are known to cause liver toxicities in humans; use proteome mining methods to identify targets that may react with drug compounds or their metabolites; develop statistical and computational programs of structure-activity relationships properties to predict the ADME or toxicity properties of drug candidates; and develop multi-compartment models that consist of cultured hepatocytes and

intestinal cells and blood to model how drug candidates will be processed and metabolized by these cells and the compounds carried in blood.

Advances or Other Highlights

In addition to meeting the FY 07 annual target, the centers continue to increase the sharing of knowledge among researchers. In particular, the development of MAL3-101 is one success story highlighted here. MAL3-101, an inhibitor of the chaperone protein Hsp70, was synthesized using methods developed with support from NIH. Using this compound as a chemical probe of biological function, it was determined that Hsp90 (but not Hsp70) plays a crucial role in protecting small-cell lung cancer cells against apoptosis (cell death). This finding has very important implications for our understanding of fundamental biology as well as for cancer treatment.

MAL3-101 and related compounds have been provided to other groups who have published on the use of these compounds in other assay systems, including assays dealing with the important process of protein folding.

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-5.4	**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

Target Context and Conditions

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.

Baseline: 2007

- (FY06) Compounds identified in screens and advanced to various stages of preclinical development

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(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.	(MET) Twenty-one promising new small molecules identified.		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$51,634	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET EFFICIENTLY by discovering twenty-one promising new compounds. Between 2003 and 2007, the NIH supported screening efforts, chemical synthesis projects, toxicology studies, and efficacy studies in animal and cell models to develop small molecule drugs, diagnostic agents, and research tools for the nervous system. Twenty-one promising new compounds have emerged from these efforts.

The NIH supported the preclinical development of two PET radiotracers for imaging amyloid plaques, a characteristic pathological feature of Alzheimer's disease [1]. These two compounds, Pittsburgh Compound B and IMPY, are now FDA-approved. Researchers are using them to study beta-amyloid accumulation in normal aging human brains and in patients with neurodegenerative diseases.

The NIH funded the early development and preclinical testing of five promising new psychiatric drugs. Dihydrexidine analog DAR-0100 [2] and XHell053 [3] were developed through the Psychoactive Drug Screening Program, and YPK3089 [4] emerged from the Anticonvulsant Screening Program. Compounds XHell053 and YPK 3089 recently entered clinical trials as potential new anxiety drugs, and DAR-0100 is in clinical testing for schizophrenia. The NIH funded the discovery, early development, dose-range studies, and rodent toxicity studies for SRX246, which may eventually be developed into a new therapeutic for stress-related affective disorders like depression and anxiety [5]. The NIH also supported the synthesis and specificity testing of biphenyl-indanone A (BINA) and preliminary preclinical studies demonstrating its potential for treating anxiety, schizophrenia, and depression [6]. A pharmaceutical company is following up on this work, developing a compound similar to BINA that has entered clinical trials for schizophrenia.

Ten new compounds showed potential for treating addiction in NIH-funded preclinical studies. The NIH supported the synthesis and animal testing of TMPD [7] for nicotine addiction and JDTic [8], RTI-336 [9], and UMB-116 [10] for cocaine addiction. Animal studies suggest that AM 4113 [11] may be developed into an appetite suppressant with fewer side effects than similar compounds. Screens for new drugs to treat alcohol abuse uncovered DCUK [12] and JR-220 [13]. These two compounds, as well as MTIP [14], MJL-1 109-2 [15], and LY379268 [16], reduced alcohol drinking in NIH-funded animal model studies. MTIP has now advanced to early clinical testing.

Four new compounds show promise for treating neurodegenerative conditions, based on NIH research. The Neurodegeneration Drug Screening Consortium identified ceftriaxone as a potential drug for ALS in a screen of 1,040 compounds previously approved by the FDA for other diseases [17]. Ceftriaxone is now being tested in ALS patients. Researchers in the NIH intramural program showed that the HDAC inhibitor trichostatin A extended survival of SMA mice and significantly improved their body weight and motor functions [18]. Small molecule inhibitors of memapsin and p38α MAPK may form the basis for future Alzheimer's

drugs. NIH-funded researchers designed and synthesized memapsin inhibitors that could interfere with formation of amyloid plaques [19], and inhibitors of p38α MAPK rescued cellular and behavioral deficits in an Alzheimer's disease mouse model.

Efficiency

Investigators have discovered twenty-one promising new compounds. These gains will begin to address the shortage of new drugs to treat disorders of the nervous system. These new small molecules may become the basis for new research tools and candidate therapeutics.

SRO-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. 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. 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

Target Context and Conditions

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 will 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.

Baseline: 2007

- (FY05) Providers trained, subjects being recruited for intervention.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Three treatments have been adapted for community-based settings.	(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.	(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.	(MET) Research on treatments for drug abuse in community settings is progressing, data from completed behavioral protocols were analyzed and initial findings were reported in journals and at conferences.	Complete goal of developing and testing of two new evidence-based treatment approaches for drug abuse in community settings.	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$10,999	$9,045	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. Research on treatments for drug abuse in community settings is progressing, data from completed behavioral protocols were analyzed and initial findings are being reported

Research on treatments for drug abuse in community settings is progressing with a focus on increasing the efficacy of treatments among communities, as follows:

- In a multi-site randomized clinical trial of MET in community drug abuse clinics, MET resulted in sustained substance use reductions among primary alcohol users.

- Research from BSFT found that: specialized family treatment was more efficacious than group intervention in reducing conduct problems, associations with anti-social peers, and substance use, and it increased engagement in treatment ; family changes were associated with changes in behavioral problems among those families entering treatment with poor family function; physicians trained to begin diagnostic work and engagement over the phone prior to bringing in families for treatment improved engagement of family members reluctant to be involved.

- The Seeking Safety protocol completed follow-up on the enrolled subjects in February and achieved data lock in April. Research from Seeking Safety found that Seeking Safety treatment led by community substance abuse counselors can reduce PTSD symptoms at a statistically significant level.

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 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 2005, the median prevalence rate of current cigarette smoking by adults among the different

states comprising the United States was 24.9%. 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 $168 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. Through the in vivo development of 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. The vaccine has been shown to be safe and well tolerated in Phase I safety studies, and has shown a statistically significant degree of efficacy in Phase II and Phase IIb clinical trials. A Phase III clinical trial is needed to further determine the efficacy of this human vaccine as a treatment for tobacco addiction.

PERFORMANCE ANALYSIS

Target Context and Conditions

Crucial knowledge gaps hinder the ability to treat tobacco addiction optimally. Identifying new medications or targets to improve treatment will depend on funds being available to support this activity. Current basic (pre-clinical) and clinical research currently being conducted to identify new and better treatment options, includes:

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, and to determine the dose for the pivotal Phase III trial. The assumption is that vaccination will reduce the reinforcing effects of nicotine and result in smoking cessation, as well as be effective in preventing smoking relapse.

The Phase II nicotine vaccine trial is ongoing. All patients have recieved all five injections over six months, and the nine-month data key findings have been reported. The primary measure of outcome was eight weeks of continuous smoking abstinence from weeks 18-26 (following the first vaccination) of the study. Analysis of the primary endpoint showed a 36% quit rate compared to 14% for placebo in the high antibody responders (top 30%). All subjects will be followed up until 12 months from their initial injection. This study was designed to establish proof of concept and the optimal dose for the two pivotal studies that the FDA will require for marketing approval.

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.

Baseline: 2007

- (FY06) Preclinical work on compounds that target nicotinic or GABA receptors is continuing based on preliminary positive results.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(MET) Four candidate medications are now being tested.	Analyze results from the FY 2006 clinical trial (Phase II) to determine whether an additional clinical trial should be initiated.	Complete goal of identifying at least two new medications to be further developed and tested for the treatment of tobacco addiction.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$8,015	$7,152	$3,875

SUMMARY OF 2007 PERFORMANCE RESULTS

Target
The FY07 target was MET and exceeded. The Phase IIb trial of a nicotine vaccine was started in FY 2006 and the 12-month data from the ongoing trial was announced in September 2007. A human laboratory study on pregabalin was started after successful completion of a pilot study. Pregabalin has been substituted for tiagabine for the new study, due to an FDA warning for tiagabine.

Advances or Other Highlights
The Phase IIb trial of the nicotine vaccine was a multi-center, randomized, double-blind, placebo-controlled study to assess efficacy in 301 heavy smokers who wanted to quit. The purpose was to determine whether vaccination with the medication would result in a higher continuous abstinence rate than without it. The study was designed to establish proof of concept and the optimal dose for a Phase III program. Nine-Month data findings showed a 36% continuous abstinence rate for high antibody responders compared to 14% for placebo. And 12-month data confirm the highly significant trends seen in 6- and 9-month data.

A clinical trial to test a glycine antagonist as a relapse prevention medication is also in progress. 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 and a behavioral intervention. This clinical trial began in FY07 and is ongoing. The primary outcome measure will be smoking abstinence.

Efficiency
Clinical trials and human lab studies are being conducted on four candidate medications, instead of the two planned, for tobacco addiction. These four medications will enable treatment via different systems/approaches:

- antibodies that will block nicotine effects currently in a Phase IIb 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
- a GABA agonist (pregabalin) that should reduce nicotine's effects on the pleasure pathway currently being tested as a proof of concept.
- and a glycine antagonist currently being tested as a relapse prevention medication in a clinical trial.

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 separate mechanisms are being explored in these trials, the likelihood is high for the development of at least one new pharmacotherapeutic approach to the single largest addictive public health problem.

SRO-5.7	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 F-18-labelled-fluorodeoxyglucose positron emission tomography (FDG-PET), F-18-labelled-fluoro-L-thymidine (FLT-PET), and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

Rationale

Clinical trials in non-small cell lung cancer (NSCLC) have demonstrated that 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 currently used for oncologic drug approvals.

Uptake of 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 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

Target Context and Conditions

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 written 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

(http://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 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.

Baseline: 2007

- (FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.
- (FY05) Trial not complete.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(Target 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. (Target 2) Perform additional analysis of test-retest repeatability data from 1st year of trial.	(MET) 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 was conducted in 2007. (MET) Additional analysis of patient data from the FDG-PET lung trial has been conducted.	Correlate patient outcome data from the lung cancer therapy trial with serial functional imaging scan results to determine the efficacy of this imaging technique.	Complete accrual in FLT-PET lung cancer trial, and perform preliminary analysis of results leading to the validation of FLT-PET as an imaging modality for assessing lung cancer response to therapy.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$4,443	$4,409	$1,391

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2006 target extended to FY 2007 was MET. 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 was written and approved by the Cancer Evaluation Therapy Program (CTEP), initiating the trial and collection of test-retest repeatability data. 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).

The FY 2007 target was MET by analysis of patient data from the FDG-PET lung trial. Analysis of the data revealed a lag in accrual linked to a shift in the standard of care for patients in the clinical trial. Completion of the test retest evaluation will occur when sufficient cases have been accrued. Approval of the FDG-PET lung trial protocol required significant collaboration with multiple public and private partners. Further analysis identified the probable cause of the lag as a shift in the standard of care for patients in the trial to bevacizamab (Avastin®). This drug was approved by FDA on October 11, 2006 for use for initial systemic treatment in combination with other chemotherapy drugs of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer.

Advances or Other Highlights

In September 2005, a public web site (http://www.acrin.org), 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.

Approval of the FDG-PET lung trial protocol required significant collaboration with multiple public and private partners. The current FDG-PET trial protocol prohibits patients using Avastin to allow for test retest evaluation. The program managers are actively evaluating options to address the recruitment lag. The cooperative group conducting the trial (ACRIN) is currently surveying the trial sites to ascertain if modification of the protocol to permit bevacizumab use or recruiting additional sites will be more efficacious in increasing enrollment. Either option should not affect the actual analysis of test-retest reliability, just the timing of the analysis.

SRO-5.8	**By 2012, 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

Target Context and Conditions

To help ensure that investigators 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. Clinical validation and testing of these and similar devices were carried out in FY 2006 and FY 2007. Provided that research and development is successful, and a device becomes available commercially, a device would be incorporated into a clinical study which would be funded by the end of FY 2008. A clinical study to test an intervention for hot flashes using a device as one endpoint would be carried out in FY 2009, FY 2010, FY 2011, and 2012.

Baseline: 2007

- (FY06) Prototype device from FY05 target should be available for additional validation testing.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(MET) NIH initiated seven research projects.	Develop and validate improved devices to measure hot flash frequency.	(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.	(MET) NIH-supported researchers continued validation of three sternal skin-conductance monitors to measure hot flash frequency.	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.	Complete 20% of planned study subject accrual.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$300	$300

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. NIH-supported researchers continued validation of three sternal skin-conductance monitors to measure hot-flash frequency. In 2006, three Small Business Innovation Research grants were awarded to validate new sternal skin-conductance monitors against self-reported measures of hot-flash frequency. These data will be collected using portable electronic devices, which will also allow investigators to collect data on other menopausal symptoms. The grantees have further optimized the sternal skin-conductance monitors, developed portable electronic devices that are used to capture self-reported measures of hot-flash frequency, and conducted preliminary tests of the combined systems.

In 2007, each grantee has been conducting small clinical trials of peri- or post-menopausal

women using their respective hot-flash monitors and correlating the monitor responses with validated survey instruments. One grantee has also been examining the effectiveness of incorporating the Motionlogger Sleep Watch 2.0 (also known as actigraphy), which distinguishes sleep from wakefulness based on activity of the wrist. The actigraph records data including percent of time in bed asleep and awake, number and timing of awakenings per night, and length of awakenings at night. Another grantee has been conducting a small clinical trial integrating an electronic recorder that utilizes a validated survey instrument. The third grantee has been conducting a pilot clinical study to assess a portable electronic device to enable users to record subjective data immediately on hot-flash events.

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, these studies 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. 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

Target Context and Conditions

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. The NIH, a world leader in genomic research, will fund research to identify genetic factors across the genome that play a role in three major diseases for which health disparities are noted. Examples of some of the diseases currently under investigation include diabetes, hypertension, and prostate cancer. 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.

Finland-United States investigation of type 2 diabetes(FUSION) involves the phenotyping and DNA analysis of 2400 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. Researchers at NIH have been engaged in FUSION, a large collaborative study of more than 2400 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) 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.

The Pima Indians of Arizona have the highest reported prevalence of type 2 diabetes mellitus (T2DM) of any population in the world. They are also a very obese population. Studies have shown that both T2DM and obesity are heritable diseases. The goal is to identify and characterize susceptibility genes for T2DM and obesity among this American Indian population using positional cloning in chromosomal regions identified through linkage studies. Results from the linkage study in Pima Indians indicate a locus linked to both obesity and T2DM on chromosome 11, and a second locus linked to T2DM alone on chromosome 1. In its next phase, a high density single nucleotide polymorphism map will be pursued which will facilitate identification of genetic variations associated with both obesity and T2DM.

Baseline: 2007

- (FY05) No FBPP data publicly available to the scientific community.
- (FY06) Scientific infrastructure established and RFP for initial scan released.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(EXT) The pooled data with documentation and web utility were made publicly available in September 2006. Public data training is scheduled for March 2007.	(Target 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. (Target 2) Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study.	(MET) The program data center successfully completed a Public Access Data Training Workshop on March 13 -14, 2007. (MET) NCI performed initial whole genome scan for C-GEMS study.	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.	Begin biologic assessment of the most likely diabetes/obesity susceptibility genes in regions of linkage/association.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$13,447	$6,707	$4583

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2006 target, extended to 2007, was MET. The pooled data with documentation and web utility were made publicly available on September 21, 2006, and the program data center successfully completed a Public Access Data Training Workshop on March 13 -14, 2007. The goals of the March training session were to introduce researchers to the new web-based system for accessing the data and to educate them about the data set, protocols, and variables measured as well as about the data access application process. One of the goals of the FBPP data generated by the four FBPP networks allow researchers in the larger scientific

community to conduct additional analyses of genes that contribute to hypertension and related conditions in multiple racial and ethnic groups. As a result, the FBPP has created a database containing a pooled data from the four FBPP networks that can be accessed online by authorized researchers.

The FY 2007 target was MET EFFICIENTLY. The NIH's Cancer Genetic Markers of Susceptibility (CGEMS) team performed a genome-wide association study (GWAS) of 550,000 SNPs in 1,172 individuals (484 with nonaggressive prostate cancer, Gleason o7 and stage A/B; 688 aggressive prostate cancer, Gleason Z7 and/or stage C/D) and 1,157 "control" individuals who did not develop prostate cancer during the same time period in the Prostate, Lung, Colorectal, and Ovary (PLCO) Screening Trial. The prostate scan was conducted in two parts, Phase 1A and Phase 1B. The data on the initial scan was released to the public on http://cgems.cancer.gov on October 19, 2006 (see press release on GWAS data release).

A strong genetic association with prostate cancer susceptibility from the genome-wide scan was found at human chromosome 8q24(at the SNP rs6983267) and was followed up with immediate replication in four other populations to validate the finding. This variant is associated with a population attributable risk of prostate cancer of 21% (in men of European ancestry). The results of the 8q24 findings were published in Nature Genetics, online April 2007. The GWAS also validated a previously identified SNP, rs1447295, within the human chromosome 8q24 region that was reported to be associated with a population attributable risk for prostate cancer of 9% (in men of European ancestry).

Six percent of the initial SNPs from the GWAS, those that had the greatest positive associations with prostate cancer (~28,000 SNPs) were carried into the first replication round to validate the findings from the primary scan (see diagram of study design). The data from the first round of replication is currently being quality controlled and analyzed. After the replication strategy is complete, it is expected that approximately 10 positive genetic variants will be identified that have a significant genetic association with the risk of prostate cancer. Validation of the initial GWAS findings is being carried out as part of intramural/extramural collaborations among the NIH's Cohort Consortium initiatives.

Advances or Other Highlights

Additional GWAS studies in multi-ethnic populations, carried out by extramural cancer investigators, have identified additional genetic associations in the chromosome 8q24 region that independently affect risk for prostate cancer in African Americans (Proc. Natl. Acad. Sci. USA 103, 14068–14073 (2006), Nature Genetics 39, 638 - 644 (2007).

Efficiency

The cost of SNP genotyping has been decreasing as the technology has advanced. During the CGEMS initiative, the research plan has been modified to allow for the inclusion of additional study participants within the replication phases, which has increased the statistical power of this research study.

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-5.10	**By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures.**

BACKGROUND

Breast cancer is a complex disease, the causes of which have eluded scientists for many decades. Improvements have been made in early disease detection, surgical and medical modalities for treatment and survival for women with breast cancer. Although scientists and clinicians understand more today about the process of carcinogenesis (the process by which normal cells are transformed into cancer cells) and genetic susceptibility, effective prevention strategies targeting the causes of breast cancer remain out of reach due to the multiplex of factors involved in breast cancer causation.

Functioning as a consortium of basic scientists, epidemiologists, research translational units, and community advocates within and across centers, the Breast Cancer Environmental Research Centers (BCERC) are investigating mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood and will hopefully lead to strategies that better prevent breast cancer.

Currently there are two broad areas in the BCERC – a basic science project and an epidemiology project. The basic science project is currently composed of 4 centers that are studying environmental effects on the molecular architecture and function of the mammary gland across the lifespan in rodents. The epidemiology project will recruit young girls into a study for assessing the association of 12 environmental agents – including endocrine disruptors that may leach from plastics such as bis-phenol a and phthalates – on markers of early puberty, which is a risk factor for breast cancer.

The purpose of this scientific program is to answer questions that focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Answering these questions will allow the translation of such findings into information that can be applied to increase awareness of the causes of breast cancer.

Prevalence/Incidence

This study is focused on early onset of female puberty and is not a disease. However, early onset of puberty is a risk factor for breast cancer, which is diagnosed in 250,000 women in America each year.

Disease Burden

Breast cancer results in 50,000 deaths in America each year. One third of the prevalence is in women of child-bearing age and causes significant economic and medical-system burdens. By one estimate, the total economic cost of breast cancer was $56 billion dollars in 2000, making this form of cancer the most costly among cancers.

Rationale

Despite intense research over the past decade into the potential environmental influences on breast cancer, few candidate exposures have been confirmed. Only irradiation is universally accepted as a cause for breast cancer. However, genomic, post-atomic blast survivor, and international migration studies indicate that breast cancer is largely an environmental disease. Much of the data suggests that time of life exposure is a critical factor in the risk of disease development. Girls in industrialized nations are increasingly experiencing markers of onset of puberty at earlier ages. This study is a first step to determine whether puberty is a critical "window of exposure" that could predispose women to eventual disease pathogenesis (the origination and development of disease). This project will attempt to examine dietary and environmental agents that might play a role in early puberty and, thus, increased breast cancer risk, as well as improved ways of assessing traits indicative of early puberty.

PERFORMANCE ANALYSIS

Target Context and Conditions

This is a seven-year study to determine the risk factors associated with early onset and altered puberty in girls. The study length was chosen to allow for in-depth observation and analysis of the girls' progression through puberty, from age 6-8 to 14.

Approximately 1200 girls are recruited in the three Centers' regions from schools and day-camps. They are examined twice annually for signs of puberty, and are asked to keep diaries, use pedometers, and answer questionnaires concerning their diet, exercise regime, and likely exposures at home and work. Blood and urine samples are collected annually at the clinics associated with the Centers and used for genome and biomarker analysis. Urine, as well as blood, is used for the regular determination of chemical to which the girls were exposed. In addition, blood samples allow for determination of gene variations that may indicate the susceptibility of an individual to a particular exposure. The samples present an unique opportunity to determine body burden for a select list of candidate exposures and to directly associate those exposures with changes in female puberty. Exposures and pubertal changes are also correlated with subtle variations in genes of interest.

The investigative teams met on multiple occasions and through tele-conferences for over a year in order to jointly draft protocols, questionnaires, train examiners, and create other investigative instruments for the study. Epidemiologists also met with laboratory biologists and outreach experts in the study to produce cross-cutting, transdisclipinary studies to facilitate in-depth analysis on animal models of exposures that are likely to alter female puberty, and to set the stage for translation of messages on life-style choices that can be transmitted to local and national communities. These activities are now underway.

Baseline: 2007

- (FY06) Analyzed urine specimens of 90 girls across study sites for selected exposures.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Complete recruitment of 1,200 girls; complete pilot analysis of selected environmental exposures.	(MET) Recruited 1244 girls and completed pilot urine analysis. Yr 2 clinical exams and data collection are on target.	Conduct Year 2 follow-up clinical exams and data collection for 75% of the cohort to examine the presence of specific markers of exposure and correlate with signs of puberty.	Conduct Year 3 follow-up clinical exams and data collection for 75% of the cohort to examine the presence of specific markers of exposure and correlate with signs of puberty.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$5,134	$5,198	$5,264

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. The study completed the recruitment of a 1244 girl cohort to determine how pre-pubertal diet, obesity, and environmental exposures, which are being directly measured for the first time, alter the time of first menstruation and later breast cancer susceptibility. Because of the limited existing data on early exposure, an important expected advance from this research is the discovery of blood and urine biomarkers in the girls that determine the presence of common chemical exposures and to establish their limits of detection. This will serve as a basis for the hypothesis in this study and others. A pilot analysis was completed on the urine of 90 girls from across the county, testing for 25 urinary analytes representing 22 separate agents from three chemical families: phytoestrogens, phthalates, and phenols.

SRO-5.11	**By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes.**

BACKGROUND

Symptoms such as pain and fatigue are associated with a wide range of acute and chronic diseases, as well as treatments for such diseases. For example, people living with HIV/AIDS often experience severe fatigue, while patients being treated for various forms of cancer may experience debilitating pain as a consequence of chemotherapy. Such symptoms can have significant, adverse effects on health outcomes and quality of life for these patients. Symptoms reduce functional status, may cause patients to reduce or abandon treatment, and can cause considerable psychological distress and even depression. Therefore, along with ongoing work in finding new and better ways to prevent and treat disease, NIH scientists are exploring new strategies for managing and reducing the symptoms associated with various health conditions. It is anticipated that these research efforts in symptom management will lead to a decreased burden of illness and improved quality of life for patients suffering from acute and chronic disease.

Rationale

Behavior and biology often interact in complex ways to influence health outcomes. For example, a behavior such as exercise may confer as yet undefined and far-reaching benefits to disease sufferers through a combination of biological and psychological mechanisms. NIH-supported researchers are currently elucidating these complex interactions and leveraging this knowledge to improve health outcomes. To date, NIH-supported scientists have successfully employed behavioral interventions to increase treatment adherence for those with chronic diseases such as diabetes and HIV/AIDS, and to improve disease prevention habits for those at risk of developing disease. The intimate relationships between biology and behavior point to behavioral strategies as promising avenues for reducing symptom burden. The successful development of such strategies could significantly improve the ability to reduce the effects of disease, disability, and psychological distress on quality of life and health outcomes.

PERFORMANCE ANALYSIS

Target Context and Conditions

Over the next several years, NIH-supported scientists will work to systematically identify and test the effectiveness of behavioral methods for improving symptom management. Efforts will initially focus on identifying candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies. Next, behavioral strategies designed to manage these candidate symptoms will be identified and assessed for the ability to impact patient quality of life. The initial years of this goal will thus provide an opportunity to assess the current state of research into using behavioral methods to manage symptoms, and to identify promising behavioral strategies for further testing in reducing the effects of disease, disability or psychological distress on health outcomes.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Conduct an analysis of current literature to identify at least three candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies.	Assess the impact on patient quality of life of a cohort of behavior-based symptom management strategies designed to manage candidate symptoms identified in FY08 analysis.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$1,026	$4,056

SRO-5.12	**By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders.**

BACKGROUND

Drug addiction is a chronic, relapsing brain disease that can begin with occasional drug use, and over time lead to intense craving and compulsive drug taking, and relapse following periods of abstinence. A considerable body of evidence indicates that mechanisms of learning underlie the development of addiction, as well as other compulsive behaviors, and some anxiety disorders (e.g., posttraumatic stress disorder, obsessive compulsive disorder, specific and social phobias). Thus, interventions that can interfere with or reverse such learning would be expected to enhance treatment of these disorders (including relapse to drug abuse).

Prevalence/Incidence

Addiction is a common disorder. According to the National Survey on Drug Use and Health (NSDUH), in 2005, there were an estimated 22.2 million persons aged 12 or older (9.1 percent of the population aged 12 or older) meeting criteria for substance abuse or dependence. Substance abuse and dependence frequently co-occur with anxiety disorders, which is the most common class of mental disorders in the U.S. Approximately 40 million American adults ages 18 and older, or about 18.1 percent of adults in a given year, have a diagnosable anxiety disorder.

Disease Burden

Drug abuse is costly to Americans, tearing at the fabric of our society and taking a huge financial toll on our resources. Beyond its inextricable link to the spread of infectious diseases, such as HIV/AIDS, sexually transmitted diseases (STDs), tuberculosis, and hepatitis C, drug abuse is often implicated in family disintegration, loss of employment, failure in school, as well as domestic violence, child abuse, and other crimes. Placing dollar figures on the problem, smoking, alcohol and illegal drugs are estimated to cost this country more than half a trillion dollars per year, with illicit drug use alone accounting for about $180 billion in crime, productivity loss, health care, incarceration, and drug enforcement. In 2005, the number of persons needing treatment for an illicit drug or alcohol use problem was 23.2 million, and only 2.3 million of them received treatment at a specialty facility. In 2004, almost one-fourth of all stays in U.S. community hospitals for patients age 18 and older involved mental health or substance use related (MHSA) disorders.

Anxiety disorders are also extremely costly to Americans. During the 1990s, the annual cost of anxiety disorders was estimated at just over $43 billion, or approximately $1500 per sufferer. The leading costs for this class of disorders were attributable to direct medical and psychiatric care ($36.3 billion per year) and lost workplace productivity ($4.1 billion per year). Of the nearly 40 million American adults with a diagnosable anxiety disorder each year, only 37% seek psychiatric or medical treatment.

Rationale

Evidence indicates that conditioning and other types of learning play an important role in the development of addiction, and susceptibility to relapse, as well as anxiety disorders. Therefore, interventions that can interfere with or reverse such learning would be expected to enhance treatment of addictive disorders and some anxiety disorders. Extinction is an active process whereby previously learned associations are weakened and new ones formed. For this to happen, the underlying neural circuits must be modified. Thus, it should be possible to identify potential targets and molecules that enhance extinction by affecting relevant neural substrates; e.g., the prefrontal cortex--involved in cognitive and executive function, reversal learning, and attention; the amygdala--involved in emotional learning; and the dorsal striatum--involved in habit formation. Ultimately, this research will be used to guide and enhance behavioral and pharmacological interventions for the treatment of drug abuse, and other compulsive behaviors, including some anxiety disorders.

PERFORMANCE ANALYSIS

Target Context and Conditions

NIH has demonstrated its commitment to this area through the release of a Request for Applications entitled "Extinction and Pharmacotherapies," with the goal of stimulating research on the mechanisms underlying extinction in order to guide the development of interventions for enhancing extinction of drug-seeking behavior. The funded research may include investigations on how manipulations of learning and memory could control drug-seeking behavior using animal models; and studies to determine the biochemical and cellular changes occurring during extinction training. Research conducted under this RFA will ultimately be used to guide and implement combined behavioral and pharmacological/molecular interventions for the treatment of drug abuse relapse.

Because of the link between learning and other types of mental disorders, e.g. anxiety disorders, including phobias, other research investigating novel strategies to assess the link between fear conditioning/extinction, behavioral expression, and neurocognitive mechanisms will also be supported in patients suffering from anxiety related behaviors, traits and disorders and in animals and other models relevant to these traits and disorders.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							Test at least two compounds or medications in animal models of extinction of drug-seeking behavior.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$9,304

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

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

Target Context and Conditions

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.

Baseline: 2007

- (FY05) Modifier genes for AMD and glaucoma have not yet been identified.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(MET) Collected samples from over 4,000 well-characterized patients with either AMD or glaucoma. Created the National Eye Disease Genotyping Network (EyeGENE).	Develop animal models of AMD and glaucoma that closely mimic the pathologic processes underlying these diseases in humans.	(MET) Animal models have been established for glaucoma and age-related macular degeneration.	Conduct studies in animal models to identify potential modifier genes.	(MET) Genes that modify risk/progression of complex eye diseases were identified and validated using animal models.	Conduct haplotype analysis to identify common risk haplotype for genes associated with primary open-angle glaucoma (POAG) through single-nucleotide polymorphism (SNP) genotyping.	Determine the phenotypic expression of naturally-occurring or chemically- or environmentally-induced genetic changes in animal models of glaucoma or age-related macular degeneration (AMD) to characterize the genetic mechanisms involved in disease pathogenesis.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$10,546	$10,546	$10546

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. Numerous genes affecting eye diseases were identified and validated using animal models. Complex diseases such as age-related macular degeneration (AMD) and glaucoma depend on the interactions of multiple genes and environmental factors. NIH-supported research developed animal models in fish, rodents, and primates to identify and validate potential modifier genes—genes that do not cause disease alone, but modify risk or progression.

Genetic, laser-induced, and diet-induced models of AMD complications have permitted genetic dissection of biochemical pathways. Building on the 2005 discovery that complement factor H is a key AMD risk factor, new studies are demonstrating that genetic variation in innate immunity markedly impacts disease manifestation. Using a laser-induced choroidal neovascularization (CNV) animal model of AMD, the presence of complement regulatory protein (CD59) controlled CNV progression. NIH has made other progress in identifying modifier genes for AMD:

- AMD shares clinical and pathological features with Alzheimer's disease: they are both late-onset, neurodegenerative diseases featuring extracellular amyloid-beta peptide deposits. An Alzheimer's therapy that acts on amyloid beta partially rescued deficits in a mouse model of AMD.
- Genetic crosses in mouse models of AMD examined the relative contributions of four quantitative trait loci—multiple interacting genes that modify the disease traits—in conferring sensitivity to retinal degeneration.
- NIH scientists improved a current genetic model by knocking out a modifier gene (Cx3cr1), creating a more characteristic and reproducible model of AMD.
- A putative human modifier gene variant (EFEMP1) inserted in mice caused

pathogenic deposits resembling those seen in AMD.

Animal models complemented human studies in identifying and validating modifier genes for glaucoma. Mutations in the myocilin gene cause primary open-angle glaucoma (POAG). In POAG patients with myocilin mutations, a mutation in peroxisomal targeting signal type 1 receptor (PTS1R) was associated with a more severe early-onset POAG phenotype. Mouse models created with the human mutations exhibited elevated intraocular pressure—the first disease gene based animal model of human POAG. Also:

- CYP1B1, a causative gene in primary congenital glaucoma and a modifier gene in POAG, is involved in metabolism of steroids and retinoids. Mouse mutants exhibit abnormalities in ocular drainage and trabecular meshwork, similar to human patients, allowing the model to be used to determine the role of CYP1B1 in glaucoma pathogenesis. Clinical studies complemented this work.
- EphrinB expression was upregulated in laser-induced monkey model of glaucoma, possibly suggesting a protective role in limiting axonal damage and inflammatory cell invasion.

Advances or Other Highlights

Building on the success of NIH-wide collaborative efforts such as the International HapMap Project and Genome-wide Association Studies accessed in the Database of Genotype and Phenotype (dbGaP), NIH made significant progress towards the goal of identifying modifier genes in humans.

Epidemiology and genetics studies explored the importance of the complement system in AMD risk. Individuals with AMD risk-conferring variants of complement factor H (CFH) have elevated factors associated with inflammation (C- reactive protein) in the choroid. Human genetic analyses suggested that absence of two genes related to CFH may account for protective effects in human subjects with AMD risk-conferring variants. Other studies showed that complement factor B variants decreased the risk of AMD; complement component 2 had a weaker, independent effect. Using clinical trial data from the Age-Related Eye Disease Study (AREDS), genetic analysis validated the independent predicative value of two risk-causing gene variants (CFH and LOC387115) in the progression from early or intermediate stages to advanced stages of AMD. In addition, NIH awarded a new bioinformatics grant to identify genetic modifiers of AMD using data collected in AREDS. The grant seeks to explain disease risk in patients who do not carry disease variants of known genetic factors (such as CFH) or protective factors in patients expressing disease variant genes.

Other clinical studies explored the "barrier hypothesis" that lipids play an important role in the development of extracellular deposits, called drusen, in AMD. Genetics and cell culture experiments confirmed a decreased risk of AMD development with a variant of apolipoprotein E and its interactions with other genes involved in AMD (Ccl2, Cx3cr1, and VEGF). Human genome-wide scans looked for genetic linkage to discriminate between choroidal neovascularization and geographic atrophy outcomes in patients with AMD. Another study identified a potential modifier gene for AMD in a mutant enzyme that normally functions to breaks down other proteins (HTRA1). To understand the macula's propensity for degeneration, comparison of gene expression between the macula and the

periphery using microarray technology revealed differences in genes associated with inflammation, angiogenesis, and the extracellular matrix.

For glaucoma, comparison of elastic fiber proteins in the optic nerve head from African American and Caucasian populations suggested that ELN and LOXL2 may be candidate susceptibility genes. Separate population analysis determined the contributions of four mutations in the optineurin gene in glaucoma. Also, genetic studies assessed the impact of a human mutation in glaucoma modifier gene myocilin.

SRO-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 and 7.8% of the risk of CVD is attributed to 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. As rates of diabetes rose the proportion of CVD risk attributable to diabetes increased by 50% from the 3rd to 4th quarter of the 20th Century. 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-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, however their effect on CVD risk remains to be determined.
- Kidney transplant recipients typically have reduced levels of kidney function, thus can be considered chronic kidney disease 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

Target Context and Conditions

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-6.2 by 2011. For example, the Goal SRO-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).

Baseline: 2007

- (FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.	(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.	(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.	(MET) FAVORIT enrolled and randomized the total trial population (4,000 patients) from sites located in the United States, Canada, and Brazil, by January 2007.	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.	Complete treatment and follow-up of participants in the ACCORD trial to determine effects of glycemia, blood pressure, and blood lipid treatment approaches to prevent CVD in diabetes.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$47,059	$52,707	$46,349

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. FAVORIT enrolled and randomized the total trial population (4,000 patients) from sites located in the United States, Canada, and Brazil, by January 2007. In 2005, the trial was not meeting the planned recruitment levels to complete 90% enrollment by September 30, 2007. Therefore, the NIH took corrective action to revitalize enrollment in FAVORIT by adding 10 recruitment sites. This enabled the FAVORIT trial to achieve the recruitment target of 4,000 participants earlier than expected in 2007. The FAVORIT trial aims to determine whether reduction of level of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in arteriosclerotic CVD compared with a control group whose homocysteine levels are expected to remain the same over time.

Advances or Other Highlights

The Look AHEAD baseline characteristics of the randomized cohort was published in Diabetes and Vascular Disease Research 3:202-215, 2006. The Look AHEAD consent for genetics studies among clinical trial participants was published in Clinical Trials 3:443-456, 2006. The Look AHEAD one-year outcome data paper was published in Diabetes Care 30:1374-1383, 2007. Two papers describing the baseline characteristics of participants in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial have been completed.

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-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

Target Context and Conditions

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 an 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 implemented 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.

Baseline: 2007

- (FY06) Initial integration of microarray and toxicologic/histopathologic data achieved

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.	(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.	(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.	(MET) Developed a consensus checklist for study data and metadata; designed prototype format for uniform deposition of data and metadata; and implemented an application to facilitate construction of formatted data and metadata files.	Complete goal of developing a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$4,210	$4,077	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. In order to achieve a consensus view on the information to include when sharing this data NIH developed a checklist of the minimal information to include when describing a study. (Fostel 2007) Researchers also worked with several international committees in creating methods to house the data and data exchange formats. By working with these groups, NIH ensures that CEBS will be compliant with the exchange format expanding the availability of data to researchers worldwide.

In addition to working with these committees, NIH has developed a format to record this data and is collaborating with two institutions to exchange data in this format with CEBS. The format is termed SIFT, Simple Investigation Formatted Text. SIFT is flexible, and is capable of being used with a variety of studies and data types. Once the exchange exercise is finished, NIH plans to publish a description of SIFT.

Lastly, NIH is working towards automating the data exchange, and has developed a prototype application termed SIFT Builder to help users record their study data and metadata in the SIFT format. Early collaborators are already using the SIFT builder to format their data

to allow for wider access by the research community.

Advances or Other Highlights

A redesign of the CEBS architecture is partly completed that will streamline the database and enhance flexibility so that data from genetic studies can be easily managed in CEBS. The new architecture will be called CEBS3

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

Target Context and Conditions

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.

Baseline: 2007

- (FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(MET) Investigators met to share findings from data analyses of studies of molecular, cellular, environmental, and genetic causes in AE.	Use advanced radiological and molecular imaging techniques to increase understanding of changes in pulmonary physiology associated with asthma exacerbations.	Identify one or more potential candidates for targeted interventions that may reduce the severity and/or frequency of AE.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$5,473	$5,471	$2,163

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET EFFICIENTLY. The NIH convened a meeting in November 2006 in which NIH-supported investigators with grants in the area of asthma exacerbations (AE), along with program staff, met to discuss preliminary results and future directions. Several investigators had already made significant progress in analyzing exciting new molecular, cellular, genetic, and environmental results that may increase our understanding of the pathobiology of AE. Examples of results of such analyses include the molecular and genetic identification of a specific allele within the IL-8 gene that is associated with more frequent AE in children. In another study, identification of a specific cellular blood group antigen, more commonly found in males, that increases the risk for AE probably due to an increased susceptibility to infection. Data on how environmental exposures trigger airways hyperresponsiveness and how inflammatory changes in the lung alter physiology to result in AE were also presented. The results of these analyses will help investigators understand the molecular, cellular, and genetics causes of AE.

Efficiency

Investigators made significant progress in analyzing the results of studies of molecular, cellular, and genetic causes in AE, allowing the target to be met ahead of schedule.

SRO-6.5	By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks.

BACKGROUND

Prevalence/Incidence

The human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic has killed more than 28 million people, surpassing tuberculosis and malaria as the leading cause of death from infectious diseases worldwide. In 2006, an estimated 39.5 million of the world's population, including 2.3 million children younger than 15 years of age, were living with HIV/AIDS. In addition, almost 3 million people died from AIDS in 2006, and more than 4 million people were newly infected with HIV, of which 530,000 were children. The steepest increases in the number of people living with HIV/AIDS were in East Asia, Eastern Europe and Central Asia. Although in the United States newly diagnosed infections have remained relatively stable at approximately 40,000 per year, the proportion of new HIV infections that occur among women, adults over 50 years of age, and some racial and ethnic groups continues to rise.

Disease Burden

The impact of the AIDS pandemic is profound. In some parts of southern Africa, adult prevalence of HIV infection is 25 percent or greater, and prevalence among pregnant women who attend antenatal clinics can be more than 40 percent. In addition to the toll the disease extracts, the pandemic also leads to a greater risk of poverty, hunger and childhood mortality. The AIDS pandemic continues to destroy families and communities and to thereby weaken and threaten the social stability and national security of developing nations. There is evidence of resurging HIV/AIDS epidemics among men who have sex with men in the United States and some European countries and of similar unacknowledged epidemics in Latin America and Asia.

Rationale

While a safe and effective HIV vaccine would be the optimal strategy for preventing HIV infection, control of the epidemic will likely require a combination of preventive approaches to more fully protect individuals and the public against HIV infection. Such approaches may include topical microbicides, antiretroviral therapy (ART) to reduce the ability of HIV-infected persons to infect others, pre-exposure prophylaxis (PrEP) ART treatment to reduce risk of HIV infection, treatment of sexually transmitted infections (STIs) that are cofactors for HIV transmission, drug abuse treatment as an HIV transmission modality for injection drug users, prophylaxis to prevent mother-to-child transmission, and strategies specifically directed at individuals or communities for reducing the risk of HIV transmission associated with sexual activity and/or with substance use.

As the number of people with HIV/AIDS continues to rise worldwide, the need for simpler, more effective treatment strategies becomes more critical. Although more effective treatment options have become available since antiretroviral therapy (ART) was shown to suppress HIV viral load to "undetectable" levels in many infected individuals, there is still a need to develop novel treatment options. ART cannot suppress the virus indefinitely, and latent virus

can still persist. In addition, some infected individuals on ART never achieve adequate viral suppression, while other patients find certain drug regimens too complex and difficult to maintain. Drug resistance also is associated with some of these regimens, as are a number of serious metabolic, cardiovascular, and morphologic complications and cancers, which cause significant morbidity and mortality. The long-term effectiveness and effects of these combination drug therapies are not known, nor is it understood how to completely restore anti-HIV-specific immune function. Optimal strategies for long-term use and sequencing of these antiretroviral regimens have not been established. Finally, the continued surge of the epidemic into resource-limited settings also necessitates the identification of simpler and less toxic regimens that can be deployed in all parts of the world.

PERFORMANCE ANALYSIS

Target Context and Conditions

In June 2006, the NIH funded six newly restructured HIV/AIDS clinical trials networks, with clinical research sites located in 24 states in the U.S. and 19 countries. These networks include the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and the Microbicide Trials Network (MTN). Each of these networks will focus their activities on one or more of NIH's six highest priorities for HIV/AIDS clinical research including: development of a safe and effective HIV vaccine; translation of laboratory findings into new drugs with clinical applications; optimization of the clinical management of HIV/AIDS, including co-infections and other HIV-related conditions; development of microbicides to prevent HIV acquisition and transmission; development of strategies to prevent mother-to-child transmission of HIV; and development of new HIV-prevention methods.

In addition to the restructured networks, NIH also supports research programs that will continue to collaboratively develop and conduct studies with the new NIH-funded networks. For example, the NIH Domestic and International Pediatric and Perinatal HIV Studies Network will continue to collaborate and enroll patients in trials that address issues in women, children, and adolescents such as those through IMPAACT and ACTG. Researchers at the Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions conduct research, both independently and in collaboration with existing research networks, to explore promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV at-risk adolescents. The ATN is collaborating with IMPAACT, ACTG, MTN, and HVTN. Plus, the Pediatric HIV/AIDS Cohort Study (PHACS), an observational study, addresses the long-term safety of fetal and infant exposure to prophylactic antiretroviral (ART) chemotherapy and the effects of perinatally acquired HIV infection in adolescents. Research on HIV co-infections and comorbidities, including hepatitis C, hepatitis B, tuberculosis, cancers, neurological disorders, and organ-specific complications, also will continue to be pursued, in collaboration with other NIH institutes and Federal agencies.

In order to effectively prevent HIV infection, a broad range of prevention strategies will be required since no single prevention strategy is likely to be 100 percent effective or accepted. Toward that end, NIH is evaluating a variety of different prevention approaches through the

HPTN, MTN, and several investigator-initiated grants and through IMPAACT, in collaboration with the Pediatric/Perinatal HIV Clinical Trials Network, specifically for the prevention of mother-to-child transmission (MTCT).

Microbides are another important potential prevention tool. Currently, there are no licensed microbicides, and given that women make up nearly half of all people living with HIV worldwide, a microbicide would provide a valuable, means for women to protect themselves from HIV infection. The MTN is currently conducting a large, multi-site trial examining the safety, acceptability, and preliminary effectiveness of two candidate topical microbicides to prevent HIV infection.

The IMPAACT network conducts studies assessing strategies to prevent mother-to-child transmission (MTCT) of HIV, and studies aimed at optimizing the treatment of HIV-infected children as well as collaborates with the ATN to conduct HIV prevention studies in adolescents. Studies in this network will: evaluate strategies to prevent MTCT during breastfeeding; evaluate approaches to optimize ART and reduce drug resistance in women and infants who are exposed to short-term ART to prevent MTCT. Plus, PHACS is examining the long-term consequences of in utero ART exposure on children.

The ACTG and INSIGHT clinical trials networks focus primarily on treatments for HIV-infected adults and adolescents. The two networks have ongoing and/or planned studies of anti-HIV therapies (including studies of therapeutic vaccines) and/or anti-HIV multi-drug regimens that will help identify treatment regimens with: increased efficacy, diminished toxicity and side effects; improved bioavailability; and minimal development of drug resistance. The purpose of these studies is to optimize regimens that facilitate treatment compliance. These networks are also undertaking studies to identify treatment regimens for use in resource-limited settings, as well as studies for patients who have failed all available treatment options and/or present with significant clinical problems as a result of HIV disease.

Within each of these networks, the research plans to develop and evaluate new interventions build on previous preclinical and clinical studies.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Establish 140 domestic and international clinical research sites to conduct HIV prevention and therapeutic clinical trials.	Complete preliminary analysis of study to determine impact of the use of therapies to control STDs that may play a role as a co-factor in HIV-acquisition.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$327,540	$327,540

SRO-6.6	**By 2015, provide at least one new or significantly improved minimally-invasive treatment for clinical use in patients using image-guided interventions.**

BACKGROUND

Image-guided interventions (IGI) have the potential to replace more invasive treatments that are commonly used today, such as more invasive surgical techniques. IGI techniques are faster, safer, and less expensive than traditional invasive procedures, and recovery time from minimally-invasive IGI procedures is shorter. An image-guided intervention is often a treatment or procedure that is also more precisely targeted. In the case of interventions such as image-guided neurosurgery, this may decrease risk of damage to normal surrounding tissue. For assessment procedures, such as biopsies, this means better targeting of smaller masses. These improved capabilities are particularly important in light of the shifting trend in medicine towards a model of early, pre-symptomatic detection of disease.

Furthermore, image-guided technologies may involve robotic manipulators that can operate in small and difficult-to-reach spaces, such as the inner ear, within the chambers of the heart or on a fetus in utero. Thus, IGI increases the variety of interventions at the clinician's disposal. In addition, image-guided interventions can be done remotely, bringing clinical expertise to underserved communities and remote locales.

Image-guided procedures have the potential to improve health care by enabling new and faster biopsy and treatment procedures, minimizing unintended damage to healthy tissue, decreasing incidents of medical error, producing fewer complications, and allowing for clinical intervention at a distance.

Feasibility testing of new image-guided interventions is being done in a variety of areas including neurosurgery, cardiovascular surgery and cancer treatment. Co-registering and fusing images from complimentary imaging techniques including MRI, CT, ultrasound, nuclear (PET), or optical imaging, for real-time use can guide treatment in the surgical environment or interventional suite. For example, robot-assisted therapeutic and diagnostic procedures, under MRI guidance, are being developed for the treatment of prostate cancer. Also, better visualization techniques are being developed to minimize the time required for catheter-based treatment of abnormal heart rhythms.

Rationale

The need to support research and development in the area of image-guided procedures has been identified at workshops sponsored by NIH and other Federal agencies. Recent Biomedical Imaging Research Opportunities Workshops (BIROW) have established the need for research into the design, development, deployment and evaluation of the new methods, devices, and procedures for image-guided interventions.

Minimally-invasive treatment will be implemented using image-guided interventions. IGIs are disruptive technologies that, in some cases, will completely replace conventional surgery or more invasive procedures. For example, it is expected that non-invasive treatments using

high-intensity focused ultrasound technology, combined with image-guidance (e.g., MRI or ultrasound) will lead to profound changes in the treatment of uterine fibroids, cancer, and other diseases. In order for these changes to occur, research is needed to develop and then validate these integrated imaging and treatment systems for specific applications.

PERFORMANCE ANALYSIS

Target Context and Conditions

Currently, the NIH supports 17 projects in the area of image-guided interventions. These include four cardiac and four neurosurgical interventions, as well as nine image-guided interventions for the treatment of cancer. The NIH also supports the National Center for Image-Guided Therapy at Brigham and Women's Hospital in Boston.

The NIH will develop an initiative to foster research on disruptive image-guided intervention technologies that create minimally-invasive, image-guided procedures to replace traditional surgery and more invasive techniques. This goal will be accomplished in two phases. During FY 2007, NIH supported technology development demonstrating the feasibility of new IGI technologies. In FY 2009, NIH will support the continued development of the most promising IGI technologies.

Investigator-initiated research is also very important to further advance the development of image-guided interventions. NIH will continue to provide support for investigator-initiated applications in this area.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Test at least one image-guided intervention in humans from the baseline of 17 active grants in FY07.	Demonstrate feasibility of at least two new image-guided intervention prototype systems that have the potential to advance into new clinical applications.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$10,997	$8,785

SRO-7.4	**By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis.**

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. A degenerative disease, it is caused by a breakdown of cartilage, the hard but slippery tissue that covers the ends of bones where they form a joint. Healthy cartilage allows bones to glide over one another, and it absorbs energy from the shock of physical movement. In OA, the surface layer of cartilage breaks down and wears away due to biochemical and mechanical factors. This results in bones under the cartilage rubbing together, causing pain, swelling, and stiffness. The body attempts to repair the damage, which may result in the growth of new bone along the side of existing bone. These attempts at repair are usually imperfect, and result in bony lumps, tenderness, pain, and swelling in the joint that permanently change the joint's shape.

A limited number of therapies exist for OA treatment. . Most are designed only to relieve pain and reduce the disability caused by bone and cartilage degeneration. However, no existing treatment inhibits the degenerative structural changes that are responsible for disease progression.

Prevalence/Incidence

OA is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. An estimated 12.1 percent of the U.S. population (nearly 21 million Americans) age 25 and older have OA. By 2030, about 72 million Americans will have passed their 65th birthday and will be at high risk for the disease.

Rationale

One barrier to the development of drugs that block joint degradation, the underlying cause of painful and disabling OA symptoms, is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, the NIH—with input from the U.S. Food and Drug Administration—partnered with private sponsors to create the Osteoarthritis Initiative (OAI), a publicly available research resource that investigators can use to identify and evaluate osteoarthritis biomarkers.

Potential biomarkers might include structural characteristics that can be observed with magnetic resonance (MR) imaging; proteins or substances in the blood or urine that indicate a breakdown or rebuilding of bone or cartilage; and genetic markers that suggest susceptibility to, or protection from, joint degradation. Once validated, the biomarkers will improve the efficiency of clinical research on OA and potential interventions. Depending on the marker, it could be used to identify appropriate participants for clinical trials of disease modifying agents, or even be validated as a surrogate endpoint of disease progression or recovery.

For example, clinicians currently rely on x rays to monitor joint damage even though the

technology is insensitive for uncovering changes in joint structure that may have clinically meaningful effects on OA symptoms. However, if researchers could use MR scans to track heretofore undetectable joint changes and could link these small but measurable changes in joint structure with patient function, such findings would enable earlier and more accurate assessment of OA, identification of potential targets for interventions, and ultimately the more efficient development of disease modifying agents to treat OA.

The OAI relates directly to the HHS Strategic Plan for FY 2004-2009:

- *Objective 4.1*—Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability. As a public-private partnership facilitated by the Foundation for the National Institutes of Health, the OAI also addresses —Accelerate private sector development of new drugs, biologic therapies, and medical technology.
- *Objective 4.2*—Accelerate private sector development of new drugs, biologic therapies, and medical technology.

PERFORMANCE ANALYSIS

Target Context and Conditions

This goal will be fulfilled through the OAI, a public-private partnership established in 2002 to develop a prospective, natural history cohort of approximately 4,800 participants. Researchers are collecting, de-identifying, and archiving biological specimens, images, and clinical data from 4,796 men and women aged 45 years or older at high risk for developing knee OA or those with early stages of the disease over a 3 year period.

The OAI resource is designed to include a variety of data elements that can be used for a range of scientifically rigorous studies that are being proposed by investigators studying OA. At annual clinic visits, participants are providing fasting blood samples and urine specimens for use in genetic and metabolic studies, answering questions about their health and behavior, undergoing both clinical and functional exams, and receiving x rays and MR scans. Examples of information to be collected follow.

- Survey data: Includes answers to questions about OA symptoms; pain severity; walking ability; endurance; balance and strength; nutrition; quality of life; co-morbidities; and prescription medicines and alternative therapies used by the participants.
- Clinical data: Includes weight, body mass index, blood pressure, heart rate, balance, and strength.
- Image data: Includes x rays of participants' knees, hands, and hips and MR images of participants' knees.

The data elements noted above are only a few examples of the information being collected about each OAI participant. When complete, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. The breadth of information that the OAI will contain will allow researchers to develop hypotheses about possible OA biomarkers of

disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease severity and progression. It also will allow scientists to identify potential disease targets and to develop tools for measuring clinically meaningful improvements. All data and images collected will be freely available to researchers worldwide to help quicken the pace of scientific studies related to OA.

In FY 2006, OAI investigators released the study's first set of clinical data and a limited number of images. Baseline survey and clinical data were available from approximately 2,000 participants. Researchers also could obtain baseline x rays and MR images for a sample of 200 participants. For 160 participants, both baseline and 12-month x rays and MR images were available.

The project described in this goal is a high priority for the NIH. Therefore, the NIH funding components participating in this goal are fully committed to supporting efforts toward its completion as outlined in the contract and consistent with current NIH fiscal year policies in effect at the time of funding.

Original Plans for FY 2007-2009
By the end of FY 2007, the available survey, clinical, and image data will be expanded to cover the baseline and 12-month clinic visits from 2,500 OAI participants. Data from the 24-month clinic visits for those participants will be available in FY 2008, as will the survey, clinical, and image (x rays and MR imaging) data from baseline and 12-month clinic visits of the remaining 2,300 OAI participants. In FY 2009, the OAI will have completed processing of the questionnaire, examination, and image data from the 24-month clinic visits for the remaining participants. The data elements and the number of participants for which data are available in a particular year are summarized in the following table:

DATA ELEMENTS

	Baseline		**12-month**		**24-month**	
	Survey and Clinical Data	***Image Data***	***Survey and Clinical Data***	***Image Data***	***Survey and Clinical Data***	***Image Data***
FY 2006	2000	200		160		
FY 2007	2500	2500	2500	2500		
FY 2008	4800	4800	4800	4800	2500	4800
FY 2009	4800	4800	4800	4800	2500	4800

Baseline: 2007

- (FY06) Baseline survey and clinical data for ~2,000 participants, baseline x rays and MR images for 200 participants, and 12-month x rays and MR images for 160 participants are available to researchers.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Survey, clinical, and image data from baseline and 12-month clinic visits of 2,500 OAI	(MET) Researchers can access baseline survey and clinical data for	Image data from baseline and 12-month clinic visits of remaining 2,110 OAI participants will be	Create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis. Survey and clinical data from the 24-

				participants will be available from the OAI Web site.	all 4796 participants and baseline images, 12-month survey and clinical data, and 12-month images for 2686 participants.	available from the OAI Web site. Survey and clinical data from the 24-month clinic visits for the initial 2,686 participants also will be available.	month clinic visits for the remaining 2,110 participants will be available for download from the OAI Web site. X ray and MR images from the 24-month clinic visits for all participants also will be available upon request.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$3,942	$4,024	$1600

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET EFFICIENTLY. Survey, clinical, and image data from baseline and 12-month clinic visits of 2,686 participants are available from the OAI Web site as scheduled. Furthermore, because of outstanding performance of the centers with regard to recruitment and retention, investigators surpassed the FY 2007 performance target with the release of baseline survey and clinical data from the remaining 2,110 participants ahead of schedule. As noted above, the OAI is a resource to facilitate a range of scientifically rigorous studies by the OA research community. To that end, participants are providing survey data about their OA symptoms at each clinic visit, where researchers gather additional health information and take images of their joints.

Recruitment closed after 4,796 participants had been enrolled.

Advances or Other Highlights

The OAI is a long-term effort, developed with support from numerous NIH components and private-sector sponsors, to create a publicly available scientific resource to identify and evaluate biomarkers of osteoarthritis for use in clinical research. By the end of FY 2007, more than 600 researchers from 41 countries had registered to access OAI data. A total of 555 clinical datasets have been downloaded.

In FY 2007, one review of the OAI and three papers as part of a pilot study using the OAI resource were published. The papers addressed the processes by which MR images are collected and the ability of the methods to quantify changes in knee cartilage. For example, one of the papers provided convincing evidence that the MR images obtained through the OAI can readily be used for quantitative assessment of cartilage, provide more precise information over current imaging strategies, and can be analyzed with existing computational methods. Such evidence illustrates that the high degree of accuracy and precision in data from the OAI MR scans will improve our understanding of the pathophysiology of knee OA and allow for the identification of sensitive biomarkers of disease onset and progression that can be used in clinical diagnosis and future clinical trials.

Efficiency

Due to outstanding performance of the centers with regard to recruitment and retention, investigators were able to surpass the FY 2007 performance target regarding baseline survey

and clinical data by releasing that information for all remaining participants ahead of schedule.

Actual numbers of participants for which certain data elements are available (and expected numbers for FY 2007):

	Baseline		**12-month**	
	Survey and Clinical Data	***Image Data***	***Survey and Clinical Data***	***Image Data***
FY 2006	2000	200		160
FY 2007	4796 (2500 expected)	2686 (2500 expected)	2686 (2500 expected)	2686 (2500 expected)

SRO-7.5	By 2009, determine the feasibility of applying at least 2 tailored interventions designed to prevent dental caries in one or more underserved populations.

BACKGROUND

Over the past several decades, America has made substantial progress in improving the oral health of the nation. Due to preventive measures such as community water fluoridation and dental sealants, the overall rates of dental caries (tooth decay) have declined significantly. However, dental caries is still the most common chronic infectious disease of childhood, and tooth loss in adulthood is a persistent problem. Many children and adults, including racial and ethnic minorities and individuals from low-income families, have continued to suffer from disparities in dental diseases. Addressing disparities such as these is essential to ensuring that all Americans can enjoy the benefits of improved oral health.

Prevalence/Incidence

In the Mexican American population. 31 percent of children have experienced tooth decay in their permanent teeth, compared with 19 percent of non-Hispanic white children. There are also disparities along economic lines. Three times as many children aged 6-11 (12 percent) from low-income families had untreated tooth decay, compared with children from families with incomes above the poverty line (4 percent).

Rationale

A number of interventions have been developed to prevent dental caries. These interventions include topical fluoride treatments, dental sealants, and community water fluoridation. In addition, educational interventions have been developed to address at-risk behaviors such as sending infants to bed with a bottle of sugary liquid. However, these interventions have often not proved successful in certain population groups at especially high risk for caries. Interventions that are typically administered by a dental professional may be impractical for individuals with limited access to dental care. For example, fluoride varnish interventions are typically applied by a dental professional several times per year. For children of migrant farmworkers, who can expect to move several times a season, such an intervention is probably not practical. Similarly, many educational and health promotion interventions have not been developed for, or tested in, ethnically or culturally diverse populations. Research is urgently needed to tailor caries prevention methods to underserved populations. In addition, it will be vital to test whether these tailored interventions can be effective under real-world conditions. If successful, the interventions could be implemented in disadvantaged communities to improve oral health.

PERFORMANCE ANALYSIS

Target Context and Conditions

NIH implements research projects that incorporate clinical studies to address dental caries in underserved populations. Several of these studies are supported through the Centers for Research to Reduce Oral Health Disparities. One of these studies is a clinical trial of a lower frequency fluoride varnish regimen among children of migrant farmworkers. These children are not only at risk for serious tooth decay, but they are less likely to have access to affordable dental care when they need it. While semi-annual fluoride varnish applications

result in small differences for at-risk young children, more intensive application regimens have been found to reduce caries in older children. This study attempts to establish equivalence of the application of a massive dose regimen (3 doses in two weeks) of fluoride varnish with a semi-annual standard application of the same fluoride varnish in preventing dental caries progression in Hispanic children. If successful, the intervention will be especially useful for children who may have only sporadic access to dental care. The study is expected to recruit between 500 and 600 children.

Another population that presents special concerns is the Hispanic population that resides near the U.S.-Mexico border, where poverty and poor health literacy contribute to high rates of severe caries in early childhood. Standard prevention tools may not be effective in this cross-border population, where language and cultural factors have been little studied. NIH has funded a clinical trial to determine the feasibility of addressing early childhood caries by intervening with both the children and their mothers from a very early age. A randomized controlled clinical trial will be conducted. The intervention group will receive oral health counseling coinciding with their well-child visits, a 3-month course of chlorhexidine (an antibacterial rinse) for the mothers starting at 4 months postpartum to potentially reduce transmission of caries, and fluoride varnish for the children every 6 months from 12 to 30 months of age. The control group will receive the counseling only. This study is expected to enroll over 500 mother-child pairs over several years.

NIH is also testing a health promotion intervention designed to prevent caries in an inner-city, low-income African American community with very poor oral health. The intervention involves motivational interviewing sessions with mothers to develop personalized goals to help prevent a child from developing tooth decay. Instead of health educators telling parents what to do, the motivational interviewing technique helps parents come up with their own reasonable solutions to meet health care needs. Follow up assessments will be made at 6 months and at 1 year, to test the longer term impact of this educational tool. The study is expected to enroll around 350 to 400 subjects over several years.

There are striking disparities in dental disease by income. Poor children suffer twice as much dental caries as their more affluent peers, and their disease is more likely to be untreated. These poor - non poor differences continue into adolescence. One out of four children in America is born into poverty, and children living below the poverty line have more severe and untreated decay. The social impact of oral diseases in children is substantial. More than 51 million school hours are lost each year to dental-related illness. Poor children suffer nearly 12 times more restricted-activity days than children from higher-income families. Pain and suffering due to untreated diseases can lead to problems in eating, speaking, and attending to learning.

Young children of low-income African American mothers are at risk of developing severe dental caries in primary teeth. This can negatively influence not only their subsequent health but also, by inducing pain and discomfort, may impair their academic performance and well-being. Previous research documents the associations of diet, oral health behaviors and weaning practices with severe dental caries. Yet mothers with low income, low education, and low work status often do not follow health-promoting practices. Current research is

inadequate to explain the process by which such social stratification, starting early in childhood, translates into poor oral health later on in life. Without understanding of the social context of low-income and disadvantaged parents, preventive interventions are doomed to failure.

In addition to the studies described above, NIH continues to seek opportunities to support high quality research aimed at developing tailored interventions to reduce caries in underserved populations.

Baseline: 2007

- (FY06) Several studies have been designed and implemented but have not yet completed enrollment.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Complete enrollment of 350 parents in a health promotion intervention to test the feasibility of motivational interviewing techniques in reducing caries among inner-city, low-income African-American children with poor dental health.	(MET) The health promotion intervention enrolled 734 parents, 384 more than anticipated	Complete a clinical trial to determine the feasibility and effectiveness of a lower-frequency fluoride varnish regimen among children of migrant farmworkers in order to reduce the incidence of dental caries.	Complete a clinical trial to determine the feasibility of an intervention combining chlorhexidine (an antibacterial rinse) in mothers and fluoride varnish in children in a disadvantaged population in order to reduce the incidence of dental caries.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$512	$225	$214

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET and EXCEEDED. The study enrollment target of 350 subjects has been exceeded, with 734 parents enrolled to date. All subjects received an initial interview to determine a baseline of specific areas of oral health knowledge, and then were randomly assigned to one of two groups. The treatment group received a tailored interventions using motivational interviewing, administered by trained, calibrated, and certified interviewers, as well as an educational video with content based on their baseline knowledge. In addition, they received a follow-up communication reiterating their tailored goals. The control group received the educational video and a generic "recipe" for decay prevention, as well as a generic follow-up brochure. Preliminary results show a positive effect from tailored interventions using motivational interviewing, on both caregivers and their children, in terms of tooth brushing frequency and checking for early decay.

Efficiency

The initial target of 350 study subjects enrolled has been exceeded, with 734 enrolled to date. This increase in sample and cell size significantly increases the statistical power of the study, and increases the number of statistical techniques that can be used.

SRO-7.7	**By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care.**

BACKGROUND

Significant advances in cancer treatment in recent years have made possible the concept of a community hospital-based cancer network. When the NCI-designated Cancer Centers were being established in the 1960s, there was a need for special care units in large hospitals to manage the side effects of the highly toxic chemotherapies of the day. Today, these treatments –and the newer generation of immunotherapies and other regimens – are less toxic, making it possible to administer more advanced care at community hospitals, often in an outpatient setting.

Rationale

Evidence suggests that cancer patients diagnosed and treated in a setting of multi-specialty care and clinical research may live longer and have a better quality of life. It is estimated that that 85 percent of cancer patients in the United States are diagnosed at hospitals in or near the communities in which they live. The other 15 percent are diagnosed at NCI-designated Cancer Centers, a network of 63 academic research institutions located in largely urban areas across the country. Many patients are not treated at the major cancer centers because of the distance from their homes, or for other personal or economic reasons.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH is launching the NCI Community Cancer Centers Program (NCCCP) as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multi-specialty care to a much larger population of cancer patients.

The program is intended to complement other NIH initiatives in seeking to:

Draw more patients into clinical trials in community-based settings. Clinical trials provide access to cutting-edge advances and state-of-the-art care, and help develop new preventatives, diagnostics, and treatments. Yet only 3 percent of adults with cancer participate in clinical trials. In underserved urban and rural communities, the adult accrual rate is even lower. These groups include populations with disproportionately high cancer rates, so their absence from clinical trials is a significant factor in ongoing healthcare disparities.

Reduce healthcare disparities. The disparity problem is complex. The NIH is working through this pilot program and a range of other programs to better understand the problem and address the causes. Research confirms that equal treatment at the same stage of disease yields equal outcomes across all populations. Equal access to optimal care could dramatically reduce cancer mortality in the United States.

Prepare sites for standardizing the collection and storage of biological specimens for cancer

research. Biospecimens play an important role in translating basic science into cancer treatments because biospecimens allow researchers to study cancer cells at the molecular level. Implementation of a national standard for how these samples are collected and stored is critical; standardization and making biospecimens more widely accessible would accelerate the translation of research into more effective treatments for patients, including treatments that are personalized for greater efficacy and fewer side effects.

Link sites to national databases supporting basic, clinical, and population-based cancer research. Explore implementation of electronic medical records. The use of electronic medical records opens broad new avenues for data-intensive research in understanding cancer. Assessing the ability of sites to create and utilize IT infrastructures that are compatible with NIH's Cancer Biomedical Informatics Grid (caBIG™) could lead to a nationwide repository of data on screened patients, high-risk patients on prevention trials, cancer patients actively being treated, and cancer survivors.

In 2009, NIH will develop metrics suitable for assessing the NCCCP pilot. The goals of NCCCP have been defined; the next step in the assessment is to identify suitable metrics that can help determine if the program is successful. This will involve a review of metrics used in similar studies, consultation with program experts, and an analysis to determine what metrics may be best suited for measuring performance of community-based research and care. Defining appropriate metrics is a critical step that may be complicated by the diversity of the communities and facilities involved in the pilot. To overcome such complications, a logic map will be created to explain how unique structures and processes may impact outcomes. This information will be used during the metrics analysis to ensure that the appropriate metrics are being used for the assessment of unique community-based research methods; ultimately leading to a high quality assessment of community-based methods for facilitating cancer research and providing patients access to optimal cancer care.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							Identify and define metrics used for the assessment of community-based research methods.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$9,880

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SRO-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

Target Context and Conditions

In FY 2007, 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, (4) the Proteomics Research Centers and (5) the Structural Genomics Center.

Baseline: 2007

- (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

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Genomic sequences were identified for 18 bacteria, 4 protozoan	(MET) Genomic sequencing projects for 30 bacteria, 1 protozoan, 1	Complete the genome sequence of at least six bacterial pathogens, two	(MET) Genomic sequencing projects of 44 bacteria, 6 protozoa, 1	Complete goal of determining the genome sequences of 45 human pathogens and 3	(MET) NIH met and exceeded this goal by determining the genome sequences		

parasites, and 3 fungi.	insect and 3 fungi were completed.	protozoan parasites, and one invertebrate vector of infectious diseases.	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.	invertebrate vectors	of 212 pathogens and 6 invertebrate vectors (above the FY03 baseline).		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$60,223	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target and the overall GPRA goal were MET and exceeded by completing genome sequences of 212 pathogens and 6 invertebrate vector genomes above the baseline. In FY 2007 NIH completed sequencing for 102 pathogen and vector genomes, including 85 bacterial pathogens, 5 protozoan parasites, 8 fungal pathogens, and 4 invertebrate vectors of infectious diseases.

By the end of FY 2007, NIH had completed genome sequencing projects for a total of 263 (cumulative) pathogen and invertebrate vectors of infectious diseases, which included 218 bacteria, 16 fungi, 20 parasitic protozoa, 1 parasitic worm, 1 plant, and 7 invertebrate vectors.

Some projects were completed earlier than anticipated largely due to advances in molecular biology that have led to remarkably fast and accurate methods for sequencing genomes. Briefly, 85 bacterial pathogen sequencing projects were completed in FY 2007, including Bacillus cereus (9 strains), Borrelia (5 strains), Camplyobacter, Clostridium botulinum (botulism; 3 strains), Clostridium butyricium, Clostridium perfringens (Epsilon toxin; 5 strains), Coxiella burnetii (Q fever; 2 strains), E.coli, Francisella tularensis (tularemia; 5 strains), Mycobacterium tuberculosis (4 strains), Salmonella (17 strains), Streptococcus sanguinis, Ureaplasma urealyticum (14 strains), Vibrio cholerae (cholera; 9 strains), Vibrio harveyi, Vibrio parahaemolyticus, and Yersinia pestis (plague; 6 strains). In addition, the genomes of 8 fungi sequenced include Coccidioides (6 strains), Penicillium marneffei, and Talaromyces stipilatus; 5 protozoa including Brugia malayi, Cryptosporidium muris, Plasmodium vivax, Schistosoma mansoni, and Toxoplasma III; and 4 invertebrate vectors of disease including Culex pipiens, Ixodes scapularis (deer tick), and 2 strains of Anopheles gambiae.

Sequencing of human pathogens and their invertebrate vectors will open up new opportunities and allow scientists to understand how these organisms function to cause and transmit human disease. In turn, this will lead to improved and novel approaches to diagnosing, treating and preventing infectious disease. Genomic information will enable

scientists to conduct functional analyses of genes and proteins in whole genomes and cells. When scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins, or the proteins can be tested for potential as vaccine candidates. Genetic variations can also be used to study the evolution, emergence and spread of virulent or drug-resistant forms of a pathogen. The availability of genomic sequences for human pathogens and disease vectors will provide an important foundation for understanding the role of genetics in infectious disease and in development of new targeted disease interventions that will benefit public health.

Advances or Other Highlights

In FY 2007, NIH supported 40 large-scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites, and invertebrate vectors including Bacillus cereus, Borrelia, Clostridium, E.coli, Enterococcus, Francisella tularensis, Listeria monocytogenes (listeriosis), Mycobacterium tuberculosis, Salmonella, Streptococcus pneumonia, Ureaplasma urealyticum, Vibrio cholerae, Coccidioides, Penicillium marneffei, Tararomyces stipitatus, Lacazia loboi, Histoplasma capsulatum, Blastomyces dermatitidis (blastomycosis), Crytosporidium muris, Plasmodium vivax, Plasmodium falciparum, and Toxoplasma. Sequencing of Dengue viruses, avian and human influenza viruses, and the invertebrate vectors Culex pipiens and Ixodes scapularis were also supported. In FY 2007, the final annotation of the Culex pipiens genome was released to GenBank. The genome sequence of Ixodes scapularis was also released to GenBank in FY 2007, with the assembly and annotation of the genome sequence anticipated in FY 2008.

Efficiency

Technological developments have resulted in a great increase in the speed and accuracy of sequencing DNA, and a drastic decrease in the cost. 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 decreased to $0.70 and, in 2007, the cost dropped to $0.55.

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 can be affected by nutritional, endocrine, and pharmacological factors. The process is critical to maintaining bone mass and preventing fracture. For example, an excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis.

Bone is composed of mineral crystals embedded in a matrix of many different proteins. Osteoblasts are 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.

Rationale

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 a limited number of 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.

PERFORMANCE ANALYSIS

Target Context and Conditions

Current evidence indicates altering cell-matrix interactions can change bone remodeling activity and bone mass. Before translating these findings into therapeutic applications, researchers must better characterize known cell-matrix interactions and identify new interactions important in the maintenance of skeletal health. Approaches to this problem will include three of the basic building blocks of biomedical science: experiments with cultured cells; study of genetically modified mice; and study of humans with genetic bone disease.

Cell cultures allow for the most detailed analysis of the molecular mechanisms underlying cell functions. However, cell cultures seldom reflect all of the factors that govern overall physiological processes. For example, although osteoblasts can be induced to produce bone matrix in culture, the interaction between cells and matrix in culture is not normal, and osteoblasts do not become recognizable osteocytes within the bone produced in culture. In contrast, genetically modified mice can provide information about consequences of the absence or excess of a specific protein in the intact organism. As a result, it is possible to

define the function of different matrix proteins and the cell surface proteins that interact with them. In addition, 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. However, the study of genetically modified mice has significant potential pitfalls. The effects of protein deficiency or excess can be difficult to predict. Mice lacking a particularly important protein may be born dead or die shortly after birth, limiting the information that can be gained. It can be difficult to isolate the regions of the mouse chromosomes necessary to generate a desired mouse. Finally, mice do not always faithfully reflect human physiology. For this reason, a third building block of science is the study of humans: patients with genetic diseases, and cells and tissues from both healthy people and people with specific diseases.

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 (TSP-2) and osteonectin, were selected for initial study, based on evidence that they play important roles in the generation and survival of osteoblasts. Over time, studies of four additional bone matrix proteins—fibronectin, connective tissue growth factor (CTGF), dentin matrix protein-1 (DMP1), and fibrillin-2—were added to the performance targets of this goal. Other proteins—biglycan and transforming growth factor beta (TGF-beta)—were included as strategic targets.

FY 2008 activities toward achieving the goal

The FY 2008 performance target entails determining the properties of bone-forming cells and bones from mice that lack the matrix protein fibrillin-2. Fibrillin-2 deficiency 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. Investigators will test the function of cultured cells from the fibrillin-2-deficient mice, particularly examining the production of other matrix proteins by the cells, and the response of the cells to molecules that regulate their functions. They will also test the material and mechanical properties of bones from the mice, to determine whether the lack of fibrillin-2 results in altered structure or strength of the bones.

The characterization of molecular interactions responsible for bone formation described in this goal is a high priority for the NIH. Therefore, the NIH funding components participating in this goal are fully committed to supporting efforts toward its completion as outlined in the Notice of Grant Award and consistent with current NIH fiscal year policies in effect at the time of funding.

Baseline: 2007

- (FY03) Information is incomplete on where thrombospondin-2 is produced; mouse model can provide this data.
- (FY06) The skeleton of a mouse lacking DMP-1 exhibits complex defects. It is unknown how this is related to bone cell function.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.	(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.	(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.	(Target 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. (Target 2) 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.	(NOT MET) Researchers determined that the fluorescent mouse was not going to provide useful information and are pursuing a different strategy to identify sites of TSP-2 production. (MET) DMP1 is needed for bone cell differentiation and maturation. Bones of mice lacking DMP1 are soft and, at a cellular level, are poorly organized like bones found in a rare form of rickets.	Determine the properties of bone-forming cells and bones from mice in which fibrillin-2 is absent.	Complete goal of identifying and characterizing two molecular interactions of potential clinical significance between bone-forming cells and components of bone.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$3,512	$3,212	$3,212

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2005 target was NOT MET despite an extension through FY 2007. Because technical difficulties prevented construction of the "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," the investigator abandoned this strategy and began pursuing a different strategy to "identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation." Now that the promoter for TSP-2 has been identified, researchers plan to study TSP-2 using a mouse model, described below, that has accommodated similarly sized genetic sequences.

Moreover, this delay is not expected to have a significant effect on progress toward the FY 2008 target, which reflects studies of a different protein and does not depend on the characterization of TSP-2 interactions with bone cells. More importantly, the overall goal is still achievable. As reported under the original FY 2007 target, researchers have made considerable progress toward the identification and characterization of clinically significant molecular interactions between bone-forming cells and DMP1. For example, NIH-funded investigators continue to study the roles of other bone components, including fibronectin and fibrillin-2.

The FY 2007 target was MET EFFICIENTLY. Early in FY 2007, investigators studying the role of DMP1 in mice published a paper linking DMP1 deficiency to a previously unrecognized form of rickets affecting members of two families. These patients, like mice lacking DMP1, had defective phosphate metabolism and increased blood serum levels of a protein called fibroblast growth factor 23 (Fgf23). Genetic sequencing revealed that the disease, autosomal recessive hypophosphatemic rickets, was caused by mutations to the gene for DMP1. Although each family was affected by a distinct mutation, both had defects in regions that had been thought to be important for proper functioning of DMP1. The essential role of these regions had not been demonstrated, however, until now.

Generation of 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.
Analysis of cells recovered from bone marrow suggested that stromal cells in the bone marrow are a principal source of TSP-2. To more precisely identify the locus of TSP-2 production, researchers intended to generate a mouse model in which the genetic elements controlling TSP-2 production also regulate a fluorescent 'reporter' protein. For most genes, the promoter sequence is immediately adjacent to the gene it regulates, and is small enough to be studied using this strategy. As reported at the end of FY 2005, however, researchers discovered that the DNA sequence thought to be the TSP-2 promoter was not amenable to this approach. Ongoing efforts to identify regions of bone and bone marrow in which TSP-2 is produced under conditions of bone loss and bone formation are described below.

Characteristics of the skeleton in mice deficient in dentin matrix protein 1 (DMP1)
The bones of mice and humans lacking DMP1 were poorly organized at the microscopic level, with bone proteins and cells appearing in rough clumps rather than being distributed evenly as part of a smooth bone surface. The bones were softer, due to deficiencies in calcium and phosphorous. Additional analysis of mouse bones revealed that the bone-forming osteoblasts failed to fully differentiate into mature osteocytes—even older osteocytes, deeply embedded in the bone matrix, continued to express proteins characteristic of undifferentiated osteoblasts and immature osteocytes.

Consequences of DMP1 deficiency for bone cell function
In mice lacking DMP1, the findings that osteoblasts fail to differentiate into osteocytes, and osteocytes fail to mature, suggest that the matrix protein is essential for proper bone cell development. Specifically, the results suggest that DMP1 has a role in downregulating osteoblast markers.

Under normal conditions, interactions between osteocytes and bone matrix proteins occur in regularly spaced microscopic structures in bone. As noted above, proper alignment of these structures appears to depend on DMP1. Researchers combined their observations about bone structure with knowledge about the organization of osteocytes relative to DMP1 in the bones of healthy animals and concluded that 1) interactions between bone matrix material and osteocytes are essential for bone matrix mineralization, and 2) DMP1 is required for these interactions.

Further characterization of bone-forming cells from mice lacking DMP1 revealed a connection between the elevated Fgf23 serum levels and increased transcription of the Fgf23 gene in osteocytes. Although Fgf23 had been shown previously to increase the amount phosphate excreted in urine, to reduce serum phosphate concentrations, and—when present at excessive levels due to a processing defect—to cause a different type of rickets, the connection between bone mineralization and phosphate excretion had not been linked previously with DMP1 production by osteocytes.

Advances or Other Highlights

Subsequent efforts to identify regions of bone and bone marrow in which TSP-2 is produced under conditions of bone loss and bone formation.

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. Since the FY 2005 report, researchers have identified the genetic sequence containing the TSP-2 promoter, determined that it was too large for the fluorescent tagging approach initially envisioned, and have explored other strategies for identifying the cells responsible for manufacturing TSP-2 protein. Soon, NIH-funded researchers hope to identify the source of TSP-2 during bone loss and bone formation by studying a mouse created by other investigators, using technology that allows transfer of much larger regions of the chromosome. Progress continues on the functions of fibronectin and fibrillin-2, the subjects of the 2006 and 2008 targets, respectively. In FY 2005, researchers demonstrated that fibronectin and biglycan (another extracellular bone matrix protein) mediate the incorporation of a third protein, called transforming growth factor beta (TGF-beta), into bone matrix. TGF-beta is well known to have important effects on many kinds of cells. Thus, one important role of fibronectin and biglycan may be to influence the exposure of bone cells to TGF-beta. Recently, NIH-funded scientists have shown that this type of cell-matrix interaction also involves fibrillins and the structurally related latent TGF-beta binding protein 1 (LTBP-1). In addition, the characterization of fibrillin-2-deficient mice (2008 target) has revealed reduced bone formation, along with significant changes in the material and mechanical properties of the bone. These abnormalities appear to reflect defects in the cells' response to TGF-beta, consistent with the results on fibronectin and LTBP-1. Thus, multiple components of the bone matrix appear to act together to control the exposure of bone cells to the potent regulator TGF-beta.

Progress continues on the functions of fibronectin and fibrillin-2, the subjects of the 2006 and 2008 targets, respectively. In FY 2005, researchers demonstrated that fibronectin and biglycan (another extracellular bone matrix protein) mediate the incorporation of a third protein, called transforming growth factor beta (TGF-beta), into bone matrix. TGF-beta is well known to have important effects on many kinds of cells. Thus, one important role of fibronectin and biglycan may be to influence the exposure of bone cells to TGF-beta. Recently, NIH-funded scientists have shown that this type of cell-matrix interaction also involves fibrillins and the structurally related latent TGF-beta binding protein 1 (LTBP-1). In addition, the characterization of fibrillin-2-deficient mice (2008 target) has revealed reduced bone formation, along with significant changes in the material and mechanical properties of the bone. These abnormalities appear to reflect defects in the cells' response to TGF-beta, consistent with the results on fibronectin and LTBP-1. Thus, multiple components of the bone matrix appear to act together to control the exposure of bone cells to the potent

regulator TGF-beta.

Efficiency

The study characterizing the effects of DMP1 on bone formation and bone cell function was published in November 2006, thereby meeting the FY 2007 target only 2 months into the fiscal year. In addition to illuminating the previously unrecognized role of interactions between osteocytes and the DMP1 protein in the mineralization of bone, the findings have direct clinical relevance as they connect defects in the gene DMP1 to four, heretofore unexplained, cases of rickets occurring in two separate families. Furthermore, the effects of the DMP1 mutations on blood levels of phosphate demonstrate a previously unsuspected link between bone cells and the kidney, which is a critical regulator of mineral levels in the circulation.

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

Target Context and Conditions

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 consisted 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 consisted 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 are being 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 began in FY 2007 and will be completed in FY 2009.

The purpose of each evaluation design study is to determine the best strategy for evaluating the program. Consideration was 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 validated 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 was determined by the design studies.

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

Baseline: 2007

- (FY05) INBRE evaluation design.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(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.	(MET) The full-scale evaluation for IDeA/INBRE was initiated with a process evaluation on 23 sites funded between FY 2001 and FY 2002.	Full-Scale Assessment of the IDeA Program: -Complete the IDeA/COBRE evaluation and analyze preliminary results.	Complete goal of assessing 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.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$218,153	$218,153	$218,153

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. The full-scale evaluation for IDeA/INBRE was initiated when the contract to conduct the INBRE evaluation was awarded on September 28, 2007. The contractor will conduct a process evaluation which will focus on the 23 INBREs that were funded during FY 2001 and FY 2002. The purpose of the evaluation is to determine if the program operations and outputs during the centers' first five years have been successful. Although it is an early assessment, enough time has elapsed for the centers to have achieved the program's process goals. Specifically, some of the process goals include implementation of administrative core, bioinformatics core and other planned cores; development of new courses; and recruitment of additional researchers. Some of the outcome goals include increasing the number of network investigators who submitted grant applications and increasing the number of science courses and programs offered. The period of performance for the 23 centers in this cohort will be FY 2001 to FY 2006.

The assessment design consists of 13 tasks identified in the Statement of Work. Task include creating a work plan, review existing data, preparing Center summaries, data coding, development of a discussion guide, conducting interviews and preparing a final report. The technical approach proposed by the selected contractor was designed to minimize the burden on INBRE center personnel as well as the duration and cost of the evaluation by relying primarily on secondary data sources. The secondary data sources include program documents, NIH databases (primarily CRISP), PubMed searches, as well as the NIH Consolidated Grant Applicant and Fellow File, and BRIN/INBRE center websites.

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

Target Context and Conditions

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 was completed in 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.

Baseline: 2007

- (FY06) Preliminary data analyses undertaken.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(MET) Preliminary item pools to measure the chosen domains (Pain, Fatigue, Physical Functioning,	Initiate administration of instrument(s) to a large demographically diverse patient sample	(MET) Administration of the PROMIS item pool to a diverse sample representing a wide range of	Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and	(MET) Data analysis was initiated in April, 2007, six months ahead of schedule. Primary analyses have been completed, and additional analyses are ongoing. The result of	Conduct primary data analyses of item responses in pain, fatigue, physical functioning, emotional distress,	Complete goal of developing an item bank and computerized adaptive testing system available to clinical

	Emotional Distress, and Social Role Participation) have been created based on exhaustive review of existing measures. Initial instruments and methodologies have been developed.	representing a wide range of chronic disease type and severity.	conditions was initiated in July, 2006.	social role participation.	these analyses are item banks ready for public release (see http://www.nihpromis.org). Publications resulting from these analyses are in process.	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.	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.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$8,401	$5,581	$7000

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target of initiating data analysis was met efficiently. Primary analyses have been completed, and additional analyses are ongoing. As a result of improved efficiencies in data collection of over 20,000 subjects, data collection for this project was completed ahead of schedule, in March 2007, allowing data analysis to begin six months ahead of schedule (April 2007). The results of these analyses are item banks ready for public release (http://www.nihpromis.org). Specifically, the analyses of the Wave 1 Pain Impact item bank suggest that there is a set of 47 items that adequately represent the Pain Impact domain. Due to the fact that severe pain items are grossly under-populated in the Wave I data, we view our results as preliminary. We are finalizing details for a large online data collection effort through the American Chronic Pain Association. Publications resulting from these analyses are in process.

Advances or Other Highlights

Currently, fatigue and emotional distress PROMIS v1.0 item banks have been released for clinical researchers to further validate and/or use in clinical research. Additional item banks will be released by January, 2008 after further analyses have been completed.

Efficiency

Due to efficiencies in data collection, data analysis began six months earlier than anticipated. As a result, data analyses has allowed for item calibrations and an initial set of item banks measuring pain, fatigue, physical functioning, emotional distress, and social role participation to be released ahead of schedule. For example, preliminary analyses from the physical functioning item bank indicate that a 10-item computerized adaptive test administration can provide an efficient and highly precise measurement of physical functioning over a wide range from physically fit to seriously disabled patients.

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, and 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 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

Target Context and Conditions

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. The newly added vision component consists of questions about visual impairment and quality of life activities as well as examination data on visual acuity, refraction, and keratotomy. The medical examination now includes a retinal assessment of the optic disc and macular areas. Integrating data from these two sources allows for a more comprehensive approach including differentiating causes of visual impairment for those individuals whose vision cannot be corrected to normal levels. Analysis of the vision data collected in the 2007-2008 survey cycle will 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. In order to achieve this goal, 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 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. NIH will receive the data from the survey after it has been collected, verified, and prepared for use by NHANES, most likely in late 2009.

Baseline: 2007

- (FY06) Very little reliable data on the prevalence of visual impairment in the U.S.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Extend NHANES and survey approximately 3,500 people.	(MET) NHANES Survey is recruiting at an annual rate of 3410 respondents.	Continue collecting data for the vision component of NHANES to reach a target of surveying approximately 7,000 people in total.	Complete preliminary analyses of the data to prepare national estimates of visual impairment.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$367	$367	$367

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target was MET. NHANES Survey 2007-2008 is recruiting at anticipated rate. Recruitment is on target to reach approximately 3500 with 3,410 participants as estimated for 2007. This year's performance creates a strong foundation for the FY08 target – completing the survey with 7000 participants. The recruitment targets have been designed to achieve stable estimates of vision impairment. Each year, approximately 4,000 people who meet survey sampling criteria agree to participate in NHANES and complete the home interview portion of the NHANES survey (Part I of the survey). As of 9/30/07 (9 months into the 24-month survey period), 2557 survey participants reported to Mobile Examination Center (Part II of the survey). Of these, 2201 participants completed the entire vision exam; an additional 201 participants completed part of the vision exam.

SRO-8.7	**By 2012, identify three (3) effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice.**

BACKGROUND

The Nation spends billions of dollars yearly on medical research. Yet, despite this enormous investment, it is estimated that only a relatively small percentage of scientific findings actually impact clinical practice (an estimated 14%), and this impact occurs slowly (an estimated 17 years after the initial publication of a clinically-relevant finding). Medical research has provided a wealth of knowledge leading to any number of innovative approaches to prevention, early detection, diagnosis, and treatments of a host of diseases and conditions. Yet, little is known about how to best ensure that the lessons learned from biomedical and health behavior research inform and improve the quality of health and human services and the availability and utilization of research-tested interventions in service systems such as medical practices, schools, the criminal justice system, and community health organizations. NIH has recognized that closing the gap between research discovery and program delivery is both a complex challenge and an absolute necessity in ensuring that all populations benefit from the Nation's investments in new scientific discoveries.

Significant barriers exist that prevent the adoption and implementation of newly devised and research-tested interventions into service systems. These barriers may occur at the individual level, practice level, or broader organizational level. For example, an evidence-based program may require extensive clinical training and additional resources, or staff may consider their existing approaches sufficient to address the majority of problems they encounter. There may be few incentives for service providers to train clinical staff in new practices. There may be financial barriers, such as an inability to get reimbursed for providing a specific intervention, or costs associated with becoming a "certified" provider of a specific evidence-based intervention. There may also be constraints that stem from the nature of a system's function and the population it serves, for example the criminal justice system, where unmet treatment needs contribute to the vicious cycle of drug abuse and criminal recidivism.

Organizational barriers, such as frequent turnover of staff or poor supervision, can also threaten the sustainability of an effective intervention, or the ability to know whether a practice is being delivered as it was designed. There may also be assumptions, rather than empirical knowledge, that the program will not work for the specific population that a service provider is working with. In addition, even if barriers to implementation are overcome, few models ensure effective implementation. Programs may be used in ways that undermine effectiveness, such as when staff adapt a program without an understanding of which components are essential for its effectiveness. Few efforts may be made to involve all staff in the implementation process, and little may be done to ensure sustainability of the program. New approaches are needed to overcome these barriers and to improve the use of strategies, to adopt and integrate evidence-based health interventions, and to change practice patterns within diverse service settings.

Rationale

More research is needed to develop new implementation models for intervention and service delivery. Recognizing this need, NIH has undertaken an initiative to broaden its portfolio in implementation research by encouraging trans-disciplinary teams of scientist and practice stakeholders to work together to develop innovative approaches for identifying, understanding, and overcoming barriers to the implementation of research-tested interventions in service settings. The initiative should lead to new implementation models that account for the diverse audience of stakeholders involved in health service delivery, including consumers, caregivers, practitioners, policymakers, employers, administrators. These implementation models will be measured and tested within real-world practice settings with the hope that these models will ultimately bridge the gap between public health, clinical research and everyday practice.

PERFORMANCE ANALYSIS

Target Context and Conditions

The identification of research-based implementation strategies to enhance the uptake of evidence-based interventions into clinical practice depends upon several important research efforts. Research is needed to better delineate the barriers preventing effective implementation of evidence-based practices. This understanding will lead to new theories of implementation and the generation of novel approaches to integrate effective interventions into clinical practice. A sound methodology for testing the effectiveness of these approaches will need to be further refined, including the development of valid and reliable common measures of implementation effectiveness. New approaches to implementation of diagnostic, preventive, and treatment interventions will need to be systematically studied in a variety of existing care systems. Processes to implement new treatment interventions may require changes in clinical or administrative infrastructure and practices. Thus, an essential component of implementation research is understanding the organizational changes needed to improve the quality of care, to adopt new technology, and to sustain practice improvements over time. Implementation questions will need to be better integrated into all clinical research efforts. Finally, new and improved implementation strategies will need to be disseminated to the many stakeholders that provide public health and clinical services.

Achievement of this goal is dependent on the influx of new investigators to the field, each building the theoretical, methodological and empirical skills to enable comprehensive trials of dissemination and implementation strategies.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Identify three (3) implementation mechanisms, strategies, or techniques to improve the uptake of effective interventions in healthcare settings.	Identify and test at least three (3) key variables for measuring implementation to improve the uptake of effective interventions in healthcare settings.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$20,744	$19,582

SRO-8.8	By 2012, identify at least one candidate intervention that extends median lifespan in an animal model.

BACKGROUND

A better understanding of the nature of aging and the mechanisms controlling longevity in animal models could enable the development of interventions to extend not only the length but also the quality of life for humans. The recent finding that resveratrol, a natural compound found in certain foods including grapes, wine, and nuts, could affect the health and survival of mammals exemplifies the promise of this research.

An important activity in this area is the Intervention Testing Program at NIH, which supports the testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a mouse model. Many interventions, including foods, diets, drugs, hormones, etc., are tested through this program, which began in 2003.

Under this program, intervention testing is conducted in two phases. The first stage is primarily a lifespan study with a few other parameters measured, and testing is conducted at all three participating sites. Phase I typically lasts 2 to 2 1/2 years. Interventions that appear to increase lifespan, based on Phase I results, move on to Phase II, which involves a broader spectrum of assays. As of 2006, ten interventions were undergoing Phase I testing, and early results are becoming available for the first compounds that were tested. As the Intervention Testing Program continues, NIH will begin Phase II testing as appropriate and will continue Phase I testing for new interventions. NIH-supported researchers will:

- Continue to solicit Phase I proposals
- Develop Phase II protocols
- Begin Phase II studies on candidate compounds from earlier cohorts, if Phase I data support this
- Conduct a final analysis when all the mice have died

Rationale

A better understanding of the nature of aging and the mechanisms controlling longevity in animal models could enable the development of interventions to extend not only the length but also the quality of life for humans. If safe and effective interventions are found, potential benefits include longer independence and reduced health care costs for the elderly. Such advances are also likely to benefit our quest for disease prevention, especially for age-related diseases such as cancer, diabetes, cardiovascular diseases, and Alzheimer's disease.

PERFORMANCE ANALYSIS

Target Context and Conditions

Implementation of this goal will occur through the Interventions Testing Program (described above). In 2008-2009, the NIH will identify at least six interventions with the potential of extending lifespan in a mouse model and begin primary (phase I) testing of those interventions. In 2010, phase II testing will begin on the most promising compounds

and will continue through the life of the goal.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Identify at least three potential interventions to extend lifespan in an animal model, and begin Phase I testing with these interventions.	Identify/begin Phase I testing of at least three more potential interventions to extend median lifespan in an animal model.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$2,286	$2,286

SRO-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).**

BACKGROUND

Prevalence/Incidence

Mediated through the brain, mood disorders disrupt every facet of a person's life: emotions, thought processes, behavior, social relationships and physical health. Major depressive disorder (MDD) is the leading cause of disability in the US for ages 15-44. MDD is a serious, prevalent and costly chronic disease which affects approximately 14.8 million American adults (6.7 percent of US population age 18 and older) annually. Current data indicate that the point prevalence of depression among people with medical illnesses in primary care settings is significant (10%-20%), and that the more severe the medical condition, the more likely a person will experience clinical depression (e.g., as high as 40% in patients with advanced heart failure or Parkinson's disease). Medically ill patients with comorbid depression are significantly more impaired, and have higher mortality, than otherwise similar patients without depression. For example, untreated depression increases the risk of dying from heart disease by as much as six-fold. Major depression is also associated with significantly higher medical costs in all facets of medical care. For instance, among individuals with diabetes, total medical expenditures are as much as 4.5 times greater for those who are depressed, even after controlling for demographics and severity of medical illness. These effects are partly due to inherent health effects of depression, such as sleep and appetite dysregulation, and through other physiologic disturbances, such as platelet aggregation, that are just beginning to be understood. In addition, medically ill patients with comorbid depression have lower adherence to recommended treatments, such as pharmacotherapy; and to self-care regimens, such as improved diet, exercise, and smoking cessation.

Rationale

The premise of this goal is that targeted research focused on early detection, prevention and treatment of depressive disorders will have a significant impact on the overall reduction of years lost to disabilities (YLDs) 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 several models of care are currently available and have proven effective in delivering adequate depression treatments, patterns for delivery of care, treatment, uptake and maintenance remain poor. Only an estimated 20 percent of patients obtain adequate treatment. Previous studies indicate that rates of underutilization are higher for racial and ethnic minorities, elderly persons, youth, and young and middle-age males. Detailed analyses across these studies found that service use is influenced by years in the United States, nativity, language, age at migration, generational status, as well as gender, age, marital status, education, income, insurance coverage, and clinical severity. Improved recognition, treatments of depression and healthcare utilization among these subgroups will help to reduce disparities in chronic depression, functional health status and co-morbid physical illnesses.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH is undertaking multiple strategies in order to develop the knowledge base to guide efforts at reducing the years lost to disability as a result of depression. The first of these strategies is to investigate further the mechanisms underlying depression that may serve as important targets for intervention, such as interactions between genes and environmental stressors that may lead to depression, or the role that vascular changes in aging play in the development of depression. A second strategy involves further refinement of existing treatments for depression, such as by determining individual characteristics associated with differential treatment response so as to better be able to personalize treatment options, or by investigating the potentially increased efficacy of combined or sequential treatments. In addition, more research is being conducted to examine treatment strategies tailored for specific populations, such as racial and ethnic minorities and the elderly. NIH is also investing in the development of better tools to measure the impact of depression, not only in terms of years lost to disability, but also its influence on social functioning in general, such as workforce roles, social roles, etc. These measurement tools will allow researchers to better gauge the effectiveness of new and improved treatments for depression in alleviating disability. Finally, improved interventions based on a better understanding of the mechanisms underlying depression will sharpen efforts to reduce or prevent negative interactions between depression and other comorbid physical disorders. More research is needed to unravel the relationship between depression and, for example, Parkinson's disease or cancer, including better methods for examining these complex interactions. Improvements in the detection, prevention, and treatment of depression are likely to positively impact the course of these and other physical diseases as well.

Baseline: 2007

- (FY05) Studies are underway to test the efficacy of differing treatment combinations or sequences for depressed patients.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.	(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.	(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.	(MET) Significant progress has been made in determining the relative efficacy of combined treatments strategies and sequential treatment algorithms of chronic or recurrent depression.	Identify at least two methodologies for examining interactions between depression and other comorbid physical disorders.	Demonstrate the effect of treatment for depression on an individual's improved functional capacity as it relates to social role function, work function and employment.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$83,738	$81,184	$79,291

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. Significant progress has been made in determining the relative efficacy of combined treatment strategies and sequential treatment algorithms in treating chronic or recurrent depression. The effectiveness of using combined treatments or multi-step treatment sequences for depression has been demonstrated in the results of two large-scale clinical trial studies — Sequential Treatment Alternatives to Relieve Depression (STAR*D) and Treatment for Adolescent Depression Study (TADS).

The NIH-funded STAR*D study examined the acute and longer term outcomes of four successive steps of treatment among individuals diagnosed with major depressive disorder, in both primary and specialty care settings. A large majority of the participants had chronic forms of depression. During each step of treatment, participants were assessed to determine their progress, and those who did not become symptom-free advanced to the next step. Rush et al. (2006) summarized the STAR*D trial outcomes in terms of rates at which patients reached remission of depression as assessed according to a self-reported measure of depression. By this criterion, over the four steps in its sequential treatment algorithm, STAR*D observed its depressed patients to reach remission at rates of 36.8%, 30.6%, 13.7%, and 13.0%, respectively. Cumulatively, these indicate that 67% of all the participants who began treatment could become virtually symptom-free within 1-4 treatment steps with the available treatment options (those that the study examined), assuming the participants stayed in treatment long enough to complete the steps. Overall, the STAR*D study findings have helped clinicians identify useful treatment steps for those who prove to be treatment resistant. They have shown that if one SSRI is not effective, following a sequential treatment algorithm that allows adding another medication as well as switching to a different antidepressant may work to benefit most patients since individuals may respond differently.

TADS examined the short- and long-term efficacy of an antidepressant (fluoxetine) and psychotherapy (cognitive behavioral therapy-CBT) alone and in combination for treating major depression in adolescents. According to TADS findings (March et al., 2007), combination treatment seems to be the most effective treatment as compared with either

medication or psychotherapy alone over the course of 12 weeks in adolescents. Although long term results of TADS found that taking fluoxetine alone or in combination with CBT over the course of 36 weeks may speed recovery, taking fluoxetine alone appeared to pose some safety concerns (e.g., vulnerability to suicidal thinking). This suggests that the combination therapy resulted in the best overall safety profile.

SRO-9.2	By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.

BACKGROUND

Prevalence/Incidence

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, some data suggest that minorities are less likely to use the emergency medical system when experiencing a stroke and to receive the standard tPA (a clot-dissolving agent) intervention if they do. The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood and will require further study. Ultimately, a combination of prevention (both primary and secondary) and intervention strategies may be needed to reduce or eliminate racial/ethnic disparities in stroke.

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

Target Context and Conditions

Reducing racial and ethnic disparities in stroke will require a reduction in stroke incidence as well as improvements in stroke outcome in minority communities. Effective prevention programs can reduce stroke incidence, while effective interventions can save lives and prevent the development of motor and cognitive problems following a stroke. NIH is investing in research on stroke intervention, stroke prevention, and combination strategies in minority communities. To more accurately represent the range of NIH efforts, NIH will expand GPRA goal 9.2 to include stroke intervention and extend the time frame accordingly. Several promising pilot studies are underway to test the feasibility of new intervention and prevention strategies. Extending the time frame will allow the NIH to follow up with full-scale studies to validate the effectiveness of these strategies in reducing stroke incidence and improving outcomes in minority communities.

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 a private community hospital, where more than 75 percent of stroke patients are African American or Hispanic. The hospital has begun building a database to gather epidemiological data on its stroke population. The hospital 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. The hospital is also initiating a phase II clinical trial to determine whether an in-hospital education program coupled with community-based case management (via “stroke navigators”) can reduce the likelihood of a secondary stroke, as compared to standard clinical practice. One of the first steps in this project is to recruit and educate practitioners to serve as “stroke navigators.” In a parallel intervention study, the hospital will test a strategy to increase the number of minority stroke patients who receive tPA.

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 stroke prevention programs in diverse communities. The first phase of the program established an infrastructure for the SPIRP. The second phase will

establish collaborative stroke prevention research projects on community-based interventions, epidemiology, and/or outcome measures. The goal of the SPIRP is to 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 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. Registry data will be used to identify strategies to reduce risk factors for stroke and develop statewide prevention and intervention programs.

NIH is also sponsoring several clinical trials on stroke interventions appropriate for minority populations. The Field Administration of Stroke Therapy trial, a multicenter, randomized, phase III clinical trial, will determine if very early administration of the neuroprotective agent magnesium sulfate improves functional outcomes, including the prevention of the development of motor and cognitive problems. The research team will administer the magnesium within two hours of a stroke, in the ambulance if necessary, and the team plans to enroll 45% Hispanic and 15% African Americans into the study. Another phase III clinical trial will explore two different therapeutic strategies for preventing small subcortical strokes, which are the most common stroke subtype affecting Hispanic Americans. Trial investigators plan to enroll 20% of the participants from this ethnic group. In a third study, NIH-funded investigators are exploring the efficacy of blood transfusions in preventing recurrences of stroke in children with sickle cell anemia who have had silent cerebral infarcts. This form of stroke is a common contributor to severe neurological disease in children with sickle cell anemia, which predominantly affects African Americans.

Baseline: 2007

- (FY05) Cooperative agreement awarded establishing SPIRP infrastructure, but stroke prevention projects have not yet begun

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.	(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.	(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).	(NOT MET) The target was not met due the complexities of developing the necessary infrastructure.	Establish a database of stroke patients and collect data for the purposes of identifying new stroke risk factors and developing effective stroke prevention strategies.	Recruit and train four practitioners to serve as community-based case managers in a secondary stroke prevention trial targeting African Americans and Hispanics.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$32,219	$30,987	$33,147

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was not met through the Stroke Prevention and Intervention Program (SPIRP) due the complexities of developing the infrastructure for community prevention programs. While the NIH is anticipating that other programs will address the overall GPRA goal (see details below), the NIH will continue to work with the SPIRP in the future towards the original target of initiating at least two collaborative, community-based prevention projects.

The NIH has made progress toward the FY 2007 Target and the overall GPRA goal through several different programs that directly impact the prevention and treatment of stroke in minority and high-risk populations. For example, the NIH has recently awarded funds for a Stroke Disparities Program with a number of hospitals to coordinate clinical studies. Specifically, the investigators are conducting three projects, focused on: 1) exploring the impact of a multilevel educational intervention on the number of patients treated with a clot-busting drug for acute ischemic stroke; 2) assessing the impact of an aggressive secondary prevention strategy in preventing recurrent stroke; and 3) evaluating the prevalence and significance of chronic small brain bleeds in individuals with intracerebral hemorrhage. All of these studies will benefit underserved and minority populations, and as a whole, this program will foster collaborative, innovative and effective research strategies to reduce the burden of stroke in populations historically at increased risk from this disease.

Advances or Other Highlights

The NIH is also providing support for an Alaska Native Stroke Registry (ANSR). Building on a thirty-year experience with chronic disease, this Registry is providing critical data on the disparity in stroke-related mortality in Alaskan Natives compared with other populations. Specifically, the goals of this project include: (1) describing the epidemiology of stroke among Alaska Natives; (2) monitoring the quality of stroke care provided; (3) guiding the design of prevention/intervention programs; and (4) evaluating the effectiveness of those programs. Over the last year the ANSR has exceeded all of its predefined benchmarks. To date, the program has enrolled 204 cases, and has recorded information on risk factors, outcome and treatment. In addition, the investigators have obtained all standard benchmark clinical markers for stroke as defined by the Joint Commission (formerly JCAHO), and have published a descriptive paper in the International Journal of Stroke (Volume 2, Issue 1, February 2007). Recruitment continues from across the state of Alaska, and ten regional health care centers now have passive stroke surveillance. The preliminary results of the ANSR have aided the investigative team in identifying hypotheses-driven intervention research questions; future studies will explore improvements in acute stroke treatment and secondary prevention.

In addition to these activities, two educational projects run by the NIH-funded Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) program are also targeted to minority populations. These include a training program for middle-school students to recognize the symptoms of an acute stroke in their family members; results from this project

published in November 2007 suggest that the intervention can improve the childrens' intent to call 911 in a stroke emergency but that other strategies will be needed to reach parents effectively. A second SPOTRIAS project is designed to determine if a culturally sensitive interactive educational program is more effective than usual care in enhancing the recognition of stroke as an emergency among a racially and ethnically diverse high-risk population (including African Americans and Caribbean Hispanics).

SRO-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 the development of magnetic resonance imaging (MRI), 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 neurochemical brain development, and Diffusion Tensor Imaging (DTI) to characterize white matter fiber tracts that form the pathways connecting different brain regions.

In the 1990s, 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. Since then, several small studies and limited longitudinal studies have allowed researchers to identify some developmental changes in the brain. Researchers have also found 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. The limitations of the 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 healthy brain development is essential in finding the neural correlates of a myriad of childhood disorders related to mental retardation, developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases, which can persist into adulthood. To define the healthy ranges and trajectories in brain growth and development in children as they mature, longitudinal studies of 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 these 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 cognitive and 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 scan and to collect clinical and behavioral 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 and clinical scientists. 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

Target Context and Conditions

NIH has brought 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 varying 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 are creating normal pediatric growth curves for the whole brain and for specific regions of interest, and are establishing the characteristics of healthy white matter fiber tract development. In addition, analytical software and image processing tools are being developed to automatically generate the volume and area of specific brain regions and of white matter fiber tracts. The neuroanatomical and clinical/behavioral data are integrated and housed in the Pediatric MRI Data Repository. The database is available to biomedical and biobehavioral researchers outside of the project

through a web-based portal to encourage further data analyses such as studies of brain-behavior relationships and comparisons to children with a variety of disorders and diseases. This effort may also serve as a model for new NIH neuroinformatics initiatives that can link to the anatomic MRI database.

Baseline: 2007

- (FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(MET) Preliminary analyses of changes of brain growth in children over time have been shared with the research community through two publications.	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.	Disseminate the database of information collected from approximately 500 children that includes anatomic magnetic resonance imaging scans, clinical data, and preliminary data collected from diffusion tensor imaging and from magnetic resonance spectroscopy via the Biomedical Informatics Research Network to enable researchers outside the project to collaborate and share information gained from subsequent analyses.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$1,415	$410	$55

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. Preliminary analyses of changes in brain growth in children over time have been shared with the research community through two publications. The preliminary findings show that there is no difference in brain growth and behavior in young children, from birth to age 4, across the sites or between genders. Researchers also report that for neurocognitive tasks, performance improves between ages 6 and 10, and then levels off during early adolescence.

Advances or Other Highlights

A total of 514 children have been enrolled in the study. Data collection for each of the three stages of data collection in this study included neuroimaging scans, and demographic, medical, cognitive, and behavioral data assessments. Of the enrolled children between the

ages of 4.5 to 20, 95 percent and 89 percent completed the second and third stages of data collection, respectively. In addition, 95 percent of these children have completed diffusion tensor imaging scans as well as the anatomical MRI scans for all three data collection time points. These data have been added to the database and are currently undergoing quality control processes. Recruitment, scans, and final data collection has been completed for 105 children younger than age 4.5. Data from 75 of these children is available to the public in a database and data from the remaining children continues to undergo final quality control. The overall project attrition rate remains at five 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

Target Context and Conditions

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. If this goal is successfully accomplished, the NIH will move forward with its goal to improve the health of individuals with hearing loss.

Baseline: 2007

- (FY06) Clinical protocols and other needed study documents are available.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
		Design and develop clinical protocols and other needed study documents.	(MET) NIH-supported scientists 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.	(MET) NIH-supported scientists successfully developed the Manual of Procedures (MOP) for the CHIMES Study and delivered it to each of the screening sites.	Obtain OMB approval for collection of information from the public.	Initiate patient enrollment at 7 hearing screening sites to enroll approximately 10,000 children.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$2,998	$2,613	$1,897

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. NIH-supported scientists successfully developed the Manual of Procedures (MOP) for the CMV & Hearing Multicenter Screening (CHIMES) Study. The MOP was also delivered it to each of the screening sites. The MOP includes data forms, data safety and monitoring plan, informed consent forms, and any other documents needed for collaborative arrangements and collection of CMV and audiometric screening and follow-up data.

Advances or Other Highlights

The NIH-supported scientists have provided guidance on how to ensure that safeguards for maintaining confidentiality are in place and effective, including compliance with the local Institution Review Boards (IRB) and applicable Department of Health and Human Services regulatory requirements. Each study site is expected to adhere to the guidelines set forth in the MOP for the CMV & Hearing Multicenter Screening Study. No changes will be made to the study procedures without approval from the CHIMES Study Investigators, the NIH and the site IRB. All key personnel involved in consenting study subjects and involved in implementing the protocol are required to obtain training in the protection of human study participants.

SRO-9.5	By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.

BACKGROUND

Chronic obstructive pulmonary disease, COPD, is a progressive disorder of the lungs characterized by a gradual loss of lung function and airflow limitation that is not fully reversible. The term COPD includes chronic bronchitis, chronic obstructive bronchitis, emphysema, or combinations of these conditions. Symptoms range from constant coughing, excess sputum production, and wheezing, to severe shortness of breath. Although no cure exists for COPD, symptoms can be managed and damage to the lungs can be slowed.

Several NIH-sponsored research programs have increased understanding of COPD and fostered new treatments. For example, the Nocturnal Oxygen Therapy Trial showed that some patients with advanced COPD live longer if given long-term oxygen therapy. The Lung Health Study showed that a smoking cessation intervention can improve long-term survival of COPD patients. The National Emphysema Treatment Trial (NETT) showed that lung-volume-reduction surgery can improve the quality and/or length of life in certain groups of patients with severe COPD. The NIH continues to conduct clinical research to improve COPD treatment. Most recently, the NIH launched a new trial to assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia (low blood oxygen level).

Prevalence/Incidence

COPD, a lung disease that over time makes it hard to breathe, is the fourth leading cause of death in the United States. Approximately 12 million adults in the U.S. are diagnosed with COPD, and more than 120,000 die from it each year. An additional 12 million adults in the U.S. may have undiagnosed COPD. In decades past, COPD was predominantly a disease of older men. Now, the disease affects men and women equally, with a slightly greater number of women now dying of COPD each year than men.

Disease Burden

COPD costs the U.S. economy an estimated $32.7 billion per year in healthcare expenditures and indirect costs of morbidity and mortality.

Rationale

Little is known about the safety or effectiveness of long-term oxygen therapy in patients who have COPD but only moderate hypoxemia. Although oxygen therapy is known to be beneficial for COPD patients who have severe hypoxemia when resting, its value for patients with less serious disease is not known and there is some concern that it may actually be harmful in such patients. Nevertheless, many physicians routinely prescribe oxygen for COPD patients with less than severe hypoxemia, who may actually represent the majority of the 1 million patients in the United States who receive long-term oxygen therapy and of the $2 billion in annual costs to the Centers for Medicare and Medicaid Services (CMS) for its provision.

In May 2004, the NIH and the CMS, recognizing major gaps in knowledge regarding the mechanisms of oxygen benefits, optimal indications for its prescription, and its effects on patient outcomes other than survival, convened a working group of scientific experts entitled "Long-Term Oxygen Treatment in COPD" to review the state of science related to oxygen therapy and to make recommendations regarding future research. The working group identified several areas for further research. The recommendations included a clinical trial to determine the efficacy of long-term oxygen therapy in patients with COPD and moderate resting hypoxemia.

PERFORMANCE ANALYSIS

Target Context and Conditions

In November 2006, the NIH and the CMS launched the Long-Term Oxygen Treatment Trial (LOTT), the largest ever randomized clinical trial of the effectiveness and safety of long-term, home oxygen therapy for COPD. The NIH will administer and oversee the study, and the CMS will cover the costs of items and medical services that are generally available through the CMS to beneficiaries enrolled in the trial. The objectives of the trial are to assess the efficacy of around-the-clock, supplemental oxygen therapy for patients with chronic obstructive pulmonary disease (COPD) and moderately severe hypoxemia, provide a scientific basis for decisions regarding the clinical use of long-term oxygen treatment, and improve clinical management of COPD. The results also will help the CMS decide whether to extend coverage for home oxygen treatment to patients with moderate disease. Currently, the CMS limits coverage of home oxygen therapy to beneficiaries with very low blood oxygen levels at rest or during exercise or sleep.

In the LOTT, researchers at 14 clinical centers across the United States will study approximately 3,300 patients with COPD. The trial is expected to progress in three phases. During the first phase LOTT investigators developed the trial protocols, model informed consent documents, and other necessary trial materials. The trial Steering Committee will develop procedures and tools for training of staff, randomization of subjects, data management, and quality assurance/quality control of study activities and data. The second phase will include training of staff, subject screening and recruitment, interventions, and follow-up with data collection and monitoring. Patient recruitment for the trial is expected to begin in 2008. Participants will be randomized to receive or not to receive supplemental oxygen for approximately 3 years. All participants will be periodically monitored; those who are not randomized to receive oxygen initially will be prescribed oxygen if their blood oxygen levels significantly worsen during the trial. The final phase of the trial will include data analysis and reporting.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Obtain approvals for initiation of trial from the Data Safety and Monitoring Board (DSMB) and all local Institutional Review Boards (IRBs). Begin enrolling patients at 14 sites and reach	Achieve cumulative enrollment of 1400 subjects.

						enrollment of 470 subjects.	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$10,176	$9,498

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 2014, 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

Target Context and Conditions

Comprehensive strategies are being 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.

Arkansas has SIDS rates that are higher than the national average. The NIH will partner with the Arkansas Department of Health (ADH) to conduct an intensified statewide SIDS risk-reduction outreach to African American communities. Working with ADH's Office of Minority Health and Health Disparities, information will be distributed statewide through the Arkansas Hospital Association (AHA) to the 45 Arkansas Hospital Association members who have obstetrical and/or maternity services. Local Hometown Health Coalitions and ADH Local Health Units across Arkansas will also participate.

A continuing education program on SIDS risk-reduction for pharmacists will also be developed. This CE module will be initially promoted at CE workshops for pharmacists in the DC metro area, who serve African American women of childbearing age and their families. This pharmacist CE program will be developed in collaboration with the D.C. Pharmacy Association, national pharmacy organizations, and the U.S. Public Health Service commissioned officer and civil service pharmacists from the Department of Health and Human Services agencies/offices.

In order to understand and eliminate the disparity in SIDS mortality and the resultant contribution to infant mortality, it is imperative to fully understand the barriers to diffusion of the Back to Sleep message into vulnerable minority or low socioeconomic status populations. The NIH recently announced a Request for Applications (RFA) to examine trends in infant care practices, and environmental and cultural influences on the diffusion of the public health recommendations in a nationally representative sample of minority and non-minority mothers. Without a better understanding of what influences infant care practices among all population groups, the delayed diffusion of effective SIDS prevention strategies will serve to exacerbate disparities, rather than eliminate them.

Baseline: 2007

- (FY05) There are no known efforts to systematically educate nurses on a community level about SIDS risk reduction.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Interviews were held with participants from each summit and 150 outreach activities resulted from each of the summits.	(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.	(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.	(MET) NIH extended the continuing education module to approximately 50 nurses in the Mississippi Delta Region.	Distribute approximately 43,000 special "Back to Sleep" campaign materials targeting African American communities in collaboration with the Arkansas Department of Health.	Conduct a continuing education program for approximately 500 pharmacists in the DC metro area.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$600	$850	$90

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. In 2007, continuing education training on SIDS risk-reduction was conducted in all nine health districts, which covers all the counties in Mississippi. A total of 21 trainings were conducted. Approximately, 50 nurses who work in both clinical and community-based settings received three continuing education credits from the Mississippi State Department of Health.

There were eighteen mini-grant recipients (two in each health district) who helped recruit participants for the SIDS risk-reduction trainings. The mini-grant recipients assisted with sponsoring SIDS Outreach Sundays across the state to promote the SIDS risk-reduction messages. In an effort to encourage the development of partnerships to reduce infant mortality and morbidity within African American communities, three SIDS risk-reduction trainings were conducted to deliver translated scientific findings concerning health disparities to African American parents, grandparents, relatives, childcare providers, babysitters, and community-based organizations. Quarterly "Baby Safety Showers" are being implemented within all nine health districts. One crib is delivered to each of the health districts to use as give-a-way during an introductory baby shower. Collaborations have been established with the Mississippi SIDS Coalition, Mississippi State Department of Health, and other local organizations to promote the use of African American SIDS risk-reduction materials, including the Resource Kit for Reducing the Risk of SIDS in African American Communities.

Advances or Other Highlights

The NIH continues to promote and disseminate the nurses' continuing education (CE) module, Continuing Education Program on Sudden Infant Death Syndrome (SIDS) Risk Reduction, which was created in collaboration with national nursing and health organizations across the country. In 2007, CE courses were conducted at four national and six regional nursing conferences. There were 413 nurses who completed the nursing modules and

received CE credit. Dissemination of the nurse CE include fulfilling requests for training from organizations identifying a need such as state public health associations, medical centers, and hospitals. The trainings at national and regional nurse organizations, as well as hospital-based trainings will provide an opportunity for nurses to come into contact with the curriculum on several levels, which can then lead to sustainability through institutionalization of the curriculum recommendations.

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 is developing 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 match SBIR recipients with the resources/partners needed for them to bring their innovative concepts to commercialization.

By consolidating the funds available through individual awards, NIH is creating a program to assist SBIR awardees as they address the technical challenges that arise during the conduct of SBIR projects. Phase II awardees are offered business planning assistance and opportunities to 'marry' their technologies with potential targeted strategic alliances and investors, and Phase I awardees learn of possible additional applications of their technologies thereby possibly opening up additional markets.

PERFORMANCE ANALYSIS

Target Context and Conditions

Several technical assistance programs aimed toward commercializing SBIR-developed products are being 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 are piloted. Effective pilots are then transitioned into programs. At that time, critical elements for monitoring performance will be identified. These critical elements are then monitored over time to report on performance and to make adjustments as needed to enhance the services.

NIH first pilots programs that expand the availability of business planning and strategizing assistance to small businesses. These pilots 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. Successful pilots are then 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 are then tracked for a period of 18 months to determine if they did in fact make an investment or partnering deal.

While a trans-NIH CAP program is implemented, a new pilot assistance program is launched in another business area of need. A pilot Technology Niche Assessment Program was offered to a group of Phase I SBIR awardees in FY 04. This program assisted with identifying the niche markets that may be applicable for the individual technologies being developed. The pilot proved to have addressed the needs of the participants, so a trans-NIH niche assessment program was implemented in late FY 05.

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 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 is done through solicited contracts with business consulting firms specifically trained to provide such services.

Baseline: 2007

- Target 1: No current programs.
- Target 2: Piloted assistance programs (i.e., CAP, Niche, etc.)
- Target 3: Pilot programs converted to program implementation.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization.	(MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.	(MET) Completed pilot Niche Assessment Program with 100 participants.	Manufacturing Assistance	(EXT) Pilot test for MAP has been extended to FY2007	Manufacturing Assistance	(MET) Completed pilot Manufacturing Assistance Program with 25 participants.		
2	Implement effective piloted programs to create a menu of technical assistance programs.	(MET) Initiated trans-NIH CAP with 130 participants.	(MET) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at an investment forum.	CAP 3rd Yr., Niche 2nd Yr.	(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.	Niche 3rd Yr., Manufacturing 1st Yr.	(MET) 125 participated in the third year trans-NIH CAP program and 80 presented their business opportunities at an investment. All 150 participants in Niche Assessment Program received their TNA™ reports	Manufacturing 2nd Yr.	
3	Report critical elements to assess advances of each technical assistance program Pilot programs converted to program implementation.	(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.	(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.	CAP 1st Yr., CAP 2nd Yr., Niche 1st Yr.	(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.	CAP 1st Yr., CAP 2nd Yr., CAP 3rd Yr., Niche 2nd Yr., Manufacturing Pilot	(MET) 1st yr CAP, partnerships and deal related activities increased. 2nd yr CAP, equity investments increased. 3rd yr CAP, commercialization progress increased. 2nd yr Niche, 87% of all participants has better understanding of target markets.	Niche 3rd Yr., Manufacturing 1st Yr.	
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.								

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$947	$329	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY 07 target of test piloting a NIH SBIR Manufacturing Assistance Program was MET. Under a contract with Dawnbreaker, Inc., 25 SBIR Phase II awardees from diverse areas of science participated in the program. Various manufacturing centers associated with the National Institutes of Standards and Technology Manufacturing Extension Partnership (MEP) assessed the participants' manufacturing needs and either helped resolve issues or provided a written strategy for resolution. For example, to improve the detection, diagnosis and therapy for human health/diseases, Mikro Systems of Charlottesville, VA, developed a manufacturing technology platform to enable cost-effective production of advanced collimators and detectors for nuclear medicine, gamma cameras, and small animal imaging with SBIR funding. Their quality system was fairly well established, however, with exposure to Lean Manufacturing principles through the pilot program, they are now transitioning from prototype production to full-scale production quantities.

The pilot's progress to date includes: (1) all projects have been completed, (2) participants have been provided final reports that include accomplishments and next steps, and (3) feedback from all participants has been received and is being analyzed.

Target 2:

The FY 07 target for implementing effective piloted programs to create a menu of technical assistance programs was MET. 3rd Year Trans-NIH Niche Assessment Program – 75 SBIR Phase I awardees were enrolled in NIH's SBIR Niche Assessment Program. Between August 2007 and July 2008, Foresight Science and Technology (the program's contractor) will provide a TNA™ (Technology Niche Analysis) for each. Foresight will perform the necessary due diligence and prepare reports specific to each company's technology that will indicate 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 will also be identified. As of November 2007, 15 reports have been completed.

Target 3:

The FY 07 target for reporting critical elements to assess advances of each technical assistance program was MET.

1st year CAP – Feedback for the 18 months following completion of the first year of the CAP program was received by 80 participants, an encouraging 74% response rate. Analysis of the data showed that 77% of the respondent companies indicated commercialization progress in the partnership and financing deals area. Overall the intensity of partnerships and deal-related activities was greater in the intervals post CAP versus that in the baseline period. 65 deals were closed since the culmination of the CAP versus 23 during the CAP. The aggregate amount of equity investment received by the responding 1st year CAP participants is approximately $30 million.

2nd year CAP – Feedback for the 9 months following completion of the second year of the CAP program was received by 75 participants, a 63% response rate. Analysis of the data

showed that of the companies that responded to the baseline tracking, 88% indicated commercialization progress in the partnership and deal related activities area. The largest number of meetings with investors and partners was 313 reported by Platypus Technologies, and the largest number of deals was 21 reported by Incell. Equity investments were raised by 19 participants. The largest equity investment of $47.3M was realized by Vical, a San Diego, CA biopharmaceutical products company that develops infectious disease vaccines.

3rd year CAP –Baseline feedback at the completion of the third-year CAP program was received by 91 companies, a 74% response rate. Analysis of the data showed that 77% of the respondents indicated commercialization progress. Twenty-nine percent indicated an increase in their revenues. Four companies (Nanoprobes, CorTechs Labs, Lynntech, and Biopsy Sciences) reported over $5M in revenues. Biopsy Sciences' Bio-SEAL (supported in the CAP program), Maxi-Cell Needle, and VMARK technologies were acquired by Angiotech for $19M. Equity investments were raised by 19 participants. Micronics, a company in Redmond, WA that specializes in micro fluidics, reported raising the largest equity funding of $18M.

2nd year Niche – 125 NIH FY 2006 & 2007 SBIR Phase I awardees and 25 3rd CAP participants received Technology Niche Analyses™ from a contractor, Foresight Science and Technology. Foresight performed due diligence and prepared reports specific to each company's technology that indicated the needs and concerns of the end-users, the competitive advantages of their technologies, additional possible markets, ad a market-entry strategy. Possible partners and/or investors were identified for consideration. All 150 participants received their reports in FY 2007. Of the 21 CAP respondents, 90% indicated the reports were helpful and provided new insights to market entry. Feedback is still being collected on the Phase I awardees; however of the 56 respondents so far, 91% felt they have a more realistic understanding of their target markets.

CTR-5	**By FY 2007, 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 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

Target Context and Conditions

Established an in-depth and long-term technology transfer marketing and management program for intramural intellectual property that required 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 focused on leveraging a text mining software engine to perform needed high-powered analyses.

Initially, the project concentrated 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 established an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that identifies and markets technologies with minimal value if marketed individually. The FY 2008 objective to further refine the automated system and add visualization tool will be accomplished in FY 2007 by establishing a fully functioning and robust text mining tool. Due to off the shelf software, this goal may be achieved earlier than expected. 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 can be developed into a product that benefits the public health.

The knowledge management system also allows 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 enables NIH to identify and contact potential CRADA partners for these critical collaborations.

Baseline: 2007

- (FY06) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(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.	(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.	(MET) A fully functioning system called Synapse has been deployed with text mining and visualization features. Synapse has significantly improved the marketing capabilities and has been adopted by other intramural and extramural entities at NIH to advance their programmatic needs. The latest version of Synapse was developed at minimal cost and with expanded capabilities. (MET) Synapse has made it possible for NIH to reach a wider business market by matching its portfolio to the research interests of biotechnology and pharmaceutical companies. *	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. * Target completed in FY 2007	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$60	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target 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 was MET. NIH also achieved the FY 2008 target 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 to eventually to be more widely distributed. A fully functioning system called Synapse has been deployed with text mining and visualization features. Synapse has significantly improved the marketing capabilities at NIH and has been adopted by other intramural and extramural entities to advance their programmatic needs. The latest version of Synapse was developed at minimal cost and expanded capabilities.

Goal Achievement

NIH achieved the goal to establish a Knowledge Management (KM) system to enable the Office of Technology Transfer (OTT) 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 NIH intramural inventions. OTT has a fully functioning and very robust text mining tool, known as Synapse, which allows staff to quickly and easily identify and target companies most likely to be interested in licensing available technology. Synapse contains seven databases that can be mined and synthesized to provide a wealth of information (i.e., identifies federal funding, identifies complementary technologies, identifies "gaps" in a technology, recommends the suitability of patenting an invention) to NIH staff and users. Synapse is user friendly, fast, accurate, and can be customized to fit the particular needs of the end user.

Initially, for cost saving and efficiency reasons, NIH tried to utilize a text mining software engine to perform the high-powered analyses. The software was found not to be reliable for OTT's purposes and the project immediately concentrated on finding a different inexpensive and effective software engine. Such an engine was quickly identified. It is built on a low cost and reliable platform that lends itself to faster programming, better adaptability, and enhanced reliability.

Once the decision was made to change platform, the project then concentrated on identifying, accessing, and integrating the data sources and databases, including PubMed, science news wires, TechTracS (OTT's proprietary version of a recordkeeping software platform for its management of intellectual property), CRISP (Computer Retrieval of Information on Scientific Projects), and the US Patent and Trademark Office (USPTO) issued life science patents. The next year additional databases were added, including RaDIUS (the RAND Federal Database of Research and Development), NIH Office of Rare Diseases classifications, and USPTO life science patent applications. Additional advanced search capabilities were programmed into the tool that allow for the portfolio synthesis envisioned by OTT. The final goal of adding visualization tools was accomplished by the end of FY 2007.

Advances or Other Highlights

Synapse provides an integrated way to mine data from invention portfolios, grant and patent databases, and biomedical research and news databases. The ability to aggregate and visualize this information quickly and seamlessly is what makes this tool so unique.

Synapse presently draws from several databases:

- TechTracS®, a proprietary database containing the NIH and FDA intramural research portfolios U.S. Patent and Trademark Office patent applications and issued patents.
- CRISP (Computer Retrieval of Information on Scientific Projects), an internal HHS/NIH database of millions of records of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions.
- RaDiUS®, a database maintained by RAND that includes all research grants and contracts awarded across federal agencies.
- Medline®, a database containing abstracts or full text of 16 million articles published in Newsfeeds from millions of records of biomedical news stories. Rare Diseases and Conditions database maintained by the NIH Office of Rare Diseases.

Synapse is used by the OTT to perform high powered analyses related to the marketing of NIH and FDA technologies. Synapse has made it possible for NIH to reach a wider business market by matching its portfolio to the research interests of biotechnology and pharmaceutical companies. NIH is able to provide individualized and targeted information to companies that previously were unaware of all the scientific possibilities available to them at NIH and the FDA.

Efficiency

NIH based it original time projection to achieve its goal on the initial text mining software engine. Projects using that software engine have been in production for many years without any working system ever being deployed. By changing software engines at the onset and using commercial off-the-shelf software, NIH saved significant amounts of money and many years in production time. At the time this goal was established and based on difficulties encountered by others building KM tools, it was realistic to anticipate the goal not being achieved until FY 2013. However, because the project was able to rapidly adjust to problems and find better and less expensive solutions, the goal to improve marketing and management of NIH intellectual property assets by building text mining capability was achieved many years earlier than ever could have been anticipated.

The success of the project can be shown by the fact that Synapse has been demonstrated worldwide and has been overwhelming endorsed as a leading edge tool by both industry and academia.

CTR-6	**By 2010, improve the efficiency and reduce the unit cost of producing authoritative serials cataloging records used to improve access to the biomedical literature in libraries worldwide.**

BACKGROUND

Journal literature is one of the primary means of communicating scientific research and discovery; thus, it is critical to have accurate and authoritative records in the NIH online catalog for serials. Getting these records created in the timeliest fashion, with all the data essential for access and retrieval, allows these records to be used promptly by researchers throughout NIH, other libraries worldwide, and all of the automated systems that depend on this data, most notably the PubMed indexing system. Therefore NIH recognizes the importance of standardizing and streamlining the cataloging process wherever possible.

Rationale

Pilot testing of the new cataloging guidelines in a dozen libraries have demonstrated a potential time and cost savings of up to 20% from current procedures. This will permit decreasing the average serial cataloging time and unit cost by 20%, for an annual savings of .3 FTE (GS-12 level), based on annual production of 1700 titles, and allow the reassignment of staff to new initiatives based on this savings.

PERFORMANCE ANALYSIS

Target Context and Conditions

The efficiency and reduction in unit cost of cataloging records will be achieved through several strategies. Cataloging procedures will be streamlined by implementing revised guidelines for serials cataloging that simplify the training and decision making process, focus on controlled access points for subjects, names and titles, and eliminate redundancies in transcription. The revised guidelines utilize title abbreviation data from the ISSN International Centre, and edit only for format, rather than content. The revised guidelines eliminate cataloger-supplied translations of Chinese, Japanese and Korean titles, and instead provide access to the vernacular data.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Reduce cataloging time by 7 minutes per title and realize a savings of 0.10 FTE.	Reduce cataloging time by 8 minutes per title and realize an additional savings of 0.10 FTE.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

CTR-7 By 2010, establish the feasibility of sharing information from already-conducted scientific studies of warfarin (coumadin^{R}) anti-coagulation, through the knowledge base PharmGKB.

BACKGROUND

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) was developed to help researchers understand how individual genetic variation contributes to differences in drug reactions. It is a publicly available repository for genetic and clinical data from pharmacogenomics research studies. Over the next three years, up to 13 international groups have agreed to share existing data sets via PharmGKB. The risk is in whether these groups will be able to effectively share data and harmonize between their non-standardized methods for conducting the studies.

Studies of warfarin (Coumadin®) were selected for this goal because the drug is widely used and individual response is highly variable. Warfarin is an anticoagulant used to prevent blood clots from forming or enlarging. Initiating warfarin therapy involves a great deal of cost and coordination because optimal dosing levels vary among individuals. Clinicians monitor patients using warfarin with frequent blood testing in order to maximize the therapeutic benefit without causing dangerous side effects.

The groups plan to use PharmGKB data to perform a meta-analysis that will yield a possible algorithm for warfarin dosing based upon genotype. If successful, this will establish a procedure for data-sharing and maximize its extractable value, with the pay-off of incorporating the pharmacogenetic information gained into establishing the starting dose for warfarin therapy (testable in a replication data set and/or a de novo clinical trial). This work will potentially lead to better patient management and ultimately reduced health care costs.

Rationale

The President's FY 2008 budget request for NIH noted that, through growing knowledge of individual genetic differences and response to environment, NIH is increasingly able to implement individually targeted or personalized treatment. One cost-effective approach to the development of individualized treatments is to make optimal use of existing information prior to commissioning new, expensive, randomized clinical trials. Warfarin therapy is one area of treatment in which NIH is poised to test the utility of this approach. An established dosing algorithm could inform the design of clinical trials. For example, a trial could test the hypothesis that use of genotyping information to set the initial dose and protocol for warfarin therapy has clinical utility and is an improvement over current practice. The GPRA goal would be proof-of-principle of a useful process for effectively sharing basic pharmacogenetic results and preparing to translate those results into clinical practice (for anticoagulation). If successful, this paradigm could be extended to personalize other medical treatments.

PERFORMANCE ANALYSIS

Target Context and Conditions

In FY 2008, NIH will ensure that all relevant information to individual dosing of warfarin has been contributed to the PharmGKB by the 13 participating groups. Work will begin on analyzing differences among the various treatment and research protocols and standardizing the datasets. In FY 2009, NIH grantees will begin a meta-analysis using standardized data.

By FY 2010, the meta-analysis will suggest whether a dosing algorithm based on these existing datasets can be used to establish initial dosing levels in clinical trials. If successful, these targets will establish the feasibility of sharing data from scientific studies to develop personalized treatments for testing in clinical trials.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
						Begin standardizing datasets in PharmGKB to prepare for the FY09 meta-analysis.	Begin meta-analysis using the standardized data from PharmGKB to determine an algorithm for warfarin dosing based upon genotype.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$1,372	$1,368

CTR-8	**By 2012, increase communication efforts and enhance outreach strategies regarding extramural research funding policy, compliance and administration as demonstrated by the type and frequency of communications and related activities.**

BACKGROUND

The NIH has a history of maintaining a collaborative relationship with the extramural research community and has a strong reputation for providing timely and clear research-funding related communications. It is vital to maintain two-way communications between NIH and the extramural community, thereby ensuring that NIH policies and requirements are effectively developed, implemented, and communicated.

The NIH plans to address its research-funding related communications needs through implementation of a broad communications strategy, including such activities as organizational consolidation of extramural research communications activities, restructuring and developing new Web site content, exploring emerging technologies, integrating and synchronizing communications efforts across NIH, and conducting ongoing evaluation of NIH grants-related communications. These efforts will allow NIH to achieve efficiencies of scale, ensure currency of information, broaden its reach into the community and ensure a consistent message.

Rationale

The magnitude of recent and upcoming changes to grants policy and process has a profound effect on grants administration and the facilitation of research within the applicant community. Clear and effective communication with the research community becomes increasingly important as NIH makes policy changes to facilitate increasingly complex and interdisciplinary science, align with federal-wide application and reporting standards, and streamline and improve the review process.

The NIH must adapt to a changing communications environment. The broad usage of the Internet, Web sites, podcasts, video availability, and other electronic media create expectations of information being immediately available and in a variety of formats. These technologies provide new opportunities to reach larger, specialized and previously underserved audiences.

Policy changes, coupled with changes in how people communicate, necessitate the development of an NIH extramural research communications office. This office would generate new efficiencies, use new technologies, and maintain effective two-way communication with the extramural community.

PERFORMANCE ANALYSIS

Target Context and Conditions

A working group of staff, stakeholders and consultants was formed in 2006 to analyze the usability and content of the existing grants Web site. In FY07, a redesign of the main NIH grants Web site was launched for the extramural community. The updated Web site

implements the recommendations of the working group and provides new content, improved search capabilities, and easier navigation. The updated Web site is an integral component of the overall communication strategy. The Web site is the central location for grants-related information and is referenced from many other types of communications and websites across NIH.

The consolidation of communications activities within the extramural research program began in FY07 by reorganizing staff into a central office while maintaining existing roles and responsibilities. In FY08, the new office will realign staff, roles and responsibilities to realize efficiencies of scale and improve message consistency. This group will be responsible for development and execution of a comprehensive communications strategy, that involves numerous activities such as development of an automated system for creating funding opportunity announcements, exploring emerging technologies, coordinating outreach activities and events, and developing outreach materials.

The consolidated office and its activities, including the improved Web site content, will set the foundation to centralize and create a single trusted source of information related to research-funding related process and policy.

Baseline: 2007

- Web site design and content prior to redesign and update effort.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
				Complete redesign of NIH's main grants Web sites and improve Web content.	(MET) NIH launched a complete redesign of its main grants website in August of 2007, involving changes to over 600 Web pages and dozens of pages of completely new content explaining the NIH grants process.	Realign staff centrally to support the execution of a comprehensive communications strategy.	Provide a single source of information on grants policy and process to integrate and synchronize related communications efforts across NIH.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$2,678	$2,913	$3,022

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 Target to complete redesign of NIH's main grants Websites and improve Web content has been MET. NIH launched a complete redesign of its main grants website in August of 2007, involving changes to over 600 Web pages and dozens of pages of completely new content explaining the NIH grants process. The site now provides applicants with advice on improving their grant application submissions and graphical process overviews with multi-layered pages of guidance and advice to applicants, In the 3 months since its launch; the website has been accessed over 3.2 million times.

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

Target Context and Conditions

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 Ruth L. Kirschstein National Research Service Award (NRSA) 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.

Baseline: 2007

- 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 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%.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
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.	(MET) Award rate to comparison groups exceeded by 12%	(MET) Award rate to comparison groups exceeded by at least 14%	N ≥ 12%	(MET) Award rate to comparison groups exceeded by at least 13%	N ≥ 12%	(MET) Award rate to comparison groups exceeded by at least 12%	N ≥ 12%	N ≥ 12%
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.	(MET) Award rate to comparison groups exceeded by 14%.	(MET) Award rate to comparison groups exceeded by at least 13%	N ≥ 12%	(MET) Award rate to comparison group exceeded by at least 13%	N ≥ 12%	(MET) Award rate to comparison group exceeded by at least 13%	N ≥ 12%	N ≥ 12%

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$1,521,910	$1,546,558	$1,547,895

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY 2007 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 1986 through 1996 were 2½ times 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	31.0% (4,583/14,796)	19.2% (2,844/14,796)
Comparison Group A	13.5% (9,754/72,007)	6.9% (5,002/72,007)
Comparison Group B	6.5% (1,370/21,163)	2.9% (611/21,163)

Target 2

The FY 2007 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 1986 through 1996 were more than 1 ½ times 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	47.0% (4,884/10,388)	30.5% (3,169/10,388)
Other Postdoctoral Fellows	29.1% (3,385/11,638)	16.8% (1,959/11,638)

Advances or Other Highlights

NIH issued more than 40 new or updated education, research training, and career development funding opportunity announcements in FY 2007, including the announcement

of the new, trans-NIH New Innovator Award. The New Innovator Award complements the K99/R00 Pathway to Independence Award, announced in 2006, and the existing K22 Career Transition Award offered by a number of NIH Institutes and Centers, all of which support promising new investigators and promote their transition to independent research careers. In FY 2007, NIH made more than 180 K99 awards and 40 K22 awards, as well as 29 New Innovator awards.

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 1,640 individuals in FY 2007. 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). 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

Target Context and Conditions

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 upgraded the general ledger/budgeting and travel modules already in production and deployed the contracts/ acquisition, property, supply, accounts payable and receivables modules. Post deployment support is provided for the property and contracts/acquisition/accounts payable and receivable/supply modules through FY 2009. 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. In October 2001, the U.S. General Services Administration (GSA) became the Managing Partner for the E-Gov Travel eGov initiative, one of 24 eGov initiatives in support of the President's Management Agenda (PMA). The GSA E-Gov Travel PMO formalized the commitment of the U.S. Department of Health and Human Services (HHS) to the migration and implementation of E-Gov Travel. NIH was granted an extension until FY 2009 to complete its migration to E-Gov Travel. NIH and Northrop Grumman have agreed upon the enhancements necessary for a seamless migration to a new travel system that will afford NIH a similar level of functionality as the current travel system.

The NBS roll-out phase supports NBS/UFMS migration activities in relation to compatible functionality. Deployment of the new travel system is planned for May 2008.

Baseline: 2007

- Target 1: (FY03) NBS without contracts/acquisition/accounts payable/supply modules
- Target 3: (FY06) NBS performance with General Ledger and Travel Modules deployed

- Target 4: (FY05) NBS without contracts/acquisition/accounts payable and receivable /supply modules
- Target 5: (FY06) NBS without the UFMS migration

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules.	(MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.	(EXT) The program steps a-g 'Integration' is being re-planned. Extended to 2006.	(FY05)Program steps a-g 'Integration' (Extended to FY06) (FY06) Program steps h-I 'Final review' (Extended to FY07)	(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. (EXT) The program steps h-I 'Final review' is being extended to 2007.	Program steps h-I 'Final review'	(MET) Deployment of property and contracts/acquisition/accounts payable and receivables has been achieved. The NBS has successfully trained the user communities in property and contracts/acquisition/accounts payable and receivables. NBS has provided access and given pre and post deployment support to all authorized end users.		
2	Deploy the service and supply fund activities module.	(MET) Identified solutions for automated amortization for Real Property and Agency Agreements.	(EXT) The program steps a-g 'Integration' deployment for service and supply fund modules are being extended to 2008.	Program steps h-I 'Final review' (Extended to FY09)	(EXT) The program steps h-I 'Final review' is being extended to FY 2009.			Program steps a-g 'Integration'	Program steps h-I 'Final review'
3	Report critical elements of General Ledger and Travel Module performance.			Reporting key performance indicators for Tracks 1,2,3 and 4	(MET) Performance metric mapping directly to the HHS strategic goals and objectives were reported against FY2004 baseline.	Reporting key performance indicators for Tracks 1,2,3 and 4	(MET) Critical elements of General Ledger and Travel Module performance (Tracks 1,2,3 & 4) were reported to include the number of NBS Help Desk tickets, percent of total NBS tickets closed, number of purchase orders approved, number of days to close the books and captured percent of server uptime statistics.	Reporting key performance indicators for Tracks 1,2,3 and 4	Reporting key performance indicators for Tracks 1,3 and 4
4	NBS roll-out and post deployment support.					NBS deployment	(MET) NBS was deployed.		
5	Commencement of NBS/UFMS migration activities.					NBS/UFMS migration activities	(MET) Commencement of NBS/UFMS migration activities have been initiated in relation to functionality.	NBS/UFMS migration activities	

6	Continue to provide NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules.							Continue to provide NBS post deployment support	Continue to provide NBS post deployment support
7	Continuation of NBS/UFMS migration activities.								Continue NBS/UFMS migration

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$26,263	$25,870	$25,870

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY07 program steps h-i 'Integration' target to deploy the property and contracts/acquisition/accounts payable and receivable/supply modules was MET. The NBS has successfully trained over 6200 users in more than 32 roles. The project team conducted predominantly classroom instructor led training supplemented by lecture and videocast formats to provide adequate training to the end user.

Authorized users have been given access to the new system functionality. The NBS Management Center (NMC) supports the deployed property and contracts/acquisition/accounts payable and receivable modules by employing standard escalation protocols for assisting users who are experiencing difficulty.

Target 3

The FY07 target to report critical elements of General Ledger (Track 1), Travel Module (Track 2), Supply and Payable/Receivable (Track 3), and Contracts/Acquisitions and Payable/Receivable (Track 4) performance was MET. Critical elements of General Ledger and Travel Module performance were reported in FY2007 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 560,515 records have been processed in the NBS Travel module since deploying for FY 2004. For FY 2007, approximately 127,841 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 23,983 patient trips were processed by the Clinical Center Travel Office during FY2007.

Target 4
The FY07 target to roll-out and post deployment support has been MET. Deployment of contracts/acquisition, accounts payable and receivable, property, and supply modules occurred in two Waves. Wave 1, included supply and payable/receivables, rolled out on February 21, 2007. Wave 2, included contracts/acquisitions and additional payable/receivable/supply functionality, rolled out on June 4, 2007. The NBS project team has provided post deployment support by providing post "go-live" training, on site support to NIH Institutes and Centers as well as various user community forums.

Target 5
The FY07 target to commence with NBS/UFMS migration activities has been MET. Commencement of NBS/UFMS migration activities have been initiated in relation to functionality. Although the 2 systems can migrate in some aspect, such as shared coding, complete migration is not feasible. There was a re-definition of UFMS this year by the HHS PMO to state that UFMS will now consist of 3 instances of Oracle: CMS' HIGLAS, NIH's NBS and a Global instance used by the remaining OpDivs. The NIH and Global instances do share a consolidated platform and hosting environment at the Center of Information Technology and future efforts will be made to consolidate reporting functionality.

Advances or Other Highlights
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 FY07 the NMC saw a 50% reduction in the number of user call assistance tickets 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 a supplementary training seminar. Topics were derived from trend analysis from monitoring NBS user call assistance tickets as well as direct user feedback.

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

Target Context and Conditions

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) is complete. All aspects of the program have been completed. The project entered 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 has been fully realized with a fully functional hospital information system. The need to manually move data from a clinical system to a research system has been 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.

Baseline: 2007

- FY04-06 results

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) The core hospital system, CRIS, went live and the legacy system was retired.	(MET) Surgery and anesthesia management system implemented; project is on task and within budget. (MET) Implemented a clinical data warehouse; project is on task and within budget.	Integrate clinical systems across the NIH Clinical Center.	(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).	(MET) The CRIS project was completed in 2007 and is now in operations and maintenance phase. This enterprise project now support all clinical and research support activities within the NIH Clinical Center and across the intramural program.		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$6,377	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 Target to complete the goal of streamlining business processes and automation of data movement by implementing, monitoring and updating the clinical research information system (CRIS) was ACHIEVED. To this end the enterprise project was folded back into the NIH Clinical Center in FY 2007 and the CRIS system is now considered to be in operations and maintenance mode. System upgrades and enhancements are part of the operating plan, but system development is completed. Over the past year, the plan to include enhancements to the CRIS system have provided additional functionality as follows:

- A major system upgrade to the core system allowed for interfaces to four additional clinical systems to provide centralized data (exercise stress tests, pain and palliative care service, endoscopy and holter monitoring).
- Physicians can now enter clinical documentation into the CRIS system which creates searchable text and eliminates paper progress notes.
- Protocol attribution was enhanced – now individual orders and results can be attributed directly to a protocol. Because a patient can be on multiple clinical protocols, direct attribution is critical for research purposes and resource allocation.
- The Nutrition System was upgraded to allow patients to enter their own menu selections directly into the computer at bedside using touch-screen technology. This has streamlined Nutrition Department patient call center operations.
- A CRIS Data Mart was developed to push CRIS data to institute clinical research management systems. This has eliminated the need to hand entry of data into institute

specific research systems.

Advances or Other Highlights

The CRIS project now allows for electronic entry of all medical orders, results retrieval and clinical documentation. The system links the core electronic medical record with electronic systems in radiology, surgery, admissions, lab, blood bank and nutrition to provide seamless flow of information within the NIH Clinical Center. All electronic information is now available to researchers through data downloads to use for both patient care and research.

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

Target Context and Conditions

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 was completed by implementing an eRA J2EE Migration Plan. This plan staged 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, 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 migration of legacy data was 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. 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.

Baseline: 2007

- Target 7: (FY06) 40% of business processes being done electronically.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Expand availability of electronic progress reporting to all grantee institutions	(MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.							
2	Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	(MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.							
3	Develop plan to integrate OPDIV's	(MET) eRA has developed plans for adding the FDA and components of the CDC.							
4	Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006.		(MET) The Target was exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) are using eRA to process new grants.	100% of eligible HHS OPDIV's	(MET) 100% of the eligible HHS OPDIVs (AHRQ, CDC, FDA, and SAMHSA) are using eRA for administration of research grants.				
5	Continue conversion of business processes: 80% of business processes being done electronically by FY 2009.		(MET) Approximately, 33% of business processes & financial status reports are done electronically.	40% electronic business processing	(MET) Approximately 40% of the transactions in the business processes are now being done electronically.	55% electronic business processing	(MET) Approximately 55% of the transactions in the business processes are now being done electronically.	75% electronic business processing	80% electronic business processing
6	By the end of FY 2007 complete migration of existing		(MET) 60%of the code has been converted. This efficiency was	(FY06) 75% code conversion	(MET) The target was met and exceeded. 100% of the code was				

	client/server applications to Web-based technology.		accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.	(FY07) 100% code conversion (Target achieved in 2006)	converted before the end of FY06, and all of the Web-based applications were deployed by the end of FY06				

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$2,500	$2,500	$2450

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 7

The FY07 target goal of 55% of the business processes being conducted electronically was MET. Individual Basic Research Grant (R01) applications, which make up a majority of all the applications that are received each year, were successfully transitioned from paper to electronic format in February 2007. Various Resource Program, Biomedical Research, and Health Disparity Endowment grant mechanisms were transitioned in May of this year. By the end of FY07, approximately 80% of all competing grant applications were received electronically. In addition, these applications are now being processed more rapidly. During the past two years, application processing speed has increased from 50 to over 225 per hour. Transition of the remaining 20% of applications that remain paper based, including training, fellowship, career development, and complex grant applications, was put on hold in January 2007, while Grants.gov continued work on a new system and associated application forms. The use of electronic notification was further expanded in FY07 with continued increases in the percentage of progress reports and financial status reports (FSRs) that were submitted electronically. All FSRs are now submitted electronically. Among other enhancements designed to streamline administrative processing, flexible NGAs (Notices of Grant Awards) were introduced in FY07, allowing organizations using non-standard award notices to access a customized template electronically rather than issuing paper notices. Work continues to fully integrate Awaiting Receipt of Application (ARA) processing, obviating the need to match electronic with paper records. Work has also begun to transition a number of second-tier process segments that are still paper based, including Letters of Intent and screening for Organizational Conflict of Interest. In addition, development has been initiated to automate progress reporting for complex non-competing applications.

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

Target Context and Conditions

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 works 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.

Baseline: 2007

- Target 1: Number of projects proposed to be completed annually: (FY06) 43
- Target 2: Number of biocontainment facilities proposed to be completed annually: (FY06) 0

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research.			44 to be completed	(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	48 to be completed	(NOT MET) 46 of the 48 construction grants were completed either early or on time. Two sites are part of larger institutional construction projects and can not be completed and	30 to be completed	22 to be completed

					NIH is seeking a legal opinion regarding final disposition of the funds.		authorized for occupancy until the entire institutional construction project is completed.		
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.					Complete 2 facilities	(MET) NIH completed 2 biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases.	Complete 4 facilities	Complete 8 facilities.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY07 target was not met. Forty-six of the 48 construction grants were completed either early or on time. Specifically, 36 grantees completed construction early and 10 grantees completed construction in 2007. For the two construction projects not completed both are part of larger institutional construction projects. One project is part of a $43 million institutional project and the other project is part of a $60 million institutional project. The NIH funded portion of these projects can not be authorized for occupancy until the entire institutional construction project is completed.

Target 2

The FY07 target was MET. NIH completed two biocontainment facilities to support biodefense and emerging infectious disease research needs, including research on Category A-C Priority agents and newly emerging infectious diseases. The facilities are part of the University of Pittsburgh and Duke University.

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 indicated 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

Target Context and Conditions

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.

Baseline: 2007

- (FY07) 100% of expiring grants eligible for renewal/recompetition will be reviewed (number of grants expiring will be determined annually).

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(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.	(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.	(MET) 100% of the 723 expiring grants eligible for renewal or recompetition were reviewed.	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.	(MET) 100% of the 728 expiring grants eligible for renewal or recompetition were reviewed.	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.	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.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 target was MET. The OAR utilized the enhanced ARIS, a database that allows tracking of all AIDS research expenditures coded to the research objectives articulated in the annual Trans-NIH Plan for HIV-Related Research (http://www.oar.nih.gov/public/public.htm), to efficiently conduct a trans-NIH portfolio analysis of 100 percent of the 728 grants eligible for renewal or recompetition. This portfolio analysis was conducted in concert with the ICs and a panel of outside experts.

Approximately 25 percent (183 grants) of the grants assessed were determined to be currently of a lower priority for funding with AIDS-designated dollars than when they were originally funded. These grants, if successfully recompeted, may no longer be funded with AIDS-designated dollars, thus allowing funds to be redirected to higher priority research projects. For example, during the portfolio analysis, a number of grants related to the basic pathogenesis of opportunistic infections were identified as low priority. Several years ago when these grants were awarded, they were aligned with high priority research objectives. However, in the past years, with the success of NIH research and the development of multi-drug antiretroviral regimens, some of these infections are no 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. In FY 2007, the highest priorities for AIDS research were vaccine research and the development of non-vaccine 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 the focus area 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 money not designated for AIDS research.

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 staff 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 this new system, known as xTrain, 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, xTrain 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 xTrain 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

Target Context and Conditions

The team designing xTrain, which includes experts in research training, grants management, computer programmers, and systems analysts, has been meeting regularly since the summer of 2006 and has presented plans for the system to advocates from the extramural community at meetings of the Commons Working Group in January and September 2007. In December 2007, NIH will begin a pilot test of the xTrain system involving training grant directors, university administrators, and NIH grants management specialists involved in more than 90 institutional research training grants at nine universities. At the conclusion of the pilot, the team will seek feedback from the xTrain testers and hone the system's workings in preparation for its broader release in spring 2008. NIH typically phases in new electronic research administration practices and procedures and the xTrain system will follow the same approach until FY 2012, after which paper appointment and termination forms will no longer be accepted.

To facilitate the implementation of xTrain, the system's development is incorporated into the performance plans of the Deputy Director for Extramural Research and the NIH Research Training Coordinator, who rely on systems analysts and developers, technical writers, grants management specialists, and policy experts.

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.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	By 2012, ensure that 100% of trainee appointment forms are processed electronically.							5%	25%

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

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

Target Context and Conditions

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.

Baseline: 2007

- Proposed annual costs: (FY06) $35,643 per grant

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Achieve average annual cost of managing construction grants			$35,643 per grant	(MET) Achieved average annual cost of $35,643 per grant.	$35,837 per grant	(MET) Achieved average annual cost of $35,837 per grant.	$36,419 per grant	$36,530 per grant

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

NIH achieved an average annual cost of managing construction grants of $35,837 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 indicated by the PART Improvement Plan.

CBRR-10	**By 2013, make freely available to researchers the results of 300 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process.**

BACKGROUND

Many of the critical biochemical processes that regulate health and disease are mediated by proteins. While the functions of some of these proteins are well understood, the majority remain obscure. Two powerful methods for determining the function of a protein are 1) to increase or inhibit its function and 2) to detect its presence under controlled circumstances. Both of these methods rely on small molecules (probes) that bind selectively to the protein of interest. Access to a broad spectrum of small molecules that bind to proteins of interest could accelerate the understanding of the biochemical processes that cause disease.

To date, most information about potentially useful small molecules has been generated by the private sector in the search for new drugs. As a result, this information is proprietary and access to these molecules and their associated data is restricted. Moreover, the private sector focuses its attention on proteins known to be causal to common diseases. Therefore, it has limited interest in many other critical proteins whose functions are yet to be defined and/or are important in rare and orphan diseases. Thus, it has little incentive to develop small molecules that bind to these proteins, limiting the knowledge base of chemical compounds that could be useful for deciphering protein function. As a result, many important proteins remain enigmatic due to the lack of small molecule probes.

A tremendous opportunity to expand the number of probes available to pubic sector biomedical laboratories has become possible due to three major advances in biomedical research. First, the human genome project revealed there may be up to a million human proteins. Second, the use of robotics and other advanced technology now allows the testing of thousands of chemicals in a single laboratory. Third, powerful computer-based information retrieval systems allow the storage and sharing of complex information. These three areas of research have converged to provide an opportunity to expand the number of probes available to decipher protein function.

Rationale

The NIH Roadmap is a set of initiatives designed to rapidly advance biomedical research through new approaches to science that are transforming. As part of the NIH Roadmap theme, Pathways to Discovery, the Molecular Libraries Program (MLP) was intended to revolutionize biomedical research by making a multitude of new probes available to the public sector researchers. This innovative program is expected to provide a scientific resource that will accelerate the discovery of protein functions that control critical processes such as development, aging and disease. The MLP is expected to have a very high impact by facilitating the understanding of basic biological mechanisms, identifying new biological targets for evaluation in disease models, and shortening the timeline for ligand and tool discovery. To facilitate the use of small molecules in public sector biomedical research laboratories, three hurdles have to be overcome. First, there must be an increase in the

number of small molecules known to bind to proteins of interest. Second, information about these probes must be freely available to the research community. Third, the small molecules must be stored and distributed appropriately. The MLP was designed to overcome these hurdles by generating and providing open access to information about the structure and biological activity of small molecules that bind to proteins of interest or alter cellular processes.

The major MLP initiative is the establishment of research centers charged with identifying potent new small molecules. These centers use advanced technology to screen thousands of small molecules for their ability to activate or inhibit protein activity or cellular processes of interest. All of the information derived from these screens is being deposited in a new public database, PubChem. Another critical aspect of the MLP is a new repository to gather, validate, store, and distribute a unique and diverse collection of small molecules. The goal described here is to further develop this new national network into a stable research resource for the discovery and development of novel molecular probes that will lead to new ways to explore the functions of proteins and signaling pathways important in health and disease.

PERFORMANCE ANALYSIS

Target Context and Conditions

The MLP plans to fund up to ten screening centers in FY2008. Some of the centers will be comprehensive centers that will, in addition to screening compounds, modify the structures of candidate probes to discover the most potent and selective probes. The comprehensive centers are expected to rapidly screen hundreds of thousands of compounds in each of dozens of assays per year. Other centers will specialize in complex screens such as those involving cellular processes, whole organisms, and/or in modifying chemical structures to make more effective probes. Together, these centers will produce a diverse set of probes that can be used by many scientists to investigate proteins, signaling pathways, and cellular processes in their field of interest.

The number and diversity of the candidate probes will be increased by collecting compounds from many sources, both industrial and academic. Enhanced quality control measures will be put in place so that the quality of the compounds is increased.

The goal depends on the development of a sufficient number of high quality, high throughput assays against targets of importance in biomedical research.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
							(FY09) Establish repository of 300,000 compounds

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$97,318

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

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	**By 2008, 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.**

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. A study of key positions within the NIH Intramural Research Program provided a framework for the initiating of a study of key positions within the NIH Extramural Research Program in 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

Target Context and Conditions

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.

Baseline: 2007

- Target 1: (FY 06) Performance indicators that addresses recruitment, retention and succession planning established
- Target 2: (FY 06) Performance indicators that addresses recruitment, retention and succession planning established
- Target 3: (FY 06) Performance indicators that addresses recruitment, retention and succession planning established

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research	(MET) Methods were implemented that addressed recruitment, retention and succession planning for key	(Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and	(MET) Recommendations developed for improving the effectiveness of recruitment, retention and succession planning	(Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession	(MET) Assessed the impact of utilizing adopted methods and processes for recruitment, development, and succession	(Target 1) Evaluate and modify performance indicators related to recruitment, development, and succession	

roles. (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.	IRP positions. (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.	processes for key scientific positions within the NIH Extramural Research Program. (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.)	for key ERP positions. (MET) Implemented leadership training for tenure-track and senior investigators and assessed the impact of utilizing adopted methods through surveys.	planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.) (Target 2) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program. (Target 3) Establish performance indicators with baselines related to recruitment, development and succession planning for the NIH Extramural Research Program.	planning for key scientific positions within the NIH Intramural Program. (MET) Implemented methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program. (MET) Performance indicators have been established for recruitment, development and succession planning for the NIH Extramural Research Program.	planning methods and processes for key scientific positions within the NIH Intramural Research Program. (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. (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.	

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$6,177	$4,281	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY 2007 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 Program has been MET. This past year, the NIH Office of Intramural Research (OIR) developed a new course and presented to female tenure-track investigators and postdoctoral fellows from the NIH Fellows Committee. The course "Influence, Self-Promotion and Negotiation for Women in Leadership Roles" was rated so highly and perceived so useful by the postdoctorals who attended that OIR will be offering a slightly modified version for all postdoctoral fellows in January 2008.

Target 2

The FY 2007 Target to implement methods to improve the effectiveness of recruitment, development and succession planning for key scientific positions within the Extramural Research Programs has been MET. The new Extramural/Office of the Director Professional

Designation Model was refined and fully implemented. The Extramural Title 42 Committee (ETFC) reviewed the responsibilities and duties of more than 2,000 NIH extramural scientific positions and categorized them using the new Model.The FY-07 Target to implement methods to improve the effectiveness of recruitment, development and succession planning for key scientific positions within the Extramural Research Programs has been met. The new Extramural/Office of the Director Professional Designation Model was refined and fully implemented. The Extramural Title 42 Committee (ETFC) reviewed the responsibilities and duties of more than 2,000 NIH extramural scientific positions and categorized them using the new Model

Target 3

The FY 2007 Target to establish performance indicators with baselines related to recruitment development and succession planning for the NIH Extramural Research Program has been MET. Along with full implementation of the new Extramural Professional Designation Model, decision criteria was developed and implemented to provide benchmarks of performance and position responsibility for all categories of Title 42 scientific positions. The Extramural Title 42 Committee (ETFC) developed and implemented structured recruitment guidance including the establishment of mandated national search and candidate peer review criteria against position requirements. Of note, each Institute and Center at NIH submitted justifications for its current Title 42 positions to remain in Title 42, along with requests to establish any new Title 42 positions. Using the new decision criteria, the ETFC reviewed each position submission and determined whether the duties and responsibilities warranted appointment under Title 42 or whether another appointment mechanism would be more appropriate, e.g., General Schedule (GS).

Advances or Other Highlights

The OIR and Office of Human Resource in consultation with Tunnell Consulting are developing benchmarks for developmental programs for the scientific staff. Several focus groups led by a Scientific Director will be held to create a proposal that will be presented to the Deputy Director for Intramural Research for consideration and implementation.

In conjunction with full implementation of the Extramural/Office of the Director Professional Designation Model, the Extramural Title 42 Committee has proposed a new compensation model for Title 42 positions. The proposed model has been submitted to the NIH Compensation Committee for refinement and future implementation.

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 Voluntary Early Retirement Authority (VERA) and Voluntary Separation Incentive Payments (VSIP) 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

Target Context and Conditions

In accordance with the PMA, NIH continues to carry out annual competitive sourcing reviews as delineated in the OMB approved NIH Green Plan for Competitive Sourcing. 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.

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 Organization (MEO) awards.

Baseline: 2007

- Target 1: Preplanning initiated for identifying functional areas
- Target 2: Transition plans developed for employees

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target / Estimate
1	Identify annually commercial activities for competitive sourcing comparison.	(MET) Nine streamlined and two standard studies conducted in FY 2004.	(MET) Thirteen streamlined and one standard studies conducted in FY 2005.	Identify annual commercial activities for competitive sourcing comparison	(MET) Identified 4 potential functional areas for review, all 4 were deemed appropriate for streamlined reviews.	Identify annual commercial activities for competitive sourcing comparison	(MET) Identified two potential functional areas for review. Both were deemed appropriate for streamlined reviews with a Most Efficient Organization (MEO).	Identify annual commercial activities for competitive sourcing comparison	
2	Complete negotiated competitive sourcing reviews annually.	(MET) Nine streamlined studies completed, with 8 work awards placed with NIH.	(MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.	Complete negotiated competitive sourcing reviews annually	(MET) Four functional areas identified for reviews were announced for competition.	Complete negotiated competitive sourcing reviews annually	(MET) Two functional areas that were identified for reviews were announced for competition.	Complete negotiated competitive sourcing reviews annually	Complete negotiated competitive sourcing reviews annually
3	Implement transition services for employees annually displaced due to prior year's competitive sourcing.	(MET) Career transition services provided for out-placed staff as a result of competitive assessments/studies.	(MET) Career transition services were provided to employees displaced.						
4	Evaluate transition services provided to employees.		(MET) Evaluation conducted during FY 2005.						

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$4,346	$3,827	$4,433

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY 2007 target "Identify annually commercial activities for competitive sourcing comparison" was MET. For FY 2007, the pre-planning step identified two functional areas for review - IT Systems Development and IT Administrative Support. Both reviews were deemed appropriate for streamlined reviews each with a Most Efficient Organization (MEO). A third function - IT E-mail Services - was granted a delay until FY 2009 due to a reorganization that is occurring at the HHS level.

Target 2

The FY 2007 target 'Complete negotiated competitive sourcing reviews annually' was MET. The two functional areas identified for review (IT Systems Development and IT Administrative Support) were announced for competition in FY 2007.

For FY 2007, the preliminary planning step identified two potential functional areas for review. The Department approved the delay of the E-mail Services review until FY 2009. The justification for this delay was due to a reorganization occurring within the Department involving HHS e-mail services.

In addition, in FY 2007 NIH completed and won four reviews that were announced in FY 2006. These reviews were: EEO Administrative Support, Clinical Center Administrative Support, IT Network Support, and IT End User Support/Technical Writers.

Advances or Other Highlights

In accordance with the PMA, NIH plans to carry out annual competitive sourcing reviews. The basis for the review 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 preliminary planning step in order to identify potential functional areas for review and the number of FTEs to be reviewed. Subsets of the identified functional areas are then deemed appropriate for review and then undergo a competition. The A-76 requirement is met once the reviews are conducted and the competition decision is made.

After each review is completed, NIH will develop transition plans to move to the new organizational structure and fill positions as proposed in the respective Most Efficient Organization (MEO) 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 the 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

Target Context and Conditions

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. SPD began to implement the plan in FY07 and monitored the success of the plan compared to the established baselines.

This monitoring will be continued into FY08 and FY09 as SPD continues to monitor satisfaction and usage of human resources content on the NIH Portal.

Baseline: 2007

- (FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
	(MET) Developed HR Community on the NIH Portal as primary site for	(Target 3) Establish baselines for the HR critical elements to monitor over time.	(MET) The critical elements to be monitored are: freshness of human	(Target 5) Implement corrective strategies with	(MET) Implemented a corrective strategies plan to	(Target 6) Continuously monitor satisfaction	(Target 6) Continuously monitor satisfaction and

	accessing HR information and resources (MET) Worked with CIT to evaluate products for measuring usage of HR information on HR Community Portal.	(Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information.	resources information; relevance of human resources information to the NIH audience; and usability of the HR tools. (MET) A Corrective Strategies Plan was developed to address improved usability and quality of HR information.	subject matter experts and customers.	improve usability and the quality of HR information. Consulted with Content Managers as well as Administrative Officers and HR staff to improve the HR content on the NIH Portal.	and usage of human resources content on the NIH Portal against the established baseline.	usage of human resources content on the NIH Portal against the established baseline.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$59	$71	$73

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY07 target to implement a corrective strategies plan to improve usability and the quality of HR information was MET. The Corrective Strategies Plan was developed and added to the NIH Office of Human Resources (OHR) Web/Portal Project Plan in FY06 and was implemented in FY07:

- Quarterly meetings with Content Managers from throughout the Office of Human Resources (OHR) and the Office of Strategic Management and Planning (OSMP) were held quarterly to gather feedback from these Content Manager to improve the presentation and usability of the HR information presented to NIH employees.
- Feedback from the "Community Leader" portlet on the HR Community was monitored for any technical difficulties as well as for any suggested improvements to the HR Community. All technical difficulties were resolved and suggested improvements were reviewed by the Web/Portal Team.
- The SPD Web/Portal Team demonstrated the HR Community and the Admin/Manager page to Administrative Officers (AOs) in the Office of the Director (OD) at NIH. Also, the SPD Web/Portal Team trained new OHR and OSMP staff in the usage of the HR Community. In these sessions, employees gave feedback on the HR Community and made suggestions for its improvement.
- The SPD Web/Portal Team pursued the purchase of a Web Content Management System (CMS). This is expected to be purchased in FY08 and should help improve both the quality and usability of HR information as well as help ensure the accuracy and timeliness of HR content.

Advances or Other Highlights

Highlights for implementing the Corrective Strategies Plan to improve the HR Portal in FY07 included:

- HR Professionals Community - http://hr.od.nih.gov/hrprofcommunity.htm - Released the HR Professionals Community as a resource for HCG staff – pages include: HR Professionals, Title 5 Staffing, Title 5 Compensation, Title 42 at NIH, HHS Careers

for HR, USAJOBS, Senior Executive Service (SES), SCoP Project – Collaboration, Calendar, Alphabetical HR Search Index, and OHR Community Map.
    - Released the new SES page on the HR Professionals Community and the HR Community - http://hr.od.nih.gov/seniorexecutiveservice.htm
    - Uploaded documents and information on the new Classification procedures for GS-14/15 Admin positions to the NIH Portal. Added links to the HR Professionals Community & the Admin/Managers page on the HR Community.
- HR Community - http://hr.od.nih.gov/hrcommunity.htm - Continuously improved/updated the HR Community as a resource for all NIH Staff – pages include: NIH Employees, Admin/Managers, New NIH Employees, Title 5 Compensation, Title 42 at NIH, Senior Executive Service (SES), Clinical Center, Career Development and Training, HR Calendar, Alphabetical HR Search Index.
    - Projects (Collaboration Space) - Set up a new project on the NIH Portal for the new CSD initiative, the Austin Project.
    - Portlets - Created new portlets for the HR Community: EHRP/Capital HR, CRS Retirement, FERS Retirement, HHS Careers, New Training and Career Development Opportunities, Series in HHS Careers, Staffing Information for Managers, and QuickClassification portlets.
    - Pages - Added new pages to the HR Community.
        - Created a Career Development and Training page to highlight career development and training opportunities for NIH staff - http://hr.od.nih.gov/career.htm
        - Created a Clinical Center page on the Human Resources Community to direct clinical center employees to HR content - http://hr.od.nih.gov/clinicalcenter.htm
        - Released the new SES page on the HR Professionals Community and the HR Community - http://hr.od.nih.gov/seniorexecutiveservice.htm
    - Admin/Manager Page - http://hr.od.nih.gov/admincommunity.htm - Enhanced the Admin/Manager Page on the HR Community to be a resource for the Administrative/Managerial community at NIH.
        - Released new portlets on the Admin/Manager page of the HR Community. The portlets are: HHS Careers, Series in HHS Careers, and Staffing Info for Managers, QuickClassification.
        - Released WiTS Reports for all ICs on the Admin/Manager page. Available only to Executive Officers (EOs) and their designees.
- ITAS Community – took over the maintenance of the ITAS Community on the NIH Portal.
- User Guides - Created two Quick Reference Guides (QRGs) for the HR Portal.
- HR Navigator Portlet - Reviewed/revised the HR Navigator portlet on the HR Portal. Added new topics and clarified/updated existing HR topics.

SMHC-6	**Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing)**

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a priority. With the ultimate goal of having a leadership cadre that can execute the agency's mission, NIH leaders and managers will collaborate to assess leadership needs and programs and develop strategies for the development and improvement of leadership competencies. As federal employees become eligible for retirement within the next few years, leadership development will be important to retaining knowledge and having available leadership talent ready to fill critical NIH leadership roles. Leadership development demands a level of strategic planning to predict and meet the needs of the NIH for a trained workforce.

Rationale

NIH values employees as a necessary organizational asset, and strives to provide them with the tools they need to succeed. NIH aims to identify and develop potential successors for mission critical and key leadership roles, which are important to science and research. As a result of a recent NIH-wide Human Capital Planning Initiative, NIH identified the creation and implementation of a leadership development program as key issues to focus on. This will ensure that the NIH has the right resources to continue to fulfill its mission, and is able to sustain operations as leadership talent retire or depart the NIH for other opportunities, or is no longer able to perform responsibilities. Appropriate leadership development is essential to the NIH to meet the continued challenges of workforce management.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH plans to develop a framework to link training and leadership development to NIH mission, goals and objectives. The framework will help NIH manage leadership continuity in key positions, retain and develop intellectual and knowledge capital for the future, and encourage individual advancement. An assessment to facilitate the design, development and implementation of the framework is a first step. NIH will apply the results of the assessment, to identify the critical areas where leadership development is needed. NIH will update training policies and develop training and development plans to support the programs, mission, goals and objectives.

An ongoing process to determine the leadership competencies will be established as an initial step towards NIH leadership competency development. To carry out the process, NIH will interview leaders and form oversight committees and outreach strategies. NIH will apply the results of the assessment to identify core competencies that are applicable across NIH, as well as specific competencies for the separate communities. This process is important to determining NIH's leadership competency demands.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Examine key area to enhance leadership skills								Leadership development methods to identify NIH leadership competencies
2	Implement recommendation from prior year assessments								N/A
3	Assess results of implementation								N/A

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$574

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SMHC-7	**Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing)**

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a priority. NIH will work to develop and implement recruitment strategies to attract and hire talent consistent with the agency's mission priorities and diversity goals. By identifying early signs of potential recruitment challenges and talent availability, NIH hopes to address anticipated future staffing needs.

Rationale

NIH is committed to creating and sustaining a trained and motivated workforce to carry out its mission. NIH has taken steps to improve human capital management through appropriate staff recruitment. Improving recruitment and staffing has been identified as a key strategy for addressing human capital challenges. This activity is essential to the NIH and will be ongoing. Both the short-term and long-term recruitment goals will make provisions for recruitment of mission critical and key occupations within the NIH. The recruitment framework will support a flexible program to be implemented based on the NIH mission, structure and culture.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH plans to conduct an agency-wide assessment that addresses recruitment issues in order to project short and long-term staffing needs. In order to succeed, NIH must recruit diverse talent in the scientific research and medical and administrative occupations. Upon the assessment, NIH will identify the critical areas where no successor is identified in order to implement a deliberate and systematic effort to ensure continuity in key positions at all levels. Subsequently, NIH will identify areas with potential recruitment challenges, and then propose a strategic plan to meet the needs of the NIH for a trained and capable workforce.

As a first step, NIH will review and re-engineer the hiring process in order to enhance efficiency and effectiveness, and most importantly, to provide greater support for the scientific mission. NIH will examine hiring processes that are currently in use to form a starting point. Recommendations will include the OPM 45-day benchmark to aim for improved hiring practices. Specifically, the reviews of the existing processes will be conducted for hiring of Title 5, 42(f) and 42(g) positions. Improvements will be measured incrementally as NIH's hiring improvements work towards the 45-day goal. Data will also be collected from outside agencies to serve as benchmarks for NIH.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Examine key area to enhance recruitment								Hiring processes for key NIH positions
2	Implement recommendation from prior year assessments								N/A
3	Assess results of implementation								N/A

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$600

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

SMHC-8	**Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing)**

BACKGROUND

As the steward of medical and behavioral research for the Nation, one of NIH's keys to success lies in its people. For that reason, NIH strives to make management improvements in human capital a top priority. With the ultimate goal of retaining a talented and diverse workforce, NIH continues to review methods and policies to improve NIH as an employer of choice in this competitive and dynamic marketplace.

Rationale

NIH understands that building a premier biomedical research organization does not end with recruitment of key talent. Integrating new employees into the NIH's professional and social culture is also critical to the short and long-term success of employees and, ultimately to accomplishing the mission of the NIH. Retaining the appropriate employee for the right job is vital in warding off loss of an experienced, trained, capable employee. Talent retention is also driven by an NIH strategic approach that assesses the likely turnover in key positions to minimize the impact of turnover. It will also give early warning of any skills shortages or likely difficulties in finding suitable replacement candidates for key positions in the near and short terms. NIH understands that a strategic retention plan must include meaningful work assignments, the opportunity to utilize skills and knowledge, opportunities for increased responsibility, work that truly makes a difference, recognition for performance, and a people-oriented work culture; all factors that keep employees engaged and committed. The NIH also plans on considering future workforce needs by assessing the gaps and identifying available talent ready to fill where needed.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NIH is working to develop means of helping managers address employee retention through management and employee partnership relationships and loyalty strategies in order to retain their talent. NIH plans on reviewing methods and policies to improve NIH as an employer of choice. These methods will be ongoing to ensure mission accomplishment, and ensure the development of intellectual capital for the future.

Retention was identified as an area in the OPM Federal Human Capital Survey that needs to be addressed as a variant by NIH. This area is currently under review and will be identified by mid 2008.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Examine key area to enhance retention								TBD in FY08
2	Implement recommendation from prior year								N/A

	assessments								
3	Assess results of implementation								N/A

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$104

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Performance Results for the FY09 GPRA Performance Target will be reported in February, 2010.

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 remains committed to efficient and effective management and oversight of its real property capital projects to support achieving bio-medical research program outcomes. An Earned Value Analysis and Management System (EVAMS) using a project data analysis framework that links cost and schedule estimates to actual results has been developed to 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 to formulate corrective action plans and improve performance. EVM helps flag and develop strategies to mitigate the risk of cost and schedule overruns providing a means to forecast final cost and schedule outcomes. The EVAMS provide NIH Project Managers with an industry recognized management system, sufficient tools and metrics 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 manage and track performance of capital, high-risk or other projects categories designated for specific management oversight.

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 the capital planning, programming, budgeting and execution process.

PERFORMANCE ANALYSIS

Target Context and Conditions

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, 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. NIH then integrated existing project management data from Lab 33, and the Northwest Parking Garage, into a 'proof-of-concept' version of the NIH EVAMS. NIH continued 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.

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 FY05.

NIH continued review of its project management systems, and benchmarked its system with public and private sector organizations.

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 continued data analysis and collection to enhance the EVMS. The services of a consultant, recognized as an EVAMS implementation specialist, were obtained to review, analyze and further validate the proof of concept version. Data verification continued into FY06 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 2006.

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) scheduled for completion in FY07 for use in future year analyses.

Baseline: 2007

- FY04-06 results

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts.	(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.	(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).	(MET) NIH fully implemented Earned Value for eligible projects.		

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$1	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY2007 target was MET. The NIH goal to 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) has been ACHIEVED. Upon completion of this goal, Program and Project Managers began use of the EVAMS to report, analyze, and validate project performance with research and supporting programs goals and objectives.

By the end of FY2007, EVAMS was used to manage the twenty-four (24) Buildings and Facilities (B&F) Program projects in NIHs portfolio. Of this total, one (1) project, or less than 5% of the program had a performance variance greater than ten-percent (10%) partly attributable to EVAMS. This tool proved to be effective in highlighting design and construction performance variances which facilitated development of strategies to mitigate potential execution risks. NIH will continue use and EVMS and enhance its processes to further ensure efficient and effective delivery of capital assets.

Advances or Other Highlights

NIH reviews the status of the projects in its facilities portfolio during brief's to the ORF Director as a means of evaluating performance and the benefits of the Earned Value Management System. These efforts will continue and lessons-learned reflected in business practice revisions.

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

Target Context and Conditions

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 the organization's ability to apply PBC methods to 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 (DCIS). For non-performance based contracts, the NIH uses the DCIS to collect contract related data and monitor performance. NIH institutes and centers 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.

Baseline: 2007

- (FY06) Obligate 42% % of eligible service contracting dollars through performance based contracting

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.	(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.	(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.	(NOT MET) The FY07 target to obligate OMB/OFPP goal of 42% of eligible service contracting dollars to PBC was not achieved. 38% of the eligible service contracting was obligated.	Obligate the FY 2008 OMB/OFPP goal of eligible service contracting dollars to PBC.	Obligate the FY2009 OMB/OFPP goal of eligible service contracting dollars to PBC

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$727	$712	$696

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY2007 target to obligate OMB/OFPP goal of 42% eligible service contracting dollars through performance-based contracting was NOT MET. In FY2007, the NIH awarded 38% of eligible dollars employing the principle of PBC. The Head of the Contracting Activity has designed a comprehensive strategy to increase awareness, understanding, and more importantly to encourage optimum utilization of PBC. This strategy focuses on areas (e.g., training/facilitator and communication) that are considered vital to meeting the HHS goals in the NIH. Specifically, the Office of Acquisition Management and Policy (OAMP) will work closely with HHS to find new and viable sources of training geared towards NIH requirements. Also, the Division of Acquisition Policy and Evaluation (DAPE) will continue to work towards increasing awareness of PBC by encouraging Project Officers and Contract Officers to attend conferences and meetings. In addition, the DAPE will continue to communicate to the acquisition community the importance of meeting the established PBC goals. Lastly, the strategy focuses on mitigating the inconsistencies associated with the PBA data reported through the Department Contracts Information System (DCIS). In order to prevent the recent inconsistencies with the PBC data, the Head of the Contracting Activity will establish a freeze date on or about the same time each year.

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

Target Context and Conditions

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.

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 was 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.

Baseline: 2007

- Target 1: Prior to FY 04 all research grants has only one Principal Investigator.
- Target 2: Prior to FY04 Paper grant applications currently received.

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Recognize Multiple Principal Investigators on Research Grants (FY2008 accomplished)		(MET) Addressed signature and regulatory issues, and develop plans for application forms and data systems associated with multiple PIs.	Complete Modifications of forms and data systems to accommodate multiple PIs.	(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	Accept applications that include information on more than one PI.	(MET) NIH issued a new policy allowing the use of multiple investigators for most types of research grants. Over 1,500 multiple	Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	

					electronic applications involving multiple PIs were received and processed by NIH.		principal investigator applications have been accepted since the policy has been in effect.		
2	Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished)		(MET) A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use.	Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements.	(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.	Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements.	(MET) An expanded pilot of 424-R&R dataset conducted using live data yielded the receipt of 37,000 applications electronically.	Refine Electronic Submission of Research Grant Applications to maximize efficiency of the process for applicants.	
3	Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished).		(MET) NIH developed and launched the NIHMS system was May 2, 2005.	Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	(MET) Receiving third party manuscript uploads met 12/05; Linking submissions met 2/06.				
4	Better balance workload associated with incoming grant applications while providing additional time for newer researchers to prepare grant applications (FY 2008 accomplished)							Implement changes to standing application receipt dates	
5	Transition to electronic post award processes by requiring e-mail notice of grant awards and mandating use of electronic closeout modules.								Transition to electronic post award processes by requiring e-mail notice of grant awards and mandating use of electronic closeout modules.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$3,500	$1,125	$900

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1
The FY07 target to accept applications that include information on more than one PI was MET efficiently. NIH expanded its pilot to recognize multiple principal investigators for the support of team science for most types of research grants for the February, 2007 receipt dates and beyond. Over 1,500 applications that include multiple principal investigators have been received this year.

Target 2
The FY07 target to Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements was MET efficiently. In February of 2007 NIH transitioned its primary type of research grant, the R01, to electronic submission through Grants.gov. Over 37,000 applications have been received electronically since October of 2006, and ~80% of all grant applications are now received electronically through the Federal portal.

Efficiency
Both FY2007 target objectives were achieved efficiently prior to planned timeframe.

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, guidelines 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 monitor the capital maintenance and repair program. The FCI is one of the required measures under the President's Management Agenda for Real Property Asset Management and is included under the "One Department, One Direction, One HHS" objectives of the Department of Health and Human Services.

PERFORMANCE ANALYSIS

Target Context and Conditions

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 and completed 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.

Baseline: 2007

- Target 1: (FY06) CIwa = 85
- Target 2: (FY06) 88.5%

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Maintain the condition of the portfolio so the average CIwa =85*	(MET) The condition of the portfolio was maintained so that the average CI was 85.	(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.	CIwa =85	(MET) The condition of the portfolio was maintained so that at least the average CI was 85.	CIwa =85	(NOT MET) The condition of the portfolio reached CIwa of 72 in FY07.	CIwa =85	CIwa =85
2	By 2010, no less than 95% of occupied GSF will have a CI greater than 65	(MET) 86% of occupied GSF had a CI greater than 65.	(MET) 87% of the occupied space had a CI greater than 65.	88.5%	(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.	90.0%	(NOT MET) The FY07 target of 90% of occupied GSF was not achieved Only 67.5% of the occupied space reached a CI > 65.	91.5%	93.0%

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$81,081	$118,966	$125,581

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY07 target to maintain the condition of the portfolio so the average CIwa =85 was NOT MET. NIH achieved an average CIwa of 72 in FY2007. This reduction resulted from NIH's efforts to further integrate the goals and objectives of OMB's PART of NIHs Building and Facilities program into the daily management practices. In this case, NIH had begun to incorporate Condition Index data into an increasingly structured approach for prioritizing projects for funding by the Repair and Improvement Program. NIH managers, when reviewing the projects proposed for building 10, and comparing its CI to other buildings, realized that the CI listed in the facilities database for building 10 was unrealistically high. NIH realized that the results and conclusions of several large scale engineering studies of Building 10 undertaken by NIH in recent years had not been incorporated into value of the deficiencies captured by the assessment and documented in the database. In broad-brush, the studies conclude that most building 10 systems other than the structure, having long outlived the projected lifespan, need replacement. This helps to understand the reduction of building 10's CI to 20. As a result of this and other observations, NIH is working to further integrate the participation and review by in-house subject matter experts (maintenance staff, facility

managers, and engineers and architects knowledgeable about our facilities) into the Facility Condition Assessment and documentation process.

Target 2

The FY2007 target to ensure that not less than 90% of occupied gross square feet (GSF) will have a Condition Index (CI) greater than 65 was NOT MET. In FY2007, 67.5% of NIH facilities reached a CI > 65. This reduction resulted from management improvement initiatives. This re-evaluation resulted in changes to Building 10's condition index of NIH facilities.

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. In FY2007, NIH targeted the business practices used to manage the Repair and Improvement (R&I) portion of the Buildings and Facilities program to achieve the goals and objectives of the OMB PART evaluation. This focused on use of the facility condition index as a budget decision tool and stressed the importance of using NIH subject Matter Experts in the process. The re-assessment resulted in a condition index of Building 10 to be 20, not the original 86. The CI = 20 aligned with the budget being invested in Building 10 to make improvements.

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 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
- Use of Earned Value Management to assess risk and variance and to help ensure completion of projects on schedule and within budget.

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

Target Context and Conditions

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.

Baseline: 2007

- Target 1: (FY06) 20 active projects
- Target 2: (FY06) ≤ 2

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
1	Manage all B&F line item projects so they are completed within 100% of the final approved total project cost.	(MET) All 19 projects were managed within the approved budget.	(MET) All twenty-one (21) projects were managed within the approved budget.	20 active projects	(MET) All twenty (20) active projects were managed within the approved budget.	24 active projects	(EXT) 23 of the 24 Active Projects were managed within budget tolerances. One project scope and budget was expanded to 2008 using the Facility Project Approval Authorization form approved by HHS.	TBD active projects	TBD active projects
2	No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope.	(MET) No projects required scope adjustments.	(MET) All projects were managed within the approved scope.	20 active projects / 10% ≤ 2	(MET) All twenty (20) of the active projects were managed within the approved scope.	24 active projects / 10% ≤ 2	(MET) Twenty three (23) of the active projects were managed within the approved scope. 1 or 4% of the 24 active projects experienced a 10% scope variance due to operational requirement changes approved by HHS.	TBD	TBD

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$1,048	$1,035	$606

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

Of the 24 B&F line items scheduled to be completed within 100% of the final approved total project cost in 2007, 23 Fully Met this objective and 1 was not met but will be met in 2008. Twenty-three (23) out of the twenty-four (24) active projects in the FY2007 portfolio were managed within budget tolerances. For the 24th project, the scope was expanded to include additional restoration construction on NIH Bethesda campus parking garage MLP-6. The request for the additional scope was submitted to HHS via the Facility Project Approval Agreement (FPAA) in April 2007 and was approved for completion August 2008. The completion of the 23 project items was made possible in part by the Earned Value Analysis and Management System (EVAMS) tool used to track and monitor project performance.

Projects managed by NIH were on the Bethesda, North Carolina, Hamilton, Montana, and Frederick, Maryland campuses.

Target 2

The FY2007 target to manage the facilities portfolio so that no more than 10% of the projects incorporate a plus or minus 10% adjustment of the approved scope was MET. One (1) of the twenty-four (24) projects in NIHs facilities portfolio experienced a scope variance of 10% or greater. This scope adjustment was required to support operational requirements and to enhance the safety and reliability of an NIH facility. This is a four–percent (4%) program variance. Project variances were reviewed and approved by DHHS. This is documented by the HHS Facility Project Approval Authorization (FPAA) form. Projects in NIHs portfolio were on the Bethesda, North Carolina, Hamilton, Montana, and Frederick, Maryland campuses.

Advances or Other Highlights

Use of the Office of Research Facilities (ORF) Earned Value Management System (EVMS) was expanded to include all projects in the portfolio eligible for evaluations. This was a function of project cost, complexity and the estimated duration.

The EVMS continues to be a valuable management tool to help ensure on time, within scope and budget delivery of NIH capital assets.

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

Target Context and Conditions

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.

Baseline: 2007

- Target 1: (FY06) 50 grantees
- Target 2: (FY06) 123 prjs

#	Key Outputs	FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
				Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
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.		(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.	50 grantees	(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.	35 expected grantees	(NOT MET) 54% 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.	21 expected grantees	0 expected grantees
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.		(MET) 100% of projects monitored the use of grant-supported space or are implementing corrective strategies.	95% of 123 projects are in compliance	(MET) 97% of the extramural construction projects were in compliance with the post award 20 year usage requirement.	95% of 143 projects are in compliance	(MET) 98% of the extramural construction projects were in compliance with the post award 20 year usage requirement.	95% of 164 projects are in compliance	95% of 179 projects are in compliance

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

Target 1

The FY07 target was not met. During FY 2007, 100% of the grantees took the necessary actions to provide the construction designs documents, however, only 54% 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.

Target 2

The FY07 target was MET. During FY 2007, 98% 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 indicated 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

Target Context and Conditions

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.

Baseline: 2007

- BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments.

FY 2004 Actual	FY 2005 Actual	FY 2006		FY 2007		FY 2008	FY 2009
		Target/ Estimate	Actual	Target/ Estimate	Actual	Target/ Estimate	Target/ Estimate
(MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.	(MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	(MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	(MET) 25% of Principal Investigators reviewed resulting in 25% of resources recommended to be reallocated.	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources	Conduct BSC reviews of 25% of Principal Investigators to assess quality of science in order to prioritize resources.

GOAL FUNDING (dollars in thousands)	FY07	FY08	FY09
	$0	$0	$0

SUMMARY OF 2007 PERFORMANCE RESULTS

Target

The FY 2007 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.

Advances or Other Highlights

The annual meeting of the chairs of the Boards of Scientific Counselors met on June 11, 2007 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 2006 was $3,186,000; this amount was reallocated within the Intramural Research Programs in FY 2006. Annual cost savings for FY 2007 will be available in 2008.

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.

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.

PROGRAM ASSESSMENT RATING TOOL (PART) IMPROVEMENT PLANS TABLE

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
CY 04	Extramural Research	Effective	• Starting at least one pilot clinical trial on promising interventions based on results of previous trials and new leads for drug discovery. • Completing treatment and follow-up of participants in the ACCORD trial to determine effects of glycemia, blood pressure, and blood lipid treatment approaches to prevent CVD in diabetes. • Completing goal of expanding the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medicines. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.
CY 05	Intramural Research	Effective	• Beginning biologic assessment of the most likely diabetes/obesity susceptibility genes in regions of linkage/association. • Formulating a biocompatible cell encapsulation agent designed to protect and track mesenchymal stem cells for administration to patients to promote cell survival and engraftment. • Reallocating laboratory resources based on extramural reviews of 25% of principal investigators each year by Boards of Scientific Counselors.
CY 05	Buildings & Facilities	Effective	• Maintaining the condition of the existing infrastructure so that the average CI is 85. • Managing all buildings and facilities projects so that they are completed within 100% of the final approved total project cost.
CY 06	Extramural Research Training and Research Career Development	Effective	• Ensuring 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 at 12% relative to appropriate comparison groups. • Ensuring 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 at 12% relative to appropriate comparison groups. • Converting 25% of trainee appointment forms to be processed electronically.
CY 03	HIV/AIDS Research	Moderately Effective	• Beginning to analyze final data from a phase III trial of a second generation vaccine. • 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.
CY 06	Extramural Construction	Moderately Effective	• Ensuring that 100% of grantees meet all construction requirements and reporting that 95% of 179 extramural construction projects are in compliance with the post award 20 year usage requirement to conduct research. • Completing 22 construction or renovation of biomedical research infrastructures and completing 8 biocontainment facilities. • Achieving average annual cost of managing construction grants of $36,530 per grant.

DISCUSSION OF NIH STRATEGIC GOALS

As mentioned previously, NIH performance goals are representative and serve as proxies for performance on the larger, research portfolio. The goals are representative, not comprehensive, and taken together represent the breadth of NIH's portfolio including basic, prevention, diagnostic, and treatment research. Because NIH takes a representative approach, the goals included in the GPRA plan are not meant to cover all programs, projects, or aspects of NIH performance. The performance goals selected for inclusion in the GPRA plan are all key measures and serve as NIH strategic goals.

In addition to supporting the Agency mission and Core Strategic Vision, the NIH budget request supports the HHS Strategic Plan (http://www.hhs.gov/strategic_plan/), the President's Management Agenda (http://www.whitehouse.gov/omb/budintegration/pma_index.html), HHS 20 Department-Wide Objectives, the Secretary's 500-Day Plan (http://www.hhs.gov/500DayPlan/), and Healthy People 2010 (http://www.healthypeople.gov/). In particular, NIH substantially contributes to HHS Strategic Goal 4: Advance scientific and biomedical research and development related to health and human services.

CROSSWALK TO HHS STRATEGIC GOALS AND OBJECTIVES

All NIH activity supports the HHS Strategic Plan. In particular, all NIH GPRA goals support HHS Strategic Goal 4: Advance scientific and biomedical research and development related to health and human services. The table below presents the NIH GPRA Goals support of HHS Strategic Goal 4.

NIH GPRA Goals	HHS Strategic Goal 4 and Objectives			
	Strategic Objective 4.1: Strengthen the pool of qualified health and behavioral science researchers.	Strategic Objective 4.2: Increase basic scientific knowledge to improve human health and human development.	Strategic Objective 4.3: Conduct and oversee applied research to improve health and well-being.	Strategic Objective 4.4: Communicate and transfer research results into clinical, public health and human service practice.
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 corticotrophin-releasing hormone antagonist antalarmin.			✓	
SRO-1.3: By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement.			✓	
SRO-1.4: By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders.		✓	✓	
SRO-2.1: By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.			✓	
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.			✓	
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.		✓	✓	
SRO-2.5: By 2011, conduct early phase trials for 5 novel molecular-targeted interventions for early diagnosis, detection, and therapy for multiple cancers.		✓		
SRO-2.6: By 2011, develop one field deployable sensor device for use in human studies and develop one biomarker to characterize the impact of environmental exposures on biological pathways.		✓		
SRO-2.7: By 2011, complete clinical testing of one candidate medical countermeasure that could be used to diagnose or treat victims of a chemical terrorist attack or accident, and complete preclinical testing for two others.			✓	
SRO-2.8: By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.		✓		
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).			✓	
SRO-3.2: By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		✓		
SRO-3.3: By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.		✓	✓	
SRO-3.4: By 2010, develop an HIV/AIDS vaccine.		✓	✓	
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.		✓		
SRO-3.6: By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.		✓		
SRO-3.7: By 2013, develop one or more improved therapies for at least one immune-mediated disease.		✓	✓	
SRO-3.8: By 2016, determine the optimal tailored treatment regimen for patients with early stage breast cancer that maximizes the benefits of chemotherapy while minimizing the side-effects of unnecessary treatment.			✓	
SRO-4.3: By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults.			✓	
SRO-4.4: By 2011, identify or study additional genes involved in communication disorders in humans and animal models.		✓		
SRO-4.5: By 2011, identify genetic and environmental factors which predispose to three complex diseases.		✓		
SRO-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.			✓	
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).			✓	
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.		✓		
SRO-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.		✓		

NIH GPRA Goals	HHS Strategic Goal 4 and Objectives			
	Strategic Objective 4.1: Strengthen the pool of qualified health and behavioral science researchers.	Strategic Objective 4.2: Increase basic scientific knowledge to improve human health and human development.	Strategic Objective 4.3: Conduct and oversee applied research to improve health and well-being.	Strategic Objective 4.4: Communicate and transfer research results into clinical, public health and human service practice.
SRO-5.5: By 2008, develop and test new evidence-based treatment approaches for drug abuse in community settings.			✓	
SRO-5.6: By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.		✓		
SRO-5.7: By 2010, validate and compare 4 imaging methods of assessing lung cancer response to therapy.		✓		
SRO-5.8: By 2012, improve device(s) to measure hot flashes and test device(s) in clinical trials.		✓	✓	
SRO-5.9: By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.		✓	✓	
SRO-5.10: By 2011, conduct studies of girls aged 6 through 8 years to determine the associations between the age of onset of puberty and progression through puberty with 12 environmental exposures.			✓	
SRO-5.11: By 2012, develop and test at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes.		✓	✓	
SRO-5.12: By 2013, identify several potential targets and/or molecules that modulate or enhance the extinction of learned behaviors and conditioned associations supporting addiction, compulsion, or anxiety disorders.		✓		
SRO-6.1: By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.		✓		
SRO-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.			✓	
SRO-6.3: By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.		✓		
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.		✓		
SRO-6.5: By 2014, develop and evaluate two new interventions for the prevention and/or treatment of HIV disease utilizing the newly restructured HIV/AIDS clinical trials networks.			✓	
SRO-6.6: By 2015, provide at least one new or significantly improved minimally-invasive treatment for patients using image-guided interventions.		✓		
SRO-7.4: By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis.		✓		
SRO-7.5: By 2009, determine the feasibility of applying at least 2 tailored interventions designed to prevent dental caries in one or more underserved populations.			✓	
SRO-7.7: By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care.			✓	
SRO-8.1: By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.		✓		
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.		✓		
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.		✓		
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.		✓	✓	
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).			✓	
SRO-8.7: By 2012, identify 3 effective implementation strategies that enhance the uptake of research-tested interventions in service systems such as primary care, specialty care and community practice.			✓	
SRO-8.8: By 2012, identify at least one candidate intervention that extends median lifespan in an animal model.		✓		
SRO-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).		✓	✓	
SRO-9.2: By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.			✓	
SRO-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.		✓	✓	
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.		✓		
SRO-9.5: By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.			✓	
Communication and Transfer of Results (CTR)				
CTR-1: By 2014, 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).				✓

NIH GPRA Goals	HHS Strategic Goal 4 and Objectives			
	Strategic Objective 4.1: Strengthen the pool of qualified health and behavioral science researchers.	Strategic Objective 4.2: Increase basic scientific knowledge to improve human health and human development.	Strategic Objective 4.3: Conduct and oversee applied research to improve health and well-being.	Strategic Objective 4.4: Communicate and transfer research results into clinical, public health and human service practice.
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.				✓
CTR-5: By 2007, improve marketing and management of NIH intellectual property (IP) assets by building data mining capability.				✓
CTR-6: By 2010, improve the efficiency and reduce the unit cost of producing authoritative serials cataloging records used to improve access to the biomedical literature in libraries worldwide.				✓
CTR-7: By 2010, establish the feasibility of sharing information from already-conducted scientific studies of warfarin (coumadinR) anti-coagulation, through the knowledge base PharmGKB.				✓
CTR-8: By 2012, increase communication efforts and enhance outreach strategies regarding extramural research funding policy, compliance and administration as demonstrated by the type and frequency of communications and related activities.				✓
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.	✓			
CBRR-2: Promote data sharing and provide information in real time by implementing the NIH Business System.				
CBRR-3: By 2007, streamline business processes and automate data movement by implementing the Clinical Research Information System (CRIS).				
CBRR-4: By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic research administration (eRA).				
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.				
CBRR-7: By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.				
CBRR-8: By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.				
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.				
CBRR-10: By 2012, make freely available to researchers the results of 300 high-throughput biological assays screened against a library of 300,000 unique compounds, and the detailed information on the molecular probes that are developed through that screening process.				✓
Strategic Management of Human Capital (SMHC)				
SMHC-3: By 2008, 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.				
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.				
SMHC-5: Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal.				
SMHC-6: Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing)				
SMHC-7: Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing)				
SHMC-8: Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing)				
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).				
POI-2: Expand the use of Performance-Based Contracting (PBC).				
POI-5: By 2010, enhance NIH's ability to demonstrate benefits for extramural research investments through changes to policy and information systems.				
POI-6: Provide responsible stewardship over existing federally owned real property assets.				
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.				
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				
POI-9: By 2012, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors				

FULL COST TABLE

Summary of Full Cost

NATIONAL INSTITUTES OF HEALTH

(Dollars in Millions)

Performance Program Area	FY 2007	FY 2008	FY 2009
NIH Budget Authority	$29,128	$29,457	$29,457
Strategic Goal 4: Scientific Research and Development*	29,128	29,457	29,457
4.1 Strengthen the Pool of qualified researchers	*(1,360)*	*(1,384)*	*(1,385)*
4.2 Increase basic scientific knowledge	*(15,440)*	*(15,639)*	*(15,628)*
4.3 Conduct and oversee applied research	*(12,323)*	*(12,428)*	*(12,439)*
4.4 Communicate and Transfer results	*(5)*	*(6)*	*(5)*
Full Cost Total	$29,128	$29,457	$29,457

* NIH achieves its mission through a single program--Research. Full cost data for the Department's sub-goals are shown as non-adds.

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.

LIST OF PROGRAM EVALUATIONS

The following program evaluations were completed during FY 2007. Further details on the findings and recommendations of the program evaluations completed during the fiscal year can be found in the ASPE Program Evaluation Database or on NIH's website (http://opasi.nih.gov/desa/eb/).

- Computing Frontiers: Prospects from Biology
- Extramural Associates Research Development Award (EARDA) Program Evaluation
- Investigating methodologies for assessing research excellence in the social and behavioral sciences
- Trans-NIH Evaluation of Customer Satisfaction with Selected Institute/Center Web Sites Using the American Customer Satisfaction Index (ACSI) Methodology
- Evaluation of Surveillance, Epidemiology, and End Results (SEER) Cancer Registry Operations
- Evaluation of the Research Training and Career Development Award Programs at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- Financial Conflicts of Interest and Human Subject Projection
- An Assessment of User Satisfaction with the NHGRI/ORD Genetic and Rare Diseases Information Center (GARD)
- Evaluation of Exhibit Program; Evaluation of New Web Resources
- Evaluation of the Research Training and Career Development Award Programs at the NIAMS
- Proposal to Perform a Phase II Outcome Evaluation of the Fogarty International Research Collaborative Award (FIRCA) program
- Evaluation of NIGMS Minority Opportunities in Research (MORE) Division
- Cancer Imaging Program: Small Animal Imaging Resource Program (SAIRP) Evaluation
- Outcome Evaluation of NCI's Activities to Promote Research Collaboration (APRC) Program
- Cross Trials Safety Analysis (Evaluation of the process for collection, classification, and analysis of safety data across NIH-sponsored clinical trials)
- Good Clinical Practice Computer Based Training Feasibility Study
- Division of AIDS-Wide Clinical Research Policy and Procedure Implementation Feasibility Study
- Evaluation of NIA Centers on the Demography and Economics of Aging
- Evaluation of the Edward R. Roybal Centers for Translational Research in the Social and Behavioral Sciences
- Innovative Molecular Analysis Technologies (IMAT) program
- Cancer Disparities Research Partnership (CDRP) Program Process and Outcome Evaluation
- Evaluation Support Contract for OER Reporting Activities
- Evaluation of the FY06 NIH Bench-to-Bedside Pilot Program
- Feasibility Study of the CIP/NCI P50 In vivo Cellular and Molecular Imaging Centers (ICMIC) Program

DATA VALIDATIONS TABLES

GOAL	FY 2007 DATA SOURCE AND VALIDATION
Scientific Research Outcomes (SRO)	
SRO-1.1	It is anticipated that results from this research will be published in 2008. For source validation information on the 2007 achievements, please contact: Patricia Powell, Ph.D 5635 Fishers Lane Rockville, MD 20892 301-443-5106 ppowell@mail.nih.gov
SRO-2.1	More information on the seven trials can be found at http://www.clinicaltrials.gov/ using the identifiers listed below: • "Peritransplant Deoxyspergualin in Islet Transplantation in Type 1 Diabetes." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00434850 • "LEA29Y (Belatacept) Emory Edmonton Protocol (LEEP)." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00468403 • "Islet Transplantation in Type 1 Diabetes." Phase III clinical trial. ClinicalTrials.gov Identifier: NCT00434811 • "B-Lymphocyte Immunotherapy in Islet Transplantation." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00468442 • "Efficacy of Islet After Kidney Transplantation." Phase III clinical trial. ClinicalTrials.gov Identifier: NCT00468117 • "Strategies To Improve Islet Survival." Phase II clinical trial. ClinicalTrials.gov Identifier: NCT00464555 The seventh clinical trial, entitled "Open Randomized Multicenter Study to Evaluate Safety and Efficacy of Low-Molecular Weight Sulfated Dextran in Islet Transplantation," is in the process of being submitted to ClinicalTrials.gov.
SRO-2.2	R01 HD050981: Computer Retrieval of Information Scientific Projects (http://crisp.cit.nih.gov/) R01 HD050966: Improving Primary Care to Prevent Childhood Obesity (http://clinicaltrials.gov/ct/show/NCT00377767;jsessionid=16EC5D8B4CE4A836031270F74AA19AD4?order=8) R01 HD050931: Primary Care Treatment for Overweight Adolescent Females (SHINE) (http://clinicaltrials.gov/show/NCT00451685) R01 HD050895: Team Positive Lifestyles for Active Youngsters (Team PLAY) (http://clinicaltrials.gov/ct/show/NCT00528164;jsessionid=B80018032AA9435C7CE03746A2377CAD?order=18)
SRO-2.4	http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/19510 Fall-Dickson, J.M., Ramsay, E.S., Imanguli, M., Guadagnini, J., Odom, J., Atlam, N., Pavletic, S. Oral chronic graft-versus-host disease symptom experience and cytokine correlates in survivors after transplantation for hematologic malignancies. (2007). Journal of Clinical Oncology (Supplement), 25 (Part I), (18S): 19510. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16503494&ordinalpos= 1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum Pavletic, Z.S., Martin, P., Lee, S.J., Mitchell, S., Jacobsohn, D., Cowan, E.W., Turner, M.L., Akpek, G., Gilman, A., McDonald, G., Schubert, M., Berger, A., Bross., P., Chien, J.W., Couriel, D., Dunn, J.P., Fall-Dickson, J.M., Farrell A., Flowers M.E., Greinix H., Hirschfeld S., Gerber L., Kim S., Knobler R., Lachenbruch P.A., Miller F.W., Mittleman B., Papadopoulos E., Parsons S.K., Przepiorka D., Robinson M., Ward M., Reeve B., Rider L.G., Shulman H., Schultz K.R., Weisdorf D., Vogelsang G.B.; Response Criteria Working Group. (2006). Measuring Therapeutic Response in cGVHD, NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. Response Criteria Working Group Report. Biology of Blood and Marrow Transplantation, 12 (3): 252-266. http://www.ampainsoc.org/db2/abstract/view?poster_id=3135#711 Fall-Dickson, J.M., Ramsay, E., Sportes, C., Castro, K., Woltz, P. (2007). Oral Pain Experience and TNFα Salivary and Plasma Expression in Hematopoietic Stem Cell Transplantation Oncology Patients: A Pilot Study. The Journal of Pain, 8(4) (Supplement 1): S102.

SRO-3.1	p38 alpha MAPK: Munoz L, Renovo HR, Roy SM, Hu W, Craft JM, McNamara LK, Chico LW, Van Eldik LJ, Watterson DM. A novel p38 alpha MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer"s disease mouse model. 2007 J Neuroinflammation. 4:21. Abeta: Maier M, Seabrook TJ, Laxo ND, et al. Short Amyloid-Beta (ABeta) Immunogens Reduce Cerebral ABeta Load and Learning Deficits in an Alzheimer's Disease Mouse Model in the Absence of an Abeta-Specific Cellular Immune Response. The Journal of Neuroscience, May 3, 2006 • 26(18):4717– 4728. Wilcock DM, Jantzen PT, Li Q, Morgan D, Gordon MN. Amyloid-beta vaccination, but not nitro-nonsteroidal anti-inflammatory drug treatment, increases vascular amyloid and microhemorrhage while both reduce parenchymal amyloid. Neuroscience 144 (2007) 950–960.
SRO-3.2	Lockwood NA, Haseman JR, Tirrell MV and Mayo KH. Acylation of SC4 dodecapeptide increases bactericidal potency against Gram-positive bacteria, including drug-resistant strains. Biochem. J. (2004) 378, 93–103. (Original publication about AC4 dodecapeptide.) Dings RPM and Mayo KH. A Journey in Structure-Based Drug Discovery: From Designed Peptides to Protein Surface Topomimetics as Antibiotic and Antiangiogenic Agents. Acc Chem Res. 2007 Oct; 40(10):1057-65. Epub 2007 Jul 28. (Recent publication describing medicinal chemistry with AC4.) Mayo, KH. NIH 2007 Progress Report for the Great Lakes Research Center of Excellence In Biodefense and Emerging Infectious Diseases. (Internal government document- for details, please contact NIH program officer Dr. Michael Schaefer mschaefer@niaid.nih.gov.) Rivoire, BL. Core D, Product Development and Manufacturing Core. Rocky Mountain Regional Center of Excellence Annual Meeting Abstract Book, October 3-4, 2007, pp 157-159. (Internal government document- for details, please contact NIH program officer Dr. Susan Garges sgarges@niaid.nih.gov.) Kern, SE and Rivoire, BL. Translational critical Path Initiative. Rocky Mountain Regional Center of Excellence Annual Meeting Abstract Book, October 3-4, 2007, pp 272-273. (Internal government document- for details, please contact NIH program officer Dr. Susan Garges sgarges@niaid.nih.gov.) Miller, SI. NIH 3/01/06 – 2/28/07 Progress Report Northwest Research Center Of Excellence: New Opportunities: Antibiotic Discovery pp. 338-362. (Internal government document- for details, please Contact NIH program officer Dr. Michael Schaefer mschaefer@niaid.nih.gov.) Grant number for 5-nitroimidazole project – publicly available abstract contains information about medicinal chemistry objectives: 1 U01 AI075527-01 -- Next-generation 5-nitroimidazoles against giardiasis (For details of project progress, please contact NIH Program officer Dr. John Rogers jrogers@niaid.nih.gov.) Prichard MN, Keith KA, Quenelle DC, Kern ER. Activity and mechanism of action of N-methanocarbathymidine against herpesvirus and orthopoxvirus infections. Antimicrob Agents Chemother. (2006) 50:1336-1341. Gowen BB, Wong MH, Jung KH, Sanders AB, Mendenhall M, Bailey KW, Furuta Y, Sidwell RW. In Vitro and In Vivo Activities of T-705 against Arenavirus and Bunyavirus Infections. Antimicrob. Agents Chemother. (2007) 51(9):3168-76. Projects mentioned in the advances section: 1-U01-AI075520-01 Nitrothiazolides:Broad-Spectrum Category B Anti-parasitic/bacterial Therapeutics 1-U01-AI075563-01 Novel broad spectrum therapeutic glycans against Category B pathogens 1-U01-AI075419-01 Broad-spectrum RNAi therapeutics for flaviviral encephalitis 1-R41-AI072854-01 Stable cationic bacteriochlorins for antimicrobial photodynamic therapy 1 R43 AI075646-01 A Bacitracin derivative for systemic use 1-R21-AI073391-01 Development of MHC-Based Therapeutics for Superantigen-Induced Toxic Shock
SRO-3.3	Denny P et al. The Proteomes of Human Parotid and Submandibular/Sublingual Gland Salivas Collected as Ductal Secretions. Submitted for publication to the Journal of Proteome Research, 2007. Dr. Eleni Kousvelari, Associate Director for Biotechnology and Innovation, NIDCR 301-594-2427 kousvelari@mail.nih.gov

SRO-3.4	Go to http://www.HVTN.org and http://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 http://www3.niaid.nih.gov/news/newsreleases/2007/step_update.htm http://www.chavi.org/ Safety and immunogenicity of Gag-Pol candidate Human Immunodeficiency Virus-1 (HIV-1) DNA vaccine administered by a needle-free device in HIV-1-seronegative subjects. Tavel, J.A., Martin, J. E., Kelly, G. G., Enama, M. E., Shen, J. M., Gomez, P. L., Andrews, C. A., Koup, R. A., Bailer, R. T., Stein, J. A., Roederer, M., Nabel, G. J., Graham, B. S. J. Acquir. Immune Defic. Syndr. 44: 601-5 (2007). Phase I safety and immunogenicity evaluation of a multiclade HIV-1 DNA candidate vaccine. Graham, B.S., Koup, R. A., Roederer, M., Bailer, R. T., Enama, M. E., Moodie, Z., Martin, J. E., McCluskey, M. M., Chakrabarti, B. K., Lamoreaux, L., Andrews, C. A., Gomez, P. L., Mascola, J. R., Nabel, G. J., Vaccine Research Center 004 Study Team. J. Infect. Dis. 194: 1650-60 (2006). Phase I safety and immunogenicity evaluation of a multiclade HIV-1 candidate vaccine delivered by a replication-defective recombinant adenovirus vector. Catanzaro, A. T., Koup, R. A., Roederer, M., Bailer, R. T., Enama, M. E., Moodie, Z., Gu, L., Martin, J. E., Novik, L., Chakrabarti, B. K., Butman, B. T., Gall, J. G., King, C. R., Andrews, C. A., Sheets, R., Gomez, P. L., Mascola, J. R., Nabel, G. J., Graham, B. S., Vaccine Research Center 006 Study Team. J. Infect. Dis. 194:1638-49 (2006). Phase I clinical evaluation of a six-plasmid multiclade HIV-1 DNA candidate vaccine. Catanzaro, A. T., Roederer, M., Koup, R. A., Bailer, R. T., Enama, M. E., Nason, M. C., Martin, J. E., Rucker, S., Andrews, C. A., Gomez, P. L., Mascola, J. R., Nabel, G. J., Graham, B. S, The VRC 007 Study Team. Vaccine. 25: 4085-92 (2007). Phase II study of an HIV-1 canarypox vaccine (vCP1452) alone and in combination with rgp120: negative results fail to trigger a phase 3 correlates trial. Russell, N. D., Graham, B. S., Keefer, M. C., McElrath, M. J., Self, S. G., Weinhold, K., Montefiori, D. C., Ferrari, G., Horton, H., Tomaras, G. D., Gurunathan, S., Baglyos, L., Frey, S. E., Mulligan, M. J., Harro, C. D., Buchbinder, S. P., Baden, L. R., Blattner, W. A., Koblin, B. A., Corey, L., The National Institute of Allergy and Infectious Diseases; HIV Vaccine Trials Network. J. Acquir. Immune Defic. Syndr. 44: 203-12 (2007). Induction of HIV-1-specific T-cell responses in HIV vaccine trial participants who subsequently acquire HIV-1 infection. Horton, H., Havenar-Daughton, C., Lee, D., Moore, E., Cao, J., McNevin, J., Andrus, T., Zhu, H., Rubin, A., Zhu, T., Celum, C., McElrath, M. J. J. Virol. 80: 9779-88 (2006).
SRO-3.5	Ittiwut C, Listman J, Mutirangura A, Malison R, Covault J, Kranzler HR, Sughondhabirom A, Thavichachart N, Gelernter J. Interpopulation linkage disequilibrium patterns of GABRA2 and GABRG1 genes at the GABA cluster locus on human chromosome 4. Genomics. 2007 Oct 30; [Epub ahead of print] http://dx.doi.org/10.1016/j.ygeno.2007.08.007 Soyka M, Preuss UW, Hesselbrock V, Zill P, Koller G, Bondy B. GABA-A2 receptor subunit gene (GABRA2) polymorphisms and risk for alcohol dependence. J Psychiatr Res. 2007 Jan 4; [Epub ahead of print] http://dx.doi.org/10.1016/j.jpsychires.2006.11.006 Luo X, Kranzler HR, Zuo L, Zhang H, Wang S, Gelernter J. CHRM2 variation predisposes to personality traits of agreeableness and conscientiousness. Hum Mol Genet. 2007 Jul 1;16(13):1557-68. http://hmg.oxfordjournals.org/cgi/reprint/16/13/1557 Luo X, Kranzler HR, Zuo L, Wang S, Gelernter J. Personality traits of agreeableness and extraversion are associated with ADH4 variation. Biol Psychiatry. 2007 Mar 1;61(5):599-608. http://dx.doi.org/10.1016/j.biopsych.2006.05.017 Porjesz B, Rangaswamy M. Neurophysiological endophenotypes, CNS disinhibition, and risk for alcohol dependence and related disorders.ScientificWorldJournal. 2007 Nov 2;7:131-41.

	http://www.thescientificworld.com/headeradmin/upload/2007.06.203.pdf
SRO-3.6	Preclinical studies of the nature of stem cell migration: Hsu, L-Y, Wragg, A, Anderson, SA, Balaban, RS, Boehm, M, and Arai, AE "Automatic assessment of dynamic contrast-enhanced MRI in an ischemic rat hindlimb model: an exploratory study of transplanted mutilpotent progenitor cells" NMR in Biomedicine, published online May 15. DOI 10.1002/nbm.1166
SRO-4.3	Please see: http://clinicaltrials.gov/ct/show/NCT00063622?order=1
SRO-5.1	Go to http://www.AIDSinfo.nih.gov for information on specific protocols identified and their status. NIAID Planning and Reporting Process, FY 2007: 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. Ribaudo HJ, Kuritzkes DR, Lalama CM, Schouten JT, Schackman BR, Shikuma C, Acosta EP, and Gulick RM. Activity of efavirenz (EFV)-based regimens in treatment-naïve patients across a range of pre-treatment HIV-1 RNA levels and CD4 cell counts: ACTG 5095 The Journal of Infectious Diseases, accepted. Progression of HIV-related disease or death (POD) in the randomized SMART study: why was the risk of POD greater in the CD4-guided ((re)-initiate ART at CD4 < 250 cells/μL) drug conservation (DC) vs the virological suppression (VS) arm? Lundgren J.D.1, for the SMART Study Group; [XVI International AIDS Conf., abs. #WEAB0203] The effect of episodic CD4-guided antiretroviral therapy on quality of life: results of the Quality of Life substudy of SMART; Burman W.1, for the SMART Study Group; [XVI International AIDS Conf., abs. #THPE0145]; Award data: AI46362 Investigator: CPCRA (Fred Gordin) Riddler S.A., Haubrich R.2, DiRienzo G., Peeples L., Powderly W.G., Klingman K.L.5, Garren K.W., George T., Rooney J.F., Brizz B.9, Havlir D., Mellors J.W., AIDS Clinical Trials Group 5142 Study Team. ACTG 5142: [XVI International AIDS Conf., abs. #THLB0204] FJ Torriani, RA Parker, RL Murphy, CJ Fichtenbaum, JS Currier, MP Dubé, KE Squires, M Gerschenson, L Komarow, BR Cotter, CK Mitchell, JH Stein for the ACTG 5152 team. A5142: Antiretroviral Therapy Improves Endothelial Function in Individuals with Human Immunodeficiency Virus Infection: A Prospective, Randomized Multicenter Trial (Adult AIDS Clinical Trials Group Study) ACTG 5152s: 10th European AIDS Conference, Dublin, Ireland, Nov 17-20, 2005, American Heart Association Scientific Session, Dallas, TX, 11/13-16/2005, abs. #PS5

	Effect of Concomitantly Administered Rifampin on the Pharmacokinetics and Safety of Atazanavir Administered Twice Daily.Edward P. Acosta, Michelle A. Kendall, John G. Gerber, Beverly Alston-Smith, Susan L. Koletar, Andrew R. Zolopa, Sangeeta Agarwala, Michael Child, Richard Bertz, Lara Hosey, and David W. Haas. Antimicrobial Agents and Chemotherapy 51(9):3104-10, 2007. Pharmacokinetic evaluation of the effects of ribavirin on zidovudine triphosphate formation ACTG 5092s Study Team, FT Aweeka, M Kang, J-Y Yu, P Lizak, B Alston, RT Chung and the AIDS Clinical Trials Group 5092s Study Team. HIV Medicine 06/01/2007. 8(5):288-94. Phase 2 Study of the Safety and Efficacy of Vicriviroc, a CCR5 Inhibitor, in HIV-1-Infected, Treatment-Experienced Patients: AIDS Clinical Trials Group 5211 Gulick RM, Su Z, Flexner C, Hughes MD, Skolnik PR, Wilkin TJ, Gross R, Krambrink A, Coakley E, Greaves WL, Zolopa A, Reichman R, Godfrey C, Hirsch M, and Kuritzkes DR, for the AIDS Clinical Trials Group A5211 Team. Journal of Infectious Diseases. 1976:304-312 (2007). A Randomized Study of Antiviral Medication Switch at Lower- versus Higher Switch Thresholds: AIDS Clinical Trials Group Study 5115. Riddler SA, Jiang H, Tenorio A, Huang H, Kuritzkes DR, Acosta EP, Landay A, Ph.D., Bastow B Haas DW, Tashima KT, Jain MK, Deeks SG, Bartlett JA Antiviral Therapy. 12(4):531-41 (2007). Risk of Cancers during Interrupted Antiretroviral Therapy in the SMART Study Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, Hidalgo J, Lourtau L, Neaton JD, Tambussi G, and Abrams DI. AIDS. 21:1957-1963 (2007). Disadvantages of Structured Treatment Interruption Persist in Patients with Multidrug-Resistant HIV-1: Final Results of the CPCRA 064 Study. Lawrence J, Huppler Hullsiek K, Thackeray LM, Abrams DI, Crane LR, Mayers DL, Jones MC, Saldanha JM, Schmetter BS, and Baxter JD, for the CPCRA 064 Study Team of the Terry Beirn Community Programs for Clinical Research on AIDS. Journal of Acquired Immune Deficiency Syndromes. 43:169-178 (2006). Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study Avy Violari, Mark Cotton, Di Gibb, Abdel Babiker, Jan Steyn, Patrick Jean-Phillipe, James McIntyre on behalf of the CHER Study Team,.4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention. July 22-25, 2007. Sydney. Abstract WESS103 Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med. 2007 Jan 11;356(2):135-47.
SRO-5.2	Final enrollment report submitted to the Contracting Office and enrollment graph presented to the Data and Safety Monitoring Committee. (Contact: Louise M. Rosenbaum, OSPP/OD/NIAMS; rosenbauml@mail.nih.gov, tel. 301-496-8271)
SRO-5.3	Novel Preclinical Tools for Predictive ADME-Toxicology; RFA Number: RFA-RM-04-023 http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-023.html Funded Research; RFA-RM-04-023 Novel Preclinical Tools for Predictive ADME-Toxicology (R21) http://nihroadmap.nih.gov/molecularlibraries/fundedresearch.asp Selective compounds define Hsp90 as a major inhibitor of apoptosis in small-cell lung cancer. http://www.nature.com/nchembio/journal/v3/n8/full/nchembio.2007.10.html Chaperoning cell death: a critical dual role for Hsp90 in small-cell lung cancer. http://www.nature.com/nchembio/journal/v3/n8/full/nchembio0807-455.html
SRO-5.4	1. Research supported by NIH grants R01AG20226, R01AG18402, P01AG25204, R01AG22559, R21AG21868 and contracts HHS-N-260-2004-00010-C and N01-AG-9-2117. Klunk WE, Engler H, Nordberg A, et al.: Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann. Neurol. 55:306-319, 2004. Kung M, Hou C, Zhuang Z, Cross AJ, Maier D, and Kung HF: Characterization of IMPY as a potential imaging agent for β-amyloid plaques in double transgenic PSAPP mice. Eur. J Nuc. Med. Molec. Imaging 31:1136-1145, 2004. 2. Research supported by NIH grants R01MH42705, R01MH40537 and contract N01MH32004. Cueva JP, Giorgioni G, Grubbs RA, Chemel BR, Watts VJ, Nichols DE. Trans-2,3-dihydroxy-6a, 7,8, 12b-tetrahydro-6H-chromeno[3,4-c]isoquinoline: synthesis, resolution, and preliminary pharmacological characterization of a new dopamine D1 receptor full agonist. J Med Chem 49(23): 6848-57, 2006.

3. Research supported by NIH grant R01MH46851 and contract N01MH32004. Licata SC, Platt DM, Cook JM, Sarma PV, Griebel G, Rowlett JK. Contribution of GAPAA receptor subtypes to the anxiolytic-like, motor, and discriminative stimulus effects of benzodiazepines: studies with the functionally selective ligand SL651498 [6-fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-yl-carbonyl)-2,9-dihydro-1H-pyridol[3,4-b]indol-1-one]. J Pharmacol Exp Ther 313(3): 1118-25, 2005.

4. Research supported by NIH contract N01NS042359. Press release at http://kron.com/Global/story.asp?S=3785346

5. Research supported by NIH grants R44MH63663, R41MH63663 and contract N01MH32001. Guillon CD, Koppel GA, Brownstein MJ, Chaney MO, Ferris CF, Lu SF, et al. Azetidinones as vasopressin V1a antagonists. Bioorg Med Chem 15(5): 2054-80, 2007. http://www.azevan.com/pipeline/default.asp

6. Research supported by NIH grants R01MH74953, R01MH34007, R37MH48404.Galici R, Jones CK, Hemstapat K, Nong Y, Echemendia NG, Williams LC, de Paulis T, Conn PJ. Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. J Pharmacol Exp Ther 318(1): 173-85, 2006.

7. Research supported by NIH cooperative agreement U19DA017548. Dwoskin LP, Joyce BM, Zheng G, Neugebauer NM, Manda VK, Lockman P, Papke RL, Bardo MT, Crooks PA. Discovery of a novel nicotinic receptor antagonist for the treatment of nicotine addiction: 1-(3-Picolinium)-12-triethylammonium-dodecane dibromide (TMPD). Biochem Pharmacol 74(8): 1271-82, 2007.

8. Research supported by NIH grants R01DA09045, R01MH063266, R01MH078473 and contract N01DA-0-8801. Beardsley PM, Howard JL, Shelton KL, Carroll FI. Differential effects of the novel kappa opoid receptor antagonist JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. Psychopharmacology (Berl) 183(1): 118-26, 2005.

9. Research supported by NIH grants DA00418, DA05477, DA11530, DA133326. Carroll FI, Fox BS, Kuhar MJ, Howard JL, Pollard GT, Schenk S. Effects of dopamine transporter selective 3-phenyltropane analogs on locomotor activity, drug discrimination, and cocaine self-administration after oral administration. Eur J Pharmacol 553 (1-3): 149-56, 2006.

10. Research supported by NIH grants DA11979, DA13976. Drug Data Report 2006, 28(8); 797. Daniels A, Ayala E, Chen W, Coope A, Matsumoto RR. N-[2-(m-Methyoxyphenyl)ethyl]-N-ethyl-2-(1-pyrrolidinyl)ethylamine (UMB 116) is a novel antagonist for cocaine-induced effects. Eur J Pharmacol 542(1-3): 61, 2006.

11. Research supported by NIH grant DA007215. Chambers AP, Vemuri VK, Peng Y, Wood JAT, Olszewska T, Pittman QJ, Makriyannis A, Sharkey KA. A neutral CB1 receptor antagonist reduced weight gain in rat. Am J Physiol Regul Integr Comp Physiol. October 2007 [Epub ahead of print].

12. Research supported by NIH grant R44AA009930. Tabakoff B, Hoffman P, Vengeliene V, Spanagel R. Medications for alcohol dependence: rational drug design and DCUK. Alcoholism: Clin Exp Res 30(s2): 68A, 2006.

13. Research supported by NIH grant R01AA12600. Kehrberg AH, Lewis B, Farook JM, Wellmann KA, Littleton JM, Barron S. A novel compound, JR-220, reduces alcohol deprivation effects in rats. Alcoholism: Clin Exp Res 31(s2): 140A, 2007.

14. Research supported by NIH intramural code Z01AA000487. Gehlert DR, Cippitelli A, Thorsell A, Le AD, Hipskind PA, Hamdouchi C, Lu J, Hembre EJ, Cramer J, Song M, McKinzie D, Morin M, Ciccocioppo R, Heilig M. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: a novel brain-penetrant, orally available corticotrophin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. J Neurosci 27(10): 2718-26, 2007.

15. Research supported by NIH grants R01AA12602, R01AA015239. Funk CK, Zorrilla EP, Lee MJ, Rice KC, Koob GF. Corticotropin-releasing factor 1 antagonists selectively reduce ethanol self-administration in ethanol-dependent rats. Biol Psychiatry 61(1): 78-86, 2007.

16. Research supported by NIH grants R01AA10531, P60AA6424. Zhao Y, Dayas CV, Aujla H, Baptista MA, Martin-Fardon R, Weiss F. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-fos expression in the hippocampus and amygdale. J Neurosci 26(39):

	9967-74, 2006. 17. Research supported by Amyotrophic Lateral Sclerosis Association (ALSA) and NIH supplements to NIH grant R01NS33958. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su ZZ, Gupta P, Fisher PB. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433(7021): 73-7, 2005. 18. Research supported by NIH intramural code Z01NS002974. Avila AM, Burnett BG, Tave AA, Gabanella F, Knight MA, Hartenstein P, Cizman Z, Di Prospero NA, Pellizzoni L, Fischbeck KH, Sumner CJ. Trichostatin A increases SMN expression and survival in a mouse model of spinal muscular atrophy. J Clin Invest 117(3): 659-71, 2007. 19. Research supported by NIH grant R01AG18933. Design, synthesis, and X-ray structure of potent memapsin 2 (beta-secretase) inhibitors with isophthalamide derivatives as the P2-P3-ligands. Ghosh et al. J Med Chem 50(10): 2399-407, 2007. 20. Research supported by NIH grants T32AG000260, R37AG13939, P01AG21184, U01AG28561. Munoz L, Renovo HR, Roy SM, Hu W, Craft JM, McNamara LK, Chico LW, Van Eldik LJ, Watterson DM. A novel p38 alpha MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer's disease mouse model. J Neuroinflammation 4: 21, 2007.
SRO-5.5	Ball, S.A., Martino, S, Nich, C., Frankforter, T.L., Van Horn, D., Crits-Shristoph, P., Woody, G.E., Obert, J.L., Farentinos, C. Carroll, K.M. (2007) Site Matters: Multisite Randomized Trial of Motivational Enhancement Therapy in Community Drug Abuse Clinics. Journal of consulting and Clinical Psychology, 75 (4):556-567. http://dx.doi.org/10.1037/0022-006X.75.4.556 Santisteban, D.A., Suarez-Morales, L., Robbins, M.S., Szapocznik, J. (2006) Brief Strategic Family Therapy: Lessons Learned in Efficacy Research and Challenges to Blending Research and Practice. Family Process, 45(2):259-271. http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1545-5300.2006.00094.x Hien, D.A. (2007) Early Findings from NIDA's Clinical Trials Network "Women and Trauma" Study. Platform talk presented at the American Psychological Association Annual Convention, San Francisco, CA, August 17-20, 2007. http://forms.apa.org/convention/viewabstract.cfm?id=7843
SRO-5.6	NABI Biopharmaceuticals News Release Boca Raton, FL., November 7/PRNewswire-FirstCall: "Nabi Biopharmaceuticals Announces Successful Completion of NicVAX(R) Phase 2b Trial: Drug Shows Statistically Significant Rates of Smoking Cessation and Continuous Long-Term Smoking Abstinence at 12 Months" . http://phx.corporate-ir.net/phoenix.zhtml?c=100445&p=irol-newsArticle&ID=1074098&highlight= Rennard, S., Jorenby, D., Gonzales, D., Rigotti, N., deVos, A., Bortey, E., Adhavain, R., Hatsukami, D. "A Randomized Placebo-Controlled Trial of a Conjugate Nicotine Vaccine (NicVAX) in Smokers Who Want to Quit: 12 Month Results. Presented at The American Heart Association Scientific Sessions November 7, 2007 in Orlando, Florida. Clinical Trials.gov: Efficacy of NicVAX in Smokers Who Want to Quit Smoking http://clinicaltrials.gov/ct/show/NCT00318383?order=1 Hatsukami, DK, Rennard, S, Jorenby, D, Fiore, M, Koopmeiners, J, deVos, A, Horwith, G, and Pentel, PR. Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers. Clin Pharmacol Ther, 2005; 78(5):456-67. http://www.nature.com/clpt/journal/v78/n5/pdf/clpt2005521a.pdf Rennard, S., Jorenby, D., Gonzales, D., Rigotti, N., deVos, A., Bortey, E., Adhavain, R., Hatsukami, D. "A Randomized Placebo-Controlled Trial of a Conjugate Nicotine Vaccine (NicVAX) in Smokers Who Want to Quit: 12 Month Results. Presented at the College of Problems on Drug Dependence 69th Annual Scientific Meeting, June 16-21, 2007, Quebec City.
SRO-5.7	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). FDA Announcement of approval as first line therapy in NSCLC: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01488.html Coding information for reimbursement: https://www.spoconline.com/spoconline/avastin/reimburse/coding_nsclc.jsp

	Business news article that describes Avastin as standard of care when discussing newer drugs: http://today.reuters.com/news/articleinvesting.aspx?type=comktNews&rpc=33&storyid=2007-11-20T113552Z_01_L20474792_RTRIDST_0_NOVARTIS-ANTISOMA.XML
SRO-5.8	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
SRO-5.9	The website for the data release/web utility can be viewed at http://www.biostat.wustl.edu/fbpp/FBPP.shtml. Initial prostate GWAS data release: http://cgems.cancer.gov/news/pr_2006_10_18.pdf Prostate cancer association with Human Chr 8: http://cgems.cancer.gov/news/pr_2006_04_01.pdf
SRO-5.10	Annual PHS progress reports and published results (Wolff MS, Teitelbaum SL, Windham G, Pinney SM, Britton JA, Chelimo C, Godbold J, Biro F, Kushi LH, Pfeiffer CM, Calafat AM. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. Environ Health Perspect. 2007;115:116-121.) http://www.jstor.org/view/00916765/sp070003/07x0253s/0?frame=noframe&userID=80e75804@nih.gov/01c0a80a6500501d0941f&dpi=3&config=jstor
SRO-6.1	Target performance 1) Molecular genetics of AMD and current animal models. Angiogenesis. 2007;10(2):119-32. http://www.springerlink.com/content/r541165276117906/fulltext.pdf 2) CD59, a Complement Regulatory Protein, Controls Choroidal Neovascularization in a Mouse Model of Wet-Type Age-Related Macular Degeneration. J Immunol 2007 178: 1783-1790. http://www.jimmunol.org/cgi/content/full/178/3/1783 3) Targeting age-related macular degeneration with Alzheimer's disease based immunotherapies: Anti-amyloid-beta antibody attenuates pathologies in an age-related macular degeneration mouse model. Vision Res. 2007 Sep 19; [Epub ahead of print] http://dx.doi.org/10.1016/j.visres.2007.07.025 4) Quantitative genetics of age-related retinal degeneration: a second F1 intercross between A/J and C57BL/6 strains. Mol Vis. 2007 Jan 25;13:79-85. http://www.molvis.org/molvis/v13/a9/ 5) Murine ccl2/cx3cr1 deficiency results in retinal lesions mimicking human age-related macular degeneration. Invest Ophthalmol Vis Sci. 2007 Aug;48(8):3827-36. http://www.iovs.org/cgi/content/full/48/8/3827?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=murine&searchid=1&FIRSTINDEX=0&volume=48&issue=8&resourcetype=HWCIT 6) The R345W mutation in EFEMP1 is pathogenic and causes AMD-like deposits in mice. Hum Mol Genet. 2007 Oct 15;16(20):3411-22. http://hmg.oxfordjournals.org/cgi/content/full/16/20/2411?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=R345W+mutation&searchid=1&FIRSTINDEX=0&volume=16&issue=20&resourcetype=HWCIT 7) Glaucoma-causing myocilin mutants require the Peroxisomal targeting signal-1 receptor (PTS1R) to elevate intraocular pressure. Hum Mol Genet. 2007 Mar 15;16(6):609-17. http://hmg.oxfordjournals.org/cgi/content/full/16/6/609?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=Glaucoma-causing&searchid=1&FIRSTINDEX=0&volume=16&issue=6&resourcetype=HWCIT 8) Expression of mutated mouse myocilin induces open-angle glaucoma in transgenic mice. J Neurosci. 2006 Nov 15;26(46):11903-14. http://www.jneurosci.org/cgi/content/full/26/46/11903?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=mouse+myocilin&searchid=1&FIRSTINDEX=0&volume=26&issue=46&resourcetype=HWCIT 9) Role of CYP1B1 in glaucoma. Annu Rev Pharmacol Toxicol. 2007 Oct 3; Epub ahead of print, Vol 48. http://arjournals.annualreviews.org/doi/pdf/10.1146/annurev.pharmtox.48.061807.154729 10) Genotype and phenotype correlations in congenital glaucoma. Trans Am Ophthalmol Soc. 2006;104:183-95. http://www.aosonline.org/xactions/2006/1545-6110_v104_p183.pdf 11) Expression of ephrinB1 and its receptor in glaucomatous optic neuropathy. Br J Ophthalmol. 2007 Sep;91(9):1219-24. http://bjo.bmj.com/cgi/content/full/91/9/1219?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=glaucomatous+optic&searchid=1&FIRSTINDEX=0&volume=91&issue=9&resourcetype=HWCIT Other Highlights 12) Individuals homozygous for the age-related macular degeneration risk-conferring variant of complement factor H have elevated levels of CRP in the choroid. PNAS, 2006 Nov 14; 103(46):17456-61. http://www.pnas.org/cgi/content/full/103/46/17456 13) Extended haplotypes in the complement factor H (CFH) and CFH-related (CFHR) family of genes protect against age-related macular degeneration: Characterization, ethnic distribution and evolutionary implications. Ann

	Med. 2006; 38 (8):592-604. http://www.informaworld.com/smpp/ftinterface~content=a768564693~fulltext=713240928 14) Haplotypes spanning the complement factor H gene are protective against age-related macular degeneration. Invest Ophthalmol Vis Sci. 2007 Sep; 48(9):4277-83. http://www.iovs.org/cgi/content/full/48/9/4277 15) Protective effect of complement factor B and complement component 2 variants in age-related macular degeneration. Hum Mol Genet. 2007 Aug 15;16(16):1986-92. http://hmg.oxfordjournals.org/cgi/content/full/16/16/1986 16) Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. JAMA. 2007 Apr 25;297(16):1793-800. http://jama.ama-assn.org/cgi/content/full/297/16/1793 17) NIH Grant # R21 EY018127 18) An apolipoprotein E variant may protect against age-related macular degeneration through cytokine regulation. Environ Mol Mutagen. 2006 Oct;47(8):594-602. http://www3.interscience.wiley.com/cgi-bin/fulltext/112693059/PDFSTART 19) Genetics of pigment changes and geographic atrophy. Invest Ophthalmol Vis Sci. 2007 Jul;48(7):3005-13. http://www.iovs.org/cgi/content/full/48/7/3005 20) Expanded genome scan in extended families with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2006 Dec;47(12):5453-9. http://www.iovs.org/cgi/content/full/47/12/5453 21) A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science. 2006 Nov 10;314(5801):992-3. http://www.sciencemag.org/cgi/content/full/314/5801/992 22) Disease susceptibility of the human macula: differential gene transcription in the retinal pigmented epithelium/choroid. Exp Eye Res. 2007 Sep;85(3):366-80. http://dx.doi.org/10.1016/j.exer.2007.05.006 23) Population differences in elastin maturation in optic nerve head tissue and astrocytes. Invest Ophthalmol Vis Sci. 2007 Jul;48(7):3209-15. http://www.iovs.org/cgi/content/full/48/7/3209 24) Variation in optineurin (OPTN) allele frequencies between and within populations. Mol Vis. 2007 Feb 2;13:151-63. http://www.molvis.org/molvis/v13/a18/ 25) Myocilin Gly252Arg mutation and glaucoma of intermediate severity in Caucasian individuals. Arch Ophthalmol. 2007 Jan;125(1):98-104. http://archopht.ama-assn.org/cgi/content/full/125/1/98
SRO-6.2	Please contact Dr. Patrick Donohue in OSPPA/NIDDK for access to the July 2006 FAVORIT Data Management Report.
SRO-6.3	Checklist publication: Fostel, J. M., Burgoon, L., Zwickl, C., Lord, P., Corton, J. C., Bushel, P. R., Cunningham, M., Fan, L., Edwards, S. W., Hester, S., Stevens, J., Tong, W., Waters, M., Yang, C., and Tennant, R. (2007). Toward a checklist for exchange and interpretation of data from a toxicology study. Toxicol Sci 99, 26-34. http://toxsci.oxfordjournals.org/cgi/content/full/99/1/26 SIFT Builder demo and example: see attached SIFT Builder Users Guide
SRO-6.4	One of the grantees who attended the November meeting refers to it in his progress report for 2007 (R01 HL080258-03).
SRO-7.4	*Performance target (data release) and data access* August 29, 2007, memo to the OAI Steering Committee from Susan Rubin and the OAI data team. Current information about data available to researchers is available through http://www.oai.ucsf.edu/datarelease/. *Publications* Eckstein F, Kunz M, Schutzer M, Hudelmaier M, Jackson RD, Yu J, Eaton CB, Schneider E. Two year longitudinal change and test-retest-precision of knee cartilage morphology in a pilot study for the osteoarthritis initiative. Osteoarthritis Cartilage. 2007 Jun 7; [Epub ahead of print] PMID: 17560813 Eckstein F, Kunz M, Hudelmaier M, Jackson R, Yu J, Eaton CB, Schneider E. Impact of coil design on the contrast-to-noise ratio, precision, and consistency of quantitative cartilage morphometry at 3 Tesla: a pilot study for the osteoarthritis initiative. Magn Reson Med. 2007 Feb;57(2):448-54. PMID: 17260363 Duryea J, Neumann G, Brem MH, Hoh W, Noorbakhsh F, Jackson RD, Yu J, Eaton CB, Lang P. Novel fast semi-automated software to segment cartilage for knee MR acquisitions. Osteoarthritis Cartilage. 2007 May:15(5):487-92. PMID: 17469126

	Eckstein F, Mosher T, Hunter D. Imaging of knee osteoarthritis: data beyond beauty. Curr Opin Rheumatol. 2007 Sep;19(5):435-443. PMID: 17762608
SRO-7.5	Dr. Ruth Nowjack-Raymer Program Director, Health Disparities Research Program (301) 594-5394, ruth.nowjack-raymer@nih.gov Award #U54DE014261-06
SRO-8.1	2 - Anopheles gambiae M Strain: http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?cmd=retrieve&val=SPECIES_CODE+%3D+%22ANOPHELES+GAMBIAE+S%22&file=trace S Strain: http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?&cmd=retrieve&val=SPECIES_CODE%20%3D%20%22ANOPHELES%20GAMBIAE%20M%22&retrieve=Submit 9 -Bacillus cereus 03BB108 ABDM01000000 AH1134 ABDA01000000 AH187 AAUF01000000 AH820 AAUE01000000 B4264 ABDI01000000 G9842 ABDJ01000000 H3081.97 ABDL01000000 NVH0597-99 ABDK01000000 W ABC201000000 5-Borrelia 156a ABCV01000000 Bo126 ABCW01000000 ZS7 ABCX01000000 ACA-7 ABCU01000000 VS116 ABCY01000000 1-Camplyobacter ATCC BAA381 CP000776 9-Clostridium Clostridium botulinum Bf ABDP01000000 C ABDQ01000000 NCTC 2916 ABDO02000000 Clostridium butyricium 5521 ABDT01000000 Clostridium perfringens C ABDU01000000 E ABDW01000000 B-ATCC 3626 ABDV01000000 CPE F4969 ABDX01000000 NCTC 8239 ABDY01000000 2-Coxiella burnetii RSA 334 AAYJ01000000 MSU GOAT AAUP02000000 1-E.coli SECEC SMS3-5 ABAQ02000000 5-Francisella Francisella tularensis novicidia GA99-3548 ABAH01000000 GA99-3549 AAYF01000000 Francisella tularensis tularensis FSC022 AAYD01000000 Francisella tularensis holarctica FSC033 AAYE01000000 Francisella tularensis holaractica FSC257 AAUD01000000 4-Mycobacterium tuberculosis Haarlem AASN01000000 KZN 605 ABGN00000000 KZN4207 ABGL00000000 KZN 1435 ABGM00000000 17-Salmonella Salmonella enterica CVM23701 ABAO01000000 Kentucky CVM29188 ABAK01000000

	Kentucky CDC 191 ABEI01000000 Hadar RI05P066 ABFG01000000 Newport SL254 ABEN01000000 Heidelberg SL476 ABEM01000000 Heidelberg SL486 ABEL01000000 Schwarzengrund CVM19633 ABAL01000000 Schwarzengrund SL480 ABEJ01000000 Dublin CT_02021853 ABAP01000000 Agona SL483 ABEK01000000 Javiana GA_MM04042433 ABEH01000000 I-CVM23701 ABAO01000000 S.Saint Paul SARA23 ABAN01000000 S.Saint Paul SARA29 ABAN01000000 Virchow SL491 ABFH01000000 Weltevreden HI_N05-537 (SL484) ABFF01000000 Streptococcus sanguinis CP000387 14-Ureaplasma urealyticum serovar 1 ABES01000000 serovar 2 ABFL01000000 serovar 3 AAYM01000000 serovar 4 AAYO01000000 serovar 5 AAZR01000000 serovar 6 AAZQ01000000 serovar 7 AAYP01000000 serovar 8 AAYN01000000 serovar 9 AAYQ01000000 serovar 10 ABET010000000 serovar 11 AAZS01000000 serovar 12 AAZT01000000 serovar 13 AAEV01000000 serovar 14 ABET01000000 11 Vibrio 9 Vibrio cholerae 1587 AAUR01000000 2740-80 AAUT01000000 623-39 AAWG01000000 MAK 757 AAUS01000000 MZO-3 AAUU01000000 B33 AAWE01000000 MZO-2 AAWF01000000 395 AAKG01000000 NCTC 8457 AAWD01000000 Vibrio harveyi HYQI AAWP01000000 Vibrio parahaemolyticus AQ3810 AAWQ01000000 6-Yersinia pestis biovar Orientalis F1991016 ABAT01000000 biovar Orientalis MG05-1020 AAYS01000000 biovar AntiquaUG05-0454 AAYR01000000 biovar Antiqua E1979001 AAYV01000000 biovar Antiqua B42003004 AAYU01000000 biovar Mediaevalis K1973002 AAYT01000000 6 Coccidioides Coccidioides immitis RMSCC 3703 ABBC01000000 Coccidioides immitis RS AAEC01000000 Coccidioides immitis H538.4 AASO01000000 Coccidioides immitis RMSCC 2394 AATX01000000 Coccidioides posadasii Silveira ATCC 28868 ABAI01000000 Coccidioides posadasii RMSCC 3488 ABBB01000000

	Penicillium marneffei ABAR01000000 Talaromyces stipilatus ABAS00000000 Brugia malayi AAQA01000000 Crytosporidium muris AAZY01000000 Plasmodium vivax AAKM00000000 Schistosoma mansoni ED003497 Toxoplasma III AAYL01000000 Culex pipiens AAWU00000000 Ixodes scapularis EW781064-EW964897
SRO-8.2	Progress toward studies using genetically altered mouse strains is described in Grant Progress Report is part of the official file on grant AR49682, which is maintained by the NIH Extramural Research Program. *DMP1* Feng JQ et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet.* 2006 Nov;38(11):1310-5. Epub 2006 Oct 8. *Fibronectin and LTBP-1* Chen Q et al. Potential role for heparan sulfate proteoglycans in regulation of TGF-beta by modulating assembly of latent TGF-beta binding protein. *J. Biol. Chem.* 2007 Sep;282(36:26418-30. *Fibrillin-2* Characterization of fibrillin-2-deficient mice is described in the Grant Progress Report submitted by the University of Medicine and Dentistry of New Jersey as part of the application for continued funding of this project. The Grant Progress Report is part of the official file on grant AR42044, which is maintained by the NIAMS Extramural Research Program
SRO-8.4	The contract award number is: HHSN268200700155P. 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.
SRO-8.5	PROMIS v1.0 item banks, their psychometric properties, and initial data analysis highlights are available on the PROMIS website (http://www.nihpromis.org).
SRO-8.6	NIH project officer: Mary Frances Cotch, Ph.D. Chief, Epidemiology Branch Division of Epidemiology and Clinical Research National Eye Institute National Institutes of Health 5635 Fishers Lane, Suite 1100 Bethesda, MD 20892-9301 Courier address: Rockville, MD 20852 Phone (301) 496-1331 E-mail: mfc@nei.nih.gov
SRO-9.1	March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The Treatment for Adolescents With Depression Study (TADS): Long-term effectiveness and safety outcomes. Arch Gen Psychiatry, 2007 Oct;64(10):1132-43. http://archpsyc.ama-assn.org/cgi/content/full/64/10/1132 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. American Journal of Psychiatry 2006;163:1905-1917. http://ajp.psychiatryonline.org/cgi/ijlink?linkType=ABST&journalCode=ajp&resid=163/1/28
SRO-9.3	The NIH MRI Study of Normal Brain Development, online at: http://www.bic.mni.mcgill.ca/nihpd/info/index.html. Almli CR, Rivkin MJ, McKinstry RC and Brain Development Cooperative Group (2007). The NIH MRI study of normal brain development (Objective-2): Newborns, infants, toddlers, and preschoolers. NeuroImage, 35 (1), 308-325. (http://dx.doi.org/10.1016/j.neuroimage.2006.08.058) Waber CP, deMoor C, Forbes PW, Almli CR, Botteron KN, Leonard G, Milovan D, Paus T, Rumsey J, and the Brain Development Cooperative Group (2007). The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. Journal of the International Neuropsychological Society, 13, 1-18.

	(http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=1024408)
SRO-9.4	1. CHIMES Study Website: http://main.uab.edu/Sites/chimes 2. Manual of Procedures, The Natural History of CMV-Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn, CMV & Hearing Multicenter Screening (CHIMES) Study, 2007.
Communication and Transfer of Results (CTR)	
CTR-1	FY07 Mississippi SIDS Outreach Progress Monthly Reports. To obtain a copy of the report, please contact Shavon Artis at the National Institute of Child Health and Human Development at (301) 435- 3459.
CTR-4	Contract N01-LM-7-5535 with Dawnbreaker Contract N01-LM-5-5510 with Foresight Science and Technology 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 Second Interval Tracking Report (July 1, 2006 - March 31, 2007) 4. NIH-CAP 2004-05 Final Report and Analysis 5. NIH-CAP 2005-06 First Interval Tracking Report (July 1, 2006 – March 31, 2007) 6. NIH-CAP 2006-07 Baseline Tracking Report (September 1, 2006 – June 30, 2007) Contact: Kay Etzler SBIR/STTR Program (301) 435-2713
CTR-5	For source validation information, including Synapse information, please contact: Bonny Harbinger, PhD, JD Deputy Director Office of Technology Transfer National Institutes of Health 6011 Executive Boulevard, Suite 325 Rockville, Maryland 20852 Telephone: 301-435-2843 More information on Synapse can be found at: http://ott.od.nih.gov/synapse/index.html
CTR-8	See http://grants.nih.gov/grants/oer_redesign_20070801.htm for announcement of the Web site launch.
Capacity Building and Research Resources (CBRR)	
CBRR-1	"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 IMPAC II database. Contact: Jennifer Sutton Research Training Coordinator Office of Extramural Programs (301) 435-2686
CBRR-2	All project performance metrics and associated communications are stored in the NBS project database. Contact: Kevin Green NBS Program Management Office (301) 451-0005
CBRR-3	Current OMB report in ProSight: https://prosight.hhs.gov/prosight/Portfolios/View.htm?window=form&itemID=1405&formID=1064&tabID=1398 1. Central collection of all patient care data within the NIH intramural program in electronic form. This enables access to patient care data for care throughout the NIH campus and enables secondary use of data for research purposes. 2. Decreased number of lost test results. 3. Increased ability to aggregate and analyze data. OMB 300 filings. Contact: Elaine Ayres Assistant Director for Ethics and Technology Clinical Center (301) 594-3019

CBRR-4	System queries and reports provide the data to determine the percentage of electronic transactions in the system. Contact: Thomas Boyce Interim eRA Program Manager Office of Extramural Research and Reports Management (301)-594-4490
CBRR-6	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. National, State, and University Officials Celebrate Opening of Center for Vaccine Research, Directed by Dean Burke 9/26/07 http://www.publichealth.pitt.edu/content.php?page=1064&context=ContextNews Duke Takes Local Approach to Global Biological Threats 2/13/07 http://www.dukemednews.org/news/article.php?id=10013
CBRR-7	ARIS is an internal management database. For more information, please contact Karin Lohman, Ph.D. at (301) 496-0357.
CBRR-9	Data used to calculate cost saving are maintained in either an internal database or total number of labor hours. For more information, please contact Susan A. Daniels, Ph.D. at (301) 435-0864or Lori Mulligan at (301) 435-0866.
Strategic Management of Human Capital (SMHC)	
SMHC-3	OIR Website, OIR Mentoring and Training Guide Contact: Dan Dupuis, Acting Deputy Director Office of Strategic Management Planning (301)-402-0622
SMHC-4	President's Management Agenda scorecards for NIH and HHS: - NIH Scorecard 2007 4th Quarter - HHS FY07 4th Quarter - Final Scorecard Contact: Name: Michael Tulenko Title: Director, Office of Competitive Sourcing Office: HHS/OS/ASAM Phone: 202-690-5803 Federal Business Opportunities announcements of two FY 2007 competitive sourcing reviews: - IT Systems Development: http://www.fbo.gov/spg/HHS/NIH/OoA/N06LM05/Modification%2001.html - IT Administrative Support: http://www.fbo.gov/spg/HHS/NIH/OoA/NO6LM06/Synopsis.html
SMHC-5	• HR Community Map (showing HR Communities & Pages) - http://hr.od.nih.gov/HRSystems/Portal/map.htm • HR Portal User Guides - http://hr.od.nih.gov/HRSystems/hrssuserguides.htm#portal
Program Oversight and Improvement (POI)	
POI-1	Office of Research Facilities Development and Operations DHHS Quarterly Buildings and Facilities Status Report Division of Capital Project Management Director"s Briefing on Capital Projects Contact: Clarence Dukes Program Manager, Strategic Initiatives Federal Programs Office of Research Facilities, Division of Technical Resources Policy and Program Assessment Building 13, Room 201 (301) 496-5078
POI-2	Obligations to PBC eligible service contracts are reported in DCIS. The obligations are reported throughout the fiscal year as monies were committed to various contracts throughout NIH. For source validation information, please contact: Derrick Montford Division of Acquisition Policy and Evaluation OAMP/OA/OM/OD Phone: 301-496-6014
POI-5	Notice of policy change in the NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-017.html, dated November 20, 2006, entitled "Establishment of Multiple Principal Investigator Awards for the Support of Team Science Projects". The NIH transition timeline for electronic submission of grant applications is posted at http://era.nih.gov/ElectronicReceipt/strategy_timeline.htm.
POI-6	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
POI-7	NIH Quarterly Report to DHHS HHS Facility Project Approval Agreement (N-05-001) and N-05-104 Contact: Clarence Dukes, Program Manager, Strategic Initiatives Programs, Office of Research Facilities, Division of Technical Resources (301) 496-5078
POI-8	NCRR Construction Grants Management System. For more information please contact Patricia Newman at (301) 435-0864.
POI-9	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.