DEPARTMENT of HEALTH and HUMAN SERVICES

National Institutes of Health

FY 2008 Annual Performance Report

NATIONAL INSTITUTES OF HEALTH
FY 2008 ANNUAL PERFORMANCE REPORT

INTRODUCTION

This FY 2008 Annual Performance Report provides information on the National Institutes of Health's actual performance and progress in achieving the goals established in the FY 2008 Annual Performance Plan which was published in February 2008.

The goals and objectives contained within this document support the Department of Health and Human Services' Strategic Plan (available at http://aspe.hhs.gov/hhsplan/2007/).

TRANSMITTAL LETTER
DRAFT Letter

I am pleased to present the Annual Performance Plan for FY 2008. This plan supported the President's and Secretary's priority initiatives and the goals and objectives in the HHS FY 2004-2009 Strategic Plan.

One of the greatest challenges facing our society is the skyrocketing growth of health care costs: health care currently accounts for more than $2 trillion in expenditures. The Centers for Medicare and Medicaid Services project that by 2016, the Nation's health care costs will reach a staggering $4.1 trillion. The most expensive way to practice medicine is to do it the way we do it now, where every interaction between patient and medical care system can involve as many as twenty people. Biomedical research supported by the NIH is an essential component in the effort to reduce this expense.

The Nation's return on investment in NIH includes declines in death rates for cardiovascular diseases and increase in cancer survivorship–only two examples of the many advances driven by NIH. These investments in NIH have brought us to where we can now clearly envision an era when the treatment paradigm of medicine will increasingly become more predictive, personalized, and preemptive, with greater participation by patients in the active management of their health. We expect to move away from today's costly and predominantly curative model of health care, which requires us to wait for the disease to occur before intervening, to a preemptive model.

The development of this performance report is consistent with the Government Performance and Results Act (GPRA). NIH uses GPRA and many other performance monitoring tools, such as peer review, site visits, and performance-based contracting, to continually assess program performance and to plan future research programs. NIH's effectiveness is recognized by the Office of Management and Budget through the Performance Assessment Rating Tool (PART) in six NIH programs assessed to date that comprise over 95 percent of our budget—the AIDS Research Program and Extramural Construction Program, which were scored as moderately effective—and the Extramural Research Program, Intramural Research Program, Extramural Research Training and Research Career Development Program, and Buildings and Facilities Program, which were all scored as effective.

The performance data reported for FY 2008 is accurate, complete and reliable. NIH has no material inadequacies in the data provided.

The NIH is one of the world's greatest assets for progress in health through rigorous science and evidence-based knowledge. NIH represents an investment in the health of the Nation and its global competitiveness in a century characterized by opportunities to make rapid progress in the life sciences across all of its applications.

Raynard Kington, M.D., Ph.D.

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OVERVIEW

The National Institutes of Health FY 2008 Annual Performance Report 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).* The matrix of research goals reflects low- to high-difficulty in achieving the outcome by the number of years the program estimates that it will take to achieve results. NIH research encompasses the support and conduct of investigations across the full range of the biomedical research continuum, including basic research, observational and population-based research; behavioral research; prevention research; health services research; translational research; and clinical research. Although each area of research has unique objectives, each may benefit from findings that may be applied to transdisciplinary research.

- *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 projects tailored to underserved populations. 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, ensure well-trained foreign collaborators, and facilitate scientists' aptitude for multidisciplinary teamwork. Capacity building also encompasses improving and maintaining the Nation's biomedical research infrastructure. 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. 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.

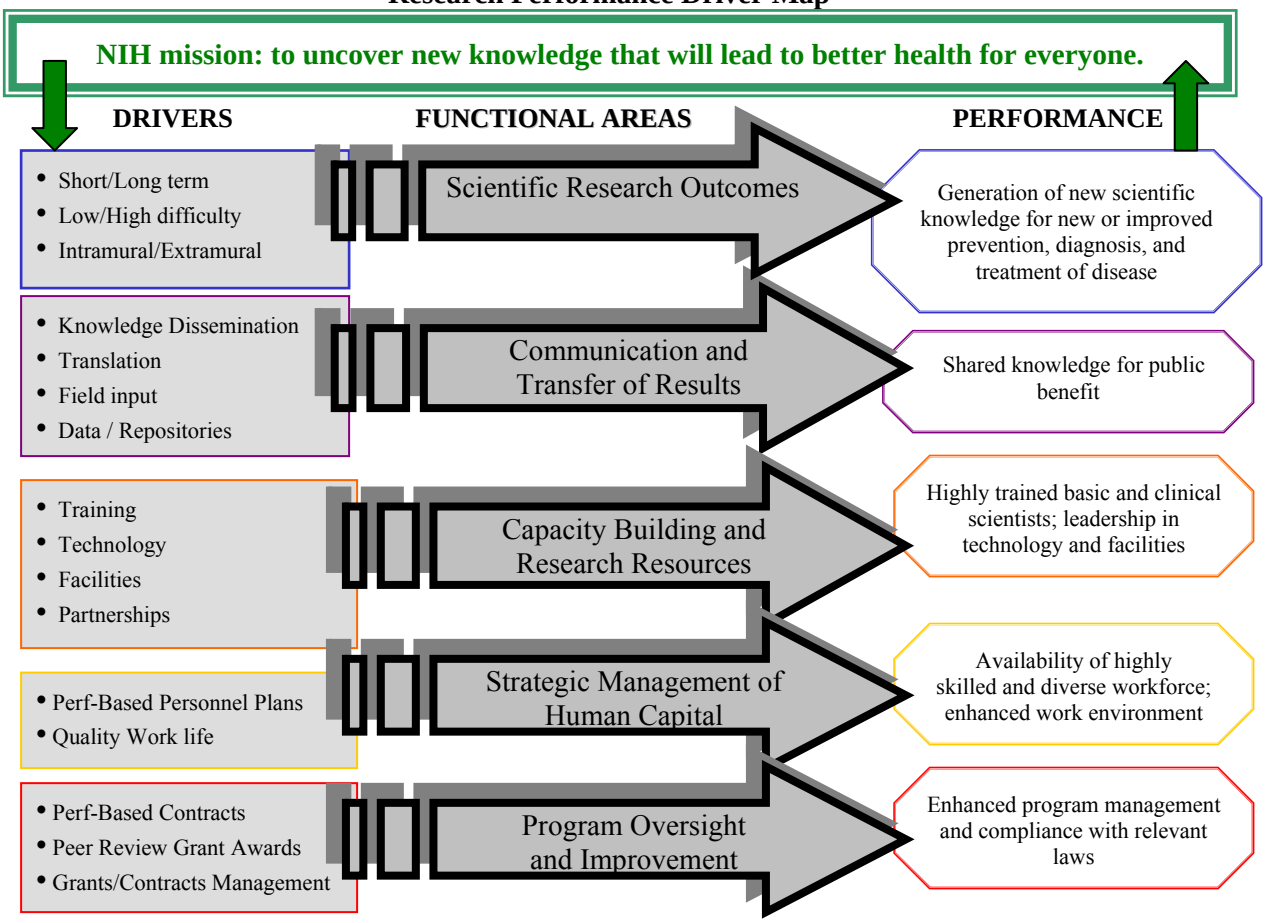
- *Strategic Management of Human Capital (SMHC).* NIH recognizes human capital as one of the most important resources of the organization. A qualified workforce, working in an environment that utilizes its strengths, fosters the effective and efficient implementation of the NIH research program. NIH 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.

Summary of Performance Goals per Fiscal year by Functional Area

Functional Area	FY05	FY06	FY07	FY08	FY09
Scientific Research Outcomes	36	35	36	45	47
Communication and Transfer of Results	5	5	4	5	4
Capacity Building and Research Resources	5	8	7	7	8
Strategic Management of Human Capital	3	3	3	3	5
Program Oversight and Improvement	7	7	7	6	6
Totals	56	58	57	66	70

National Institutes of Health: Balanced Portfolio
Government Performance and Results Act (GPRA)
Research Performance Driver Map



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 2008 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 and 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 agendas. 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. 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 step 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 66 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 Division of Program Coordination, Planning, and Strategic Initiatives 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 PERFORMANCE TARGETS AND 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 Performance Targets and Results Table

FY	Long Term Performance Goals	Total Targets	Targets with Results Reported *	% of Targets with Results Reported	Total Targets Met	Total Targets Extended	Total Targets Not Met	% of Targets Met
2005	56	82	78	95%	77	4	1	94%
2006	58	75	70	93%	69	5	1	92%
2007	57	76	75	99%	66	1	9	87%
2008	66	80	79	99%	72	1	7	90%
2009	70	83			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 51 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.

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
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.	**5.2** 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. **5.5** 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.	**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 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.

Difficulty	1-3 YEARS	4-6 YEARS	7-10 YEARS
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 providing patients access to optimal cancer care.	**8.2** By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals. **8.4** By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding. **8.5** By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease. **8.6** By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES). **8.7** 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.	**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 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

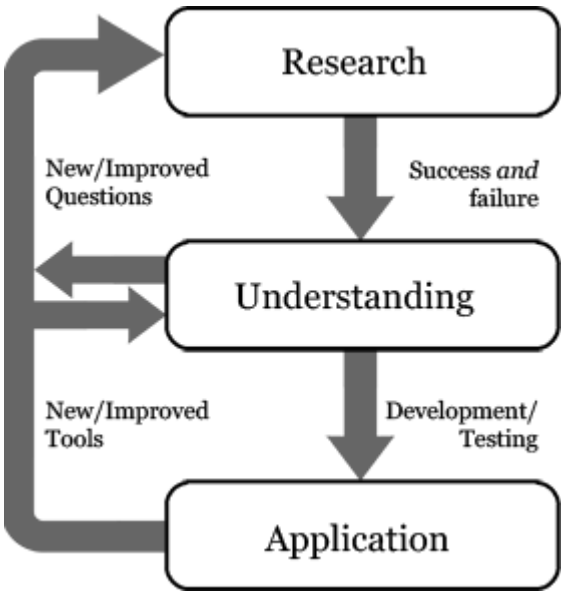
elements used to determine the level of risk/ambition/difficulty include predictability of outcomes, absence of clear pathways, delivery time, and needed resources.

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. Often considerable time will pass before a new approach to the problem (a new scientific opportunity) emerges. In addition, findings that did not validate a specific hypothesis may be used in other research efforts leading to new scientific knowledge. Thus, each NIH research result has merit and may prove critical in the realm of scientific discoveries.

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

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

SRO-1.1	**By 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 cause of death not attributable strictly to genetic factors, after tobacco and diet/activity patterns. Nearly 18 million American adults suffer from alcohol use disorders, i.e., alcohol abuse and alcohol dependence. Children also are at risk for alcohol related problems. 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 2008

- (FY06) Toxicology studies of antalarmin have been performed in monkeys and a phase IIa clinical trial of rimonabant has been conducted.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(EXT) For the drug antalarmin, the FDA requires further toxicology studies. Extended to 2007.	(MET) Toxicology studies of antalarmin in non-human primates were conducted as required by FDA.	Test antalarmin for relapse prevention in alcoholics. 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.	(NOT MET) Antalarmin studies were discontinued because of toxicity concerns.	

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target, extended from FY 2007, was NOT MET. Although a Phase I/II clinical trial of the drug rimonabant was conducted in 2007, a Phase I clinical trial of antalarmin has not been conducted because of toxicity concerns. Therefore, the 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, was NOT MET as antalarmin trials are not currently being pursued.

The results of initial toxicology studies of antalarmin raised concern about potential toxicity in humans, so clinical studies were deferred until the toxicological effects of antalarmin could be evaluated further as required by the Food and Drug Administration (FDA). Non-human primates, rats and dogs were tested and the results of these studies indicate antalarmin produces toxic effects above a certain dose for each species. For example, antalarmin caused kidney and liver toxicity in rats and neurotoxicity, GI problems and weight loss in monkeys.

This raises the possibility that antalarmin at or above certain doses may cause toxicity in humans. Since safe effective doses of antalarmin in humans are unknown and the margin of safety between effective and harmful doses may be not be large, antalarmin will not be pursued in the near future for testing in humans.

NEW STRATEGY

As a result of the safety issues encountered with antalarmin, NIH will pursue other compounds as potential treatments for alcohol dependence. Compounds under consideration may include a mechanistically diverse range of candidate molecular targets and may encompass different stages of development, i.e. preclinical and clinical. Pursuing a mechanistically diverse range of therapies will not only improve the likelihood of developing an effective treatment but also may pave the way for personalized medicine. While NIH is not currently planning to pursue antalarmin, finding new treatments for alcoholism remains a priority. Therefore a new goal will be proposed in the spring of 2009.

Advances or Other Highlights

Given the problems encountered with antalarmin, NIH is actively pursuing other CRH1 antagonists which have either completed toxicity studies or completed clinical studies for other psychiatric disorders. Some of the toxicity observed with this and other CRH1 antagonists may be mechanism-related; therefore, NIH explored another molecular target, the NK1 receptor. This receptor and its cognate ligand, substance P, play a key role in the control of stress responsiveness, similar to the CRH1 receptor. The results of a recent study indicate that NK1 antagonism may have an activity profile similar to that expected from CRH1 antagonists. First, deletion of the NK1 receptor in mice blocked voluntary consumption of alcohol. Second, oral administration of a NK1 receptor antagonist (LY686017) to recently detoxified alcoholics markedly reduced alcohol cravings induced by exposure to stress and alcohol-associated stimuli. Finally, the NK1 receptor antagonist reduced responses to negative emotional stimuli as measured by brain functional magnetic reasonance imaging (fMRI). This NK1 antagonist is therefore a promising candidate for more extensive clinical testing.

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.

Baseline 2008

- (FY07) Current robotic aides do not have feedback mechanisms.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Develop a suite of control and assessment software to allow treatment planning and evaluation.	(MET) Developed 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. Scientists have developed systems that can be used to guide an upper extremity robot to learn a patient's ability to complete a movement, to assist the patient in completing the movement, and to provide only the assistance needed. An adaptive controller ascertains a dynamic model of the patient's arm and develops a model of the patient's ability and effort. Based on these models, separate control algorithms for impeding and assisting movement can be developed and used.

Advances or Other Highlights

Researchers are also developing and refining devices specifically aimed at regaining function in the forearm and wrist, in the hand, and in the elbow and shoulder. To better engage patients in completing certain rehabilitative movements, investigators are exploring ways to integrate some of the devices with existing off-the-shelf video games.

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 understanding of the underlying causes 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 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 cell, from individuals with AUDs offer a potential solution for this problem. Immortalized cell lines consist of cells that replicate indefinitely when maintained under proper culture conditions. These cell lines provide an unlimited, renewable resource 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 cell line 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 from 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, may lead to severe and life-threatening complications, including heart disease, blindness, peripheral neuropathy, foot ulcers, and kidney failure. Treatment of type 1 diabetes 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

During FY 2005-07, the Clinical Islet Transplantation (CIT) Consortium investigators focused on: (a) the development of clinical protocols and a manufacturing batch record, (b) submission of protocols to health authorities, (c) completion of clinical trial agreements with industry partners, and (d) solving unforeseen problems that emerged regarding acquisition of raw materials and reagents for islet manufacture. During FY 2008-10, the targets are to initiate and complete enrollment in the CIT clinical trials.

The CIT is conducting 2 types of trials: (1) Phase II pilot studies of innovative interventions and (2) Phase III studies of consensus procedures. For the pilot studies, goals over the next three years will be: 1) to identify and terminate studies in which the intervention is demonstrably unsafe or less effective than consensus therapy, and 2) to continue enrolling patients in all the other studies. For those studies that achieve complete enrollment, the primary endpoint data are expected to be available for analysis in FY 2011. For the Phase III studies, the primary endpoint data will be available for analysis in FY 2012 with the caveat that the appropriate number of patients is enrolled in each trial.

Keys to achieving these goals will be:
1. Timely enrollment at all sites: enrollment will be monitored on a monthly basis, and impediments to enrollment will be identified and eliminated as necessary and possible.
2. Timely and accurate entry of data into the study database: all clinical sites will be monitored and where problems are identified, appropriate training/remediation procedures will be implemented.
3. Maintenance of regulatory compliance: all CIT studies are carried out under IND #9336, which is held by NIH.
4. Assurance of uninterrupted availability of the reagents and raw materials needed for islet manufacture: the CIT investigators and NIH will continue to evaluate alternate sources of these materials, and work with the FDA to determine where substitutions are possible without jeopardizing the integrity of the studies.

Baseline 2008

- (FY07) Zero subjects accrued in each trial.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) NIH initiated enrollment of individuals in five Phase III clinical trials and two Phase III clinical trials to evaluate the effectiveness of islet transplantation.	Continue enrollment into all trials, to reach target enrollments.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET and EXCEEDED as evidenced by enrollment of >100 subjects for assignment into the seven trials, with assignment to occur at the time that a pancreas becomes available.

- "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 http://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 FY07, 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. In FY08, A second collagenase enzyme, Vitacyte, was qualified for use in the CIT islet manufacturing procedure. More information on the CIT trials and recruitment of study subjects can be found at http://www.CITisletstudy.org.

Efficiency

As the Consortium developed five additional innovative clinical trials in the interest of moving the field of islet transplantation forward, NIH was able to begin enrollment in all seven 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.**

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 benefited greatly from new approaches to modify factors pervasive in the environment that promote overconsumption 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 six studies are evaluating the effects of interventions delivered in primary care settings to treat and/or prevent obesity in children and adults. 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. Specifically, the Weight Loss Maintenance Trial compared 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 2008

- (FY06) Few trials have adequately tested the effects of diets differing in macronutrient composition.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) Delivery of the 2-year interventions being tested in the POUNDS Lost trial has been completed.	Complete goal of evaluating the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. Delivery of the 2-year interventions being tested in the POUNDS Lost trial has been completed. All data collection for the trial was completed in January 2008. Results of the study are expected to be reported in FY 2009. The purpose of this study is to test the effectiveness for weight loss and weight maintenance of four diets differing in macronutrient composition: moderate in fat (40 percent energy) with two different protein levels (15 percent and 25 percent), and low in fat (20 percent energy), also with 15 percent and 25 percent protein levels.

Advances or Other Highlights

Three papers on the main results of the Weight Loss Maintenance Trial have now been

published. The Weight Loss Maintenance Randomized Trial found that adults who lost weight in a six-month lifestyle change program were able to keep more of the weight off for two years with brief, monthly personal counseling compared to a self-directed group. A web-based intervention also helped participants sustain their weight loss, but the benefit waned during the last six months of the trial. Investigators have provided data on a model of weight-reduced state as one of relative leptin deficiency.

Efficiency

Recruitment for the POUNDS Lost trial was completed 6 months early allowing the delivery of the 2-year interventions to be met early as well. This is a significant accomplishment for a Randomized Clinical Trial.

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 2008

- (FY06) Potential strategies for reducing symptom burden of patients with a chronic disease/illness identified.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) One intramural collaboration was established.	(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.	(MET) Researchers completed two studies that evaluated interventions for reducing pain. Both studies explored the biological mechanisms of analgesia in oral surgery models of acute pain.	Complete the goal of developing and testing 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Researchers completed two studies that evaluated interventions for reducing pain. Both studies explored the biological mechanisms of analgesia in oral surgery models of acute pain. In one study, scientists examined the mechanisms of two pain-reducing drugs, ketorolac and rofecoxib. Both of these drugs are nonsteroidal anti-inflammatory analgesics (NSAIDs) that are thought to reduce pain and inflammation by inhibiting cyclooxygenase, or COX, enzymes. Researchers compared expression levels of several proteins and their related genes in patients who had been treated with one of the two drugs to patients who not received either drug. The study examined tumor necrosis factor-α (TNF-α), a protein that plays an important role in inflammation. Its

expression is regulated by several biological factors, including COX, phosphodiesterase (PDE), and cyclic adenosine monophosphate (cAMP). Researchers found that neither drug had any effect on TNF-α gene expression. However, both of the drugs significantly reduced gene and protein expression of phophodiesterase type 4(PDE4D). This finding indicates a novel mechanism which may contribute to the analgesic and anti-inflammatory effects of these two COX-inhibiting drugs.

In a second study, researchers explored genetic mechanisms that could explain why some individuals respond differently to pain-reducing drugs than others. The molecular mechanisms that underlie pain vary among individuals over time and among different types of pain to produce wide inter-individual differences in pain perception and responses. Gender, ethnicity, temperament, and genetic factors, for example, contribute to individual variation in pain sensitivity and responses to analgesics. Testing a relatively small genomic region with a few hundred single nucleotide polymorphisms (SNPs) provides limited information. However, genome wide association studies (GWAS) provide an opportunity to overcome the limitations of candidate gene association studies. Using the GWAS approach, researchers identified a candidate SNP that was associated with responses to the pain reducing drug ketorolac. This SNP is involved with a gene that codes for a zinc finger protein, a type of protein that binds to DNA. This study suggests that genetic variations in or near genes that encode DNA binding proteins or protein interaction mediators play a role in clinical responses to analgesic drugs. These observations also suggest that differences in the way individuals respond to analgesic drugs may be induced by variations in genes that modulate DNA transcription.

Research remains ongoing to develop and test interventions for reducing symptom burden caused by symptoms such as acute pain. The two studies discussed here improve our understanding of the biological mechanisms that underlie pharmacological interventions such as NSAID analgesics. Future research will continue to provide a better understanding of the pain-reducing mechanisms of this widely used class of drugs and could lead to the development of more effective analgesics and better symptom management for patients experiencing pain.

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. Achievement of this goal is conditional on receiving the requested levels of funding.

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 that most appropriately recapitulate the human cancers. Such tests will validate the targets and demonstrate drug target effect in preclinical models and/or 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.

Baseline 2008

- (FY07) Novel targets have been identified.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Identify two novel targeted cancer interventions.	(MET) NIH investigators identified two novel targeted cancer interventions, indenoisoquinolines and 111In-Herceptin®.	Evaluate two targeted interventions using preclinical testing.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. NIH investigators identified two novel targeted cancer interventions; 1) indenoisoquinolines and 2) 111In-Herceptin®. Indenoisoquinolines have been identified as a novel class of cytotoxic molecules that exert their biological affects by inhibiting topoisomerase I, a protein essential for transcription and replication. 111 Indium CHX-A' ' DTPA Trastuzumab (111In Herceptin®) is a novel imaging agent that may facilitate the detection of certain types of cancer using a non-invasive approach.

Advances or Other Highlights

NIH investigators are pursuing the use of a class of compounds called indenoisoquinolines, derived from camptothecin, as anti-cancer agents. One advantage of this new class is that the compounds are more chemically stable than camptothecin. Indeniosiquinolines specifically target topoisomerase I (Top 1). Specifically, two indeniosiquinoline small molecules have been identified. Encouraging results in preclinical research studies are setting the stage for testing in the early phase clinic trial setting. NIH investigators have successfully identified a histone gamma-H2AX assay to assess whether the indeniosiquinolines have successfully inhibited Top1. This assay is a critically important component to assessing whether the agent has "hit its target" with gamma-H2AX serving as a sensitive biomarker.

NIH investigators are currently developing a radiolabeled imaging agent (111In Herceptin®). Preliminary data demonstrates the feasibility of using 111In Herceptin® as a tumor-targeted monoclonal antibody probe for multimodality imaging. Potential uses of imaging agents targeting epithelial growth factor receptors (EGFRs) include more accurate sampling of tissue, patient selection for drug trials, monitoring of therapies directed at EGFR or its downstream clients which impact EGFR expression, developing immuno-conjugates for delivering specific drug therapy and radioimmunotherapy in which therapeutic isotopes are attached to the antibody. Recognition of the role of EGFRs in the growth and progression of

tumors has had widespread implications for cancer treatment. Imaging represents a potentially important avenue of research because of its non-invasive nature and can assist in making better decisions about treatments. Imaging techniques can help doctors find cancer, tell how far cancer has spread, guide delivery of specific treatments, or find out if a treatment is working.

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 4-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. Robust biomarkers are needed that can be reliably detected in easily obtained biological samples that reflect biological responses to environmental stressors in human population studies. This involves a continual effort by the investigators over the reporting period.

Existing technologies are being adapted to detect analytes and identify biomarkers to improve the capabilities of exposure assessments. Currently, existing sensor technologies are focused on individual analytes with little temporal and spatial resolution as opposed to 'real world' environmental exposures. Similarly, biomarkers used in current studies are limited by a focus on individual gene or protein expression changes in the absence of information on pathway behavior. These sensor and biomarker discovery methods have many known limitations such as misclassification error, individual variability, temporal uncertainty, and sequential inaccuracy. These limitations in exposure assessment methodologies have produced conflicting data and hampered our ability to prevent, predict, and treat disease.

To overcome the known limitations of current technologies, enhancement and then validation are critical. In FY08 and FY09 the NIH will test sensor devices and biomarker profiles in laboratory settings, which will set the stage for later validation in larger

populations. In FY10 sensors and candidate biomarkers will undergo benchmark testing prior to population level analyses.

Baseline 2008

- Assessments of environmental exposures or biological response on a pathway level are inadequate.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Refine current technologies to demonstrate analyte specificity and sensitivity in benchtop assays, and identify pathways of response for important environmental exposures	(MET) Refined colorimetric array technology to improve specificity and sensitivity in detecting and measure toxic exposures. Characterized lung cell response pathways to cigarette smoke exposure, and blood cell response pathways to carcinogens.	Enhance current technologies to allow detection of multiple analytes, and use novel technologies to characterize the response in biological pathways to environmental exposures

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. NIH researchers refined colorimetric technology to improve analyte specificity and sensitivity, and research lung and blood cell responses to environmental exposures. Researchers have demonstrated the ability of a colorimetric array of nanoporous pigments to detect, identify and quantitate potentially toxic environmental exposures specifically a family of aliphatic amines, such as butylamine which is used in the manufacture of pesticides. Aliphatic Amines are non-aromatic organic compounds and functional groups that contain a basic nitrogen atom with an unshared electron pair. In this study, the researchers found that nanospheres synthesized from nanoporous pigments respond with specific changes in color, which can be monitored by changes in absorbance in red, green, and blue wavelengths. An array of 36 distinct such elements is capable of specifically detecting 11 closely related aliphatic amines which are known to be toxic industrial chemicals. The patterns of array response are highly reproducible and are quantitative at levels as low as 5 parts per billion, demonstrating high analyte sensitivity.

NIH researchers completed a preliminary study comparing the patterns of gene expression changes in smokers and nonsmokers in cells from the nose, mouth and lung. Patterns in the nasal samples correlated well with those in the lung cells and show promise as a biomarker from noninvasive samples that can be used to characterize pathway responses to cigarette smoke exposure. In addition, NIH researchers developed a simple method to isolate blood proteins from dried blood spots for detection of protein adducts, a means to monitor internal exposure to carcinogens. This method was applied to measuring exposure to benzene and products of benzene metabolism. Dried blood spots may be ideal for measuring exposures to carcinogens because many states have extensive sample archives collected postnatally.

Advances or Other Highlights

Researchers developed technology to detect gene mutations in single cells. This technology will make it possible to detect early molecular markers for numerous diseases, including blood cancers. A required step in the development of this technology is the ability to generate uniform nanoliter-size droplets with high-throughput capability. This group of researchers has successfully developed a microfabrication device that is capable of generating 1 million droplets/hour. This technology has been applied in preliminary studies to monitor mutations in the p53 gene, a gene that is commonly mutated in many cancers.

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.

Baseline 2008

- (FY07) Several new potential therapeutic targets have been identified through basic research on the biological effects of chemical exposure

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Determine whether three molecules associated with chemical injury show promise as new therapeutic targets	(MET) Modifying the activity of TRPA1, GluR5K5, and EP had protective effects in models of chemical injury	Develop a prototype technology to diagnose chemical exposure in an emergency setting

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. CounterACT researchers have shown that modifying the activity of three different receptors associated with chemical injury may be viable strategies for protecting the body from damage. Researchers have identified a family of sensory protein receptors that activate nerve endings in response to chlorine and other toxic industrial chemicals. One particular receptor, TRPA1, was the major airway sensor for chlorine, and that mutant mice missing the TRPA1 receptor were insensitive to chlorine exposure. The efficacy of TRP blockers in preventing symptoms of chlorine exposure is now being tested.

GluR5KR, a different type of receptor, has also been validated. Inhibitors of GluR5KR prevented seizure-like electrical activity in slices of rat brain that had been pre-treated with the nerve agent soman and the effects of these inhibitors in rats exposed to soman are now being examined. .

Researchers found that activating the prostinoid receptor EP2 may be able to protect the nervous system from neurodegeneration and neuroinflammation caused by chemically triggered seizures. EP2 is a component of a pathway that had been linked to neuronal injury following prolonged seizures. The CounterACT researchers found that activating EP2 in cell culture toxicity assays reduced levels of inflammation and toxicity markers. Follow-up experiments are underway using rodents exposed to a nerve agent analog.

Advances or Other Highlights

Midazolam continues to show promise for the treatment of nerve agent-induced seizures. The definitive animal efficacy studies required for FDA approval and conducted in collaboration with the Department of Defense are nearly completed, with positive results. The clinical trial was temporarily halted by the FDA, based on concerns about the study design, but the hold has been lifted and patient recruitment has begun.

Cobinamide, a new cyanide antidote, is advancing quickly through preclinical development. CounterACT researchers found that cobinamide provides increased survival over current treatments (sodium nitrite, sodium thiosulfate, and cobalamin). Preclinical safety and pharmacology studies are being conducted at the CounterACT Preclinical Development Facility. An IND submission is planned within 1-2 years. Capitalizing on the ability of cobinamide to tightly bind cyanide, a device for detecting cyanide in human blood or urine has been developed and will be tested in a clinical study comparing this new technique to standard tests. This is being done as an add-on to an NIH-supported trial on sodium nitroprusside, a high blood pressure treatment that generates cyanide when metabolized.

Galantamine, an FDA-approved Alzheimer’s Disease drug, lowered death rates when administered to animals prior to nerve agent exposure. CounterACT researchers are currently optimizing treatment regiments (doses and timing) for both sexes, at different ages, using a guinea pig model. Studies are also underway to confirm preliminary studies showing that galantamine reduces mortality and morbidity when given after nerve agent exposure.

CounterACT researchers have discovered that intravenous administration of the growth

factor neuregulin prior to exposure to nerve agent analogs protects rats from mortality and severe neurological symptoms. Neuregulin also appears to have positive effects when administered after chemical exposure. Experiments are underway to confirm these results. Pharmacology and toxicology studies are being conducted at the CounterACT Preclinical Development Facility.

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.

Baseline 2008

- (FY07) Oligonucleotides show promise in enabling cells to repair or bypass MD-causing mutations

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Test a new strategy to improve the efficacy of an oligonucleotide-based therapy in animal or cell models	(MET) Three oligonucleotide strategies were found to restore gene expression in cell or animal models of MD	Test a new strategy for systemic delivery of a therapeutic gene in a large animal model

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Oligonucleotides have been developed that can make gene transcription machinery "skip" whole coding fragments, also known as "exons," containing harmful DMD mutations. In the dystrophin gene, exon deletions are not as harmful as smaller mutations and "exon-skipping" is seen as a potential therapeutic alternative. Recently, researchers found a way to enhance the function of exon-skipping oligonucleotides by attaching to them a cell-penetrating peptide (the fragment of a protein that facilitates cell-entry.) Injection of these fusion compounds into mdx mice produced wide-spread dystrophin

expression and near-normal muscle architecture in all non-cardiac muscle groups.

The potential for personalized oligonucleotide therapy in patients with more unusual mutations in the dystrophin gene has been shown also. Muscle cells isolated from patients with rare mutations in the non-coding region of the dystrophin gene were restored dystrophin expression after treatment with oligonucleotides designed specifically for each of the patients' mutations.

A more experimental approach involves the use of oligonucleotides to make the protein translation machinery "fix" mutations that alter the way the coding sequence of a gene is interpreted. Often called "frame-shift mutations", these mutations can produce aberrant proteins or can cause the absence of the protein altogether. Through an NIH exploratory/developmental award in translational research, a group has shown that oligonucleotides can be used in cultured mammalian cells to correct frame-shift mutations. The researchers are now testing this technique in mdx mouse cells.

Advances or Other Highlights

1) Test a new strategy for systemic delivery of a therapeutic gene in a large animal model

NIH-funded researchers have shown that single intravenous injections of vectors carrying shortened versions of the dystrophin gene can reach all types of skeletal muscle in a canine model of DMD. Gene delivery was only successful in young pups and did not require immune suppression or additional pharmacological intervention. Unfortunately, cardiac and smooth muscle was not efficiently transduced. The results suggest that gene therapy might be more feasible in infants that have yet to develop a robust immune system and which do not yet exhibit the symptoms of DMD. There is also a plan to expand the number of dogs tested and analyzed.

Researchers are also testing a technique known as "afferent transvenular retrograde extravasation" (ATVRX) that involves use of a high pressure injection of saline in conjunction with typical gene-delivery techniques to improve gene uptake by skeletal muscles. The force from the high pressure injection seems to push the vectors from the blood vessels into the muscles, increasing the efficiency of the therapy. The technique was found to be effective for gene delivery in healthy dogs and is now being tested in dog models of DMD.

Progress has been made towards an IND by showing that vascular delivery of a microdystrophin gene vector improves muscle function in mdx mice. The delivery technology is being further refined and the safety of the construct in rhesus macaque monkeys is being tested.

In the last year, two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers have been awarded, one of which will focus on comparing and optimizing localized and systemic gene delivery methods in the dog and on testing the safety of intravenous treatments in muscular dystrophy patients.

2) Assess the activity of two promising small molecule drugs in cell and animal models

A public-private partnership funded by NIH, Parent Project Muscular Dystrophy, and PTC Therapeutics has started to chemically optimize small molecules that alter the levels of four proteins (utrophin, myostatin, IGF-1a, and α7 integrin) that have been shown to affect the muscular dystrophy disease process. For each protein, three chemical classes of compounds have been identified that produce the desired protein-level changes in an in vitro high-throughput screen. Each class of compound is being chemically altered to analyze the structure-function relationship, optimize the effect on the protein, and ensure that the compound is not harmful to cells. The compounds are also being tested in cells isolated from animal models of DMD.

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 ravages memory and thinking skills, eventually destroying the ability to carry out even the simplest tasks of daily living.

- Recent data from the Aging, Demographics and Memory Study (ADAMS), a sub-study of the NIH-supported Health and Retirement Study, indicate that some 2.4 million Americans over age 71 currently have AD. The ADAMS study is the first to estimate rates of dementia and AD using a nationally representative sample of older adults across the United States.
- The ADAMS report is the latest published study to estimate the prevalence of dementia and AD among older Americans. These assessments have provided a range of estimates, based on differing methodologies and approaches; for example, some studies have included lower age ranges than ADAMS, or have sampled participants in a specific community as a base for national extrapolations.
- Notably, widely cited estimates based on the prevalence of Alzheimer's disease in a Chicago-based community (Hebert et al., 2003), and an earlier, comparable study using data from East Boston (Evans et al., 1990) forecast the number of those age 65 or older with AD to reach 5.1 million by 2010.

Despite the varied approaches and findings, however, experts agree that as increasing numbers of Americans reach older age, the numbers of people with dementia, and AD specifically, will certainly increase until ways to delay or prevent the disease are found. Advancing age is the most common known risk factor for Alzheimer's disease.

Disease Burden

The direct and indirect costs of Alzheimer's and other dementias to Medicare, Medicaid businesses, and families are estimated to amount to more than $148 billion each year. Also significant is the physical and emotional toll AD exacts on family, caregivers, and friends. The changes in a loved one's personality and mental abilities; the need to provide constant attention for years on end; and the demands of bathing, dressing, and other caregiving duties can cause tremendous stress to the caregiver, often impacting his or her health and well-being. Not surprisingly, caregivers of people with dementia spend significantly more time on caregiving tasks than do caregivers of people with other types of illnesses.

Rationale

The few agents that are currently approved by the Food and Drug Administration for treatment of Alzheimer's disease have demonstrated only modest effects in modifying the clinical symptoms for relatively short periods. Likewise, the first and, to date, only agent shown to delay clinical diagnosis of AD in people with mild cognitive impairment (donepezil

[Aricept®]) appears to forestall the transition from MCI to full-blown AD for only a brief period of time. However, a number of promising findings are now emerging to provide directions for 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 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 scientists learn more about how those at risk can take steps to reduce the possibility of developing Alzheimer's. In late 2004, the NIH, in conjunction with several other Federal agencies, private companies, and organizations, launched the Alzheimer's Disease Neuroimaging Initiative (ADNI) to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The study could help researchers and clinicians develop new treatments and monitor their effectiveness as well as lessen the time and cost of clinical trials. The project is the most comprehensive effort to date to find neuroimaging and other biomarkers for the cognitive changes associated with MCI and AD. [FY05 and FY10 performance targets]
- Genetics. Until recently, only one risk factor gene for late-onset AD, apolipoprotein E-ε4, had been identified; in late 2007, investigators identified a second gene, SORL1. 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 is necessary to establish a data base for studies of familial inheritance of AD. Thanks to an unprecedented alliance of AD Centers, researchers, and outreach personnel, aided by the Alzheimer's Association, this target was achieved. [FY06 performance target]
- 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 ε-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. [FY07 performance target]
- 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/or

early toxicology screening. As new agents are identified, these steps will need to be taken in all of them. [FY08 performance target]

- Clinical Trials. In 2003, the NIH launched the Cholesterol-Lowering Agent to Slow Progression of Alzheimer's Disease (CLASP) study, which investigated the safety and effectiveness of the drug simvastatin to slow the progression of AD. The results of this trial were presented orally at the International Conference on Alzheimer's Disease in July 2008 in Chicago, and the results indicated that there was no effect of simvastatin on progression of Alzheimer's disease. Other clinical trials are ongoing; the NIH also plans to use the knowledge gained through the basic and mechanistic studies described above to select the most promising imaging and biological markers, as well as improved clinical and neuropsychological evaluation methods, to perform less expensive, shorter, and more efficient drug trials. [FY 03 performance target (simvastatin); FY 09 performance target and beyond]

Baseline 2008

- (FY06) It is anticipated that 1-3 promising drug candidates will emerge from NIH's research programs by FY 2008; these have not completed the preclinical steps necessary for regulatory approval.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) The NIH launched the Alzheimer's Disease Neuroimaging Initiative in late 2004.	(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.	(MET) NIH-supported investigators identified the compound MW01-2-069A, which reduced brain inflammation and behavioral deficits in a mouse model of AD.	Start at least one pilot clinical trial on promising interventions based on results of previous trials and new leads for drug discovery.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. NIH-supported investigators identified the novel compound MW01-2-069A and demonstrated its efficacy in a mouse model of Alzheimer's disease. MW01-2-069A was found to reduce inflammation related to AD pathology; behavioral deficits; and dysfunction at the synapse (the site – a tiny gap between brain cells- across which either chemical or electrical signals pass) in the mouse.

Advances or Other Highlights

NIH supports the preclinical development of new drugs for Alzheimer's disease through cooperative agreement grants funded under program announcement PAR05-148, "Alzheimer's Disease Drug Development Program." Eight projects are currently underway, including studies of anti-hypertensives, anti-inflammatory drugs, and novel small molecules. These grants include a number of steps in the drug development process, including assessment of efficacy in animal models. In 2008, the program announcement was re-issued as PAR08-266; it is anticipated that additional meritorious projects will be funded across the life of that PA. In addition, NIH supports a contract for preclinical toxicological evaluation of potential therapeutic drugs for Alzheimer's disease.

In recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. For example, in 2008, Allon Therapeutics reported the results of a clinical trial of the compound AL-108 in people with mild cognitive impairment (MCI, a precursor to Alzheimer's disease). In this study, AL-108 had a positive impact on amnestic MCI and was safe and well tolerated. The original pre-clinical toxicology studies with AL-108 were conducted through the NIH pre-clinical toxicology contract, and the results of these toxicology studies led to FDA approval of an investigational new drug application allowing Allon Therapeutics to conduct human clinical trials on AL-108, including this trial on MCI. Although NIH did not support this trial, it's certainly worth noting that it was NIH support of the preclinical work that made the trial possible.

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.

A "universal antibiotic" is defined as any broad-spectrum antibiotic/antimicrobial/anti-infective that is effective against multiple biological pathogens. This may include: antibiotics with demonstrated efficacy against multiple gram negative and/or gram positive bacterial species, possibly including drug-resistant strains or biodefense priority pathogens for which there are few or no available drugs; broad-spectrum antivirals that demonstrate activity against multiple viruses, possibly including viruses belonging to different viral families; broad spectrum anti-infectives that may have efficacy against more than one species of parasite; antimicrobials that may have activity across two or more of the groups mentioned above (bacteria, viruses and parasites); and immunomodulators that generally strengthen the body's ability to fight a variety of different infectious diseases. While some broad-spectrum antibacterial drugs are currently available, many of those are ineffective against drug-resistant bacteria or unproven against biodefense priority pathogens. No major broad-spectrum antivirals, anti-infectives or immunomodulatory drugs have been developed to date. A "universal antibiotic" with broad-spectrum activity against multiple pathogens, such as those described above, would add a significant new capability to treat infectious diseases for which few or no therapeutics currently exist.

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

NIH's standard role in product development is to support basic research (fundamental discovery and identification of product concepts), applied research (subsequent efforts to refine concepts and develop candidate products) and advanced R&D (preclinical and clinical development). Once a candidate product has been developed through Phase I/II clinical testing, the developed candidate product may move from NIH to a partner, which can be a drug company, another government agency or a public-private partnership, for commercial scale development and activities leading toward licensure, marketing, government acquisition and/or utilization (including emergency use). In the case of products of high priority to the US government for biodefense and emerging infectious diseases, Congress has created the DHHS Biomedical Advanced Research and Development Authority (BARDA) to support advanced product development activities, and Project Bioshield to facilitate acquisition of those products for the US Strategic National Stockpile.

To accomplish the goal of developing one universal or broad-spectrum antibiotic/antimicrobial/anti-infective, NIH is stimulating basic and applied 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 also supports preclinical and clinical development services to facilitate the advanced R&D phases of product development leading toward a candidate product.

Baseline 2008

- (FY07) NIH has not yet begun safety and pharmacology profile determinations for candidate compounds that have demonstrated broad spectrum activity in vitro.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) NIH began determining safety and pharmacology profiles (e.g. bioavailability) of two candidate compounds.	Conduct IND enabling toxicology and preclinical animal studies on at least 1 candidate compound that has shown broad spectrum activity in vitro.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET and exceeded. NIH began determining safety and pharmacology profiles (e.g. bioavailability) of two candidate compounds that have shown broad spectrum activity in vitro.

Cysteine proteases play a number of essential roles in the biology of parasitic organisms, including general catabolic functions and protein processing, as well as more recently characterized roles in immunoevasion, excystment/encystment, exsheathing and cell and tissue invasion. The presence of cysteine proteases in many parasitic organisms make these proteases an ideal target for anti-infectives. K777 (N-methyl-piperazine-Phe-homoPhe-vinylsulfone-phenyl) is a novel cysteine protease inhibitor under investigation as a therapeutic candidate for several parasitic diseases. K777 has shown activity against the parasites that cause Chagas' Disease, African Sleeping Sickness, schistosomiasis and cryptosporidiosis. K777-related compounds that target other cathepsin-L like proteases also potentially expand the antimicrobial spectrum of this class of drugs to cover parasites such as Giardia and Entamoeba. In addition, K777 appears to be able to disrupt cysteine protease-mediated entry of viruses into host cells. Recent studies have shown that second generation K777-related compounds are active against viral diseases such as SARS and Ebola. Thus, K777 and related compounds represent a new class of antiinfective/antimicrobial with potential broad spectrum indications.

Through the preclinical services program, NIH has supported metabolic, pharmacokinetic and NDA-enabling toxicology studies for K777 as a candidate therapeutic for Chagas' Disease. Metabolism and pharmacokinetic profiles of K777 were evaluated in one study. For the metabolism portion of the study, rat and human microsomes were incubated with K777 in vitro. Major metabolites of K777 were identified. The bioavailability of and pharmacokinetics of both oral and intravenous K777 were determined a rat model system. They found that oral bioavailability was higher in females than in males, and that the drug appeared to cycle between the liver and intestines. K777 toxicity was also studied, and they found that all rats tested with single dose, 7 day or 14 day regimens survived. Chronic administration seemed to result in increased clearance of K777 from the system. At the highest dose (300 mpk), liver damage was observed. Results of the study suggest that low doses had no observed adverse effects and would be preferable for use in future clinical studies.

NIH also supported preliminary metabolic and pharmacokinetic studies of another type of novel broad spectrum antimicrobial, FabI inhibitors, that have shown antibacterial activity against several distinct bacteria, including Mycobacterium tuberculosis (the causal agent of tuberculosis) , Staphylococcus aureus, multidrug resistant Staphylococcus aureus (MRSA), Francisella tularensis (the causal agent of tularemia) and Burkholderia pseudomallei (the causal agent of melioidosis). The last two organisms are NIH priority biodefense pathogens. Homologs of the FabI, an enoyl-ACP reductase enzyme involved in fatty acid synthesis, are found in the genomes of many bacterial species, including many Category A-C agents. Thus, FabI is an important potential broad spectrum antimicrobial target.

NIH-supported investigators have performed bioavailability, pharmacokinetic and metabolic studies on the FabI inhibitor PT04. They found that PT04 is more rapidly metabolized in mouse cells than in human cells (as expected) and that several metabolites are formed in in vitro studies with human and mouse microsomes. Bioavailability was assessed by administering PT04 to mice orally, intraperitoneally and intravenously. They identified a dose that, when administered orally, yields a blood concentration that is adequate to inhibit the growth of bacteria.

Efficiency

NIH was able to exceed the target due to focused efforts to develop broad spectrum antimicrobials, including multiple concurrent initiatives and programs working toward this goal. As a result of this multi-pronged effort, in FY2008, two broad spectrum antimicrobial candidates reached the stage of readiness to begin determination of safety and pharmacology profiles.

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

BACKGROUND

Saliva assists with intake and digestion of food as we chew and swallow. It also contains information about many physiological aspects of health and bodily function. Properties of saliva, including quantity, thickness, smell, and taste, have been associated with diseases for many years. However, in spite of ongoing saliva research, blood has been much more often used than saliva to detect disease and other biological conditions because most molecular compounds that are found in saliva are also found in blood but in larger concentrations.

For many serious health conditions, early detection offers the best hope for cure. Unfortunately, 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

Over the last several decades, scientists have begun to talk more actively about using a person's saliva to detect a range of oral and systemic diseases. Saliva is easy to collect and poses none of the risks, fears, or invasiveness concerns occasioned by blood tests. Unlike blood, which involves a painful needle stick, must be carefully processed, and often sent elsewhere for analysis, saliva can be collected quickly and painlessly and possibly analyzed right there in a dentist or doctor's office. The possibility exists for test results to be delivered within minutes, allowing patient and health professional to consult immediately and develop a plan of follow up care.

Recent research advances in two major areas, the identification of disease biomarkers and the development of biosensor micro-technology, have supported the field of salivary diagnostics and are making new diagnostic tools a reality. Miniaturization of the "lab on a chip" may allow placement of the detection device directly in the mouth, facilitating sample collection. As oral levels of most molecules and proteins of interest are lower than blood levels, sensitive analytical techniques are required. 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 substances 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 as part of research to determine the efficacy of salivary diagnostics. 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

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, development will proceed on 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 compact 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 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 information necessary for scientists to harness, from saliva, the proteomic elements that will mark clinical diseases such as caries, Sjögren's syndrome, and oral cancer.

The sequence of activities leading to knowledge of the efficacy of a compact biosensor for salivary diagnostics is complex. Advances have to be made in biomarker identification (the Human Salivary Proteome program) and in micro-technology (the Salivary-based Diagnostic Technologies program). NIH-funded research has pointed to the potential of salivary markers in cancer, auto-immune disease, and diabetes. The NIH will continue to study salivary biomarkers for these and other diseases through the proteome database. Funded research has also led to the development of hand-held prototypes of biosensors for salivary diagnostics, which will continue to be supported.

Pre-clinical research activities leading to the routine use of a compact biosensor for salivary diagnostics include the selection of a specific disease for research, identification of biomarkers in saliva that are sensitive and specific to that disease, the tailoring of those disease biomarkers to the biosensor, and preliminary engineering of the biosensor. Once basic technological needs are achieved in prototypical devices, limited refined production of the biosensor will be undertaken so that pre-clinical tests can be conducted. These pre-clinical tests would address such questions as the method of sample collection (suction, spit, or swab, for example), sample volume, sample storage, and display and recording of sample information on the biosensor. Following these pre-clinical tests, clinical trials can be developed. The clinical trials of the device will address accuracy, reliability, and utility of the device in human samples.

Baseline 2008

- (FY06) Scientists have begun efforts to design bioinformatics systems to store salivary proteomics data.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Integrated microfluidic assay systems have been developed to measure C-reactive protein in saliva.	(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.	(MET) A bioinformation management system has been designed and developed. The SPKB system currently stores searchable information on 1166 proteins.	Complete integration of the individual components of the compact device and establish the limit of detection, accuracy, precision and specificity for the device in detecting analytes associated with both oral and systemic diseases.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. The NIH designed and developed the Salivary Proteome Knowledge Base (SPKB), the only web resource dedicated to the biology, pharmacoproteomics, and pharmacogenomics of human saliva. The knowledge base is searchable by accession number, description, source material, and research group and includes sequence information, peptide coverage, and certain data elements of the experiments. Also, the listed proteins are linked to additional external protein databases for further information. Researchers can use the database in a variety of ways. For instance, scientists might select a particular uncharacterized protein and submit their own research data demonstrating that the protein also is present in the brain, where it functions in a specific way. The basic design of SPKB is complete and periodic updates, enhancement, and development of new features will continue.

As part of creating the scientific infrastructure for salivary diagnostics, the researchers needed to catalogue the genes and protein content of normal saliva, giving them a point of comparison to detect the other molecules that might appear and indicate developing disease. Toward this end, NIH supported large collaborative projects that created the first complete record of the genes and proteins found in saliva. NIH-supported scientists have finished compiling a comprehensive roster of 1166 distinct proteins that are normally present in saliva from the major salivary glands. The SPKB currently houses data from three NIH-supported salivary proteomic projects making it available online to the salivary research community.

Advances or Other Highlights

Showing the diagnostic power of the SPKB knowledge base for the first time, an NIH grantee identified 43 proteins and 16 peptides that were present at abnormally higher or lower levels in the saliva of people with primary Sjögren's syndrome. This surpasses previous efforts to identify protein biomarkers for this condition. Primary Sjögren's disease affects roughly two million Americans, primarily women, and can be difficult to diagnose. Collaborations have begun between scientists in the United States and Europe to validate the most informative of these proteins as telltale signs of Sjögren's syndrome. In addition, diagnostic tests for various cancers also are being developed. With this knowledge base of salivary genes and proteins now in place, similar findings may emerge in the years ahead and might lay the scientific foundation for point-of-care salivary diagnostics in the future.

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.

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. 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

NIH recently redesigned its strategy for HIV/AIDS vaccine research, in response to several factors. In late 2007, two Phase II trials (STEP and the related Phambili trial) of a Merck-designed HIV/AIDS vaccine were stopped before reaching the planned conclusions because the mid-trial data from the STEP study demonstrated that the vaccine failed to prevent HIV infection and also did not affect the level of HIV in those who were vaccinated but still became infected with HIV. Scientists continue to analyze data and samples from the volunteers to clarify why this vaccine might have even increased the risk of infection in a subset of study volunteers who were uncircumcised and who, at the time they enrolled in the trial, had naturally occurring neutralizing antibodies to adenovirus 5, the virus used to make the vaccine vector that delivered the HIV vaccine. In addition, recent basic and preclinical research studies in non-human primate models of AIDS suggest that the window of opportunity during which a vaccine can trigger immune responses to stop the virus from gaining a foothold is shorter than originally thought (days to a week, not several weeks). These scientific factors and significant resource constraints have driven NIH to redesign its vaccine research strategy to ensure the most efficient use of resources.

When the STEP trial was stopped, numerous consultations were held to discuss the future directions of vaccine research efforts. In March 2008, the NIH convened a summit on HIV vaccine research and development to garner input from experts in the field regarding the most appropriate balance between vaccine discovery and development. During the summit, panels of experts facilitated discussion within three broad areas: vaccine-related basic research, vaccine discovery and vaccine development; animal model development and utilization and clinical research and trials. Consensus emerged from the summit that traditional approaches to vaccination are likely not to be effective for HIV prevention. A shift in the balance between product development and discovery of innovative vaccine concepts was recommended to ensure flexibility and streamlining of discovery research. There was also consensus that NIH should be more selective in moving candidate vaccines into clinical trials and that non-human primate studies should be performed in parallel with human studies to determine whether a vaccine candidate should be developed.

To begin shifting the balance between basic and clinical HIV vaccine research, two new Requests for Applications (RFAs) were released during FY 2008. The Basic Vaccine Discovery RFA aims to accelerate vaccine discovery efforts by generating new knowledge to inform new conceptual approaches to vaccine design. The Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT) RFA aims to stimulate the development of novel, unconventional, high-risk, high-impact approaches. Awards for both initiatives are expected to be made in July 2009. As a result of this shift, new awards for two long-standing programs will be paused for at least a 2-year period, the Integrated Preclinical/Clinical AIDS Vaccine Development Program and the HIV Vaccine Design and Development Team. This will slow the opportunity to advance vaccine candidates into phase I trials.

During FY 2008, NIAID established a new branch within the Vaccine Research Program at the Division of AIDS. The new Vaccine Discovery Branch will accelerate the translation of basic discoveries about HIV into advances in vaccine design and evaluation. It will monitor scientific developments in multiple fields related to HIV vaccine discovery, build more bridges between basic researchers and HIV vaccine designers, identify gaps in knowledge pertinent to a preventive HIV vaccine and promote research to fill those gaps. In addition, the new branch will oversee the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of universities and academic medical centers established by NIH to solve major problems in HIV vaccine development and design.

Baseline 2008

- (FY06) NIH is conducting 3 phase I/II trials (HVTN 502, HVTN 050, HVTN 204) of products that might be further tested for protection across viral clades (or subtypes).

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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).	(NOT MET) NIH did not initiate a Phase IIb trial of a promising vaccine candidate.	Begin analyzing final data from a phase III trial of a second generation vaccine.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was NOT MET. The Phase IIb trial of a vaccine candidate that held promise for protecting across viral clades (or subtypes) of HIV was not initiated because a different study of a somewhat similar vaccine was stopped prematurely in September 2007.

The prematurely stopped trial was the STEP trial (HVTN 502). This study was testing Merck's vaccine candidate, the MRK Ad5 HIV-1 gag/pol/nef trivalent vaccine. This vaccine is based on a weakened adenovirus (adenovirus type 5, or Ad5), a common virus that normally causes upper respiratory infections, such as the common cold, but that has been altered to render it unable to replicate and infect humans. The trial involved 3,000 men and women who were at high-risk of acquiring HIV in Australia, Brazil, Canada, the Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico and the United States. These are regions where HIV clade B is most prevalent. The study was designed to determine if the vaccine would help participants with low initial levels Ad5 antibodies by either reducing HIV acquisition or lowering the viral set point, or level of infection, in patients who did become infected. A second hypothesis was that the vaccine would reduce risk of acquisition or lower the viral set point for the whole study population, regardless of Ad5 antibodies.

During FY 2008, an independent Data and Safety Monitoring Board (DSMB) met to review interim data obtained from the volunteers with low Ad5 antibody levels and recommended that the trial be discontinued because it would not meet its efficacy endpoints. As a result of the DSMB review, the NIH, Merck and the HIV Vaccine Trials Network (HVTN) agreed to cease immunizations with the investigational vaccine and continue scheduled follow-up site visits with all volunteers until the data could be more thoroughly evaluated and a course of action developed.

Additional analyses of the STEP data subsequently found that there was a trend toward an increased risk of HIV infection among vaccinees compared with placebo recipients; this risk was greatest among males who were both uncircumcised and had pre-existing neutralizing antibodies to Ad5. Vaccination resulted in no apparent increased risk in men who were circumcised and who lacked pre-existing neutralizing antibodies to Ad5. The data at that time included only one woman and one heterosexual man who had acquired HIV during the study. Therefore, there was little information about the effects of the vaccine in women or in heterosexual men.

The same Merck candidate HIV vaccine was also being tested in South Africa by the HVTN and the South African AIDS Vaccine Initiative in a separate NIH-sponsored clinical trial known as HVTN 503 or the Phambili trial. The independent DSMB that oversees the Phambili trial met to review all available HVTN 503 and STEP interim findings and recommended that that trial also be stopped.

Following the early termination of the STEP trial, plans to implement the PAVE 100 trial were immediately put on hold. This Phase IIb trial would have tested a vaccine candidate that had promise of providing protection across viral clades were immediately put on hold. The vaccine regimen, developed by NIH's VRC, consisted of two components; an Ad5-based "boost" component is administered to boost immune responses stimulated with the "prime" component, a DNA vaccine. Based on data from the STEP trial, PAVE 100 was redesigned and reduced in its proposed scope. The redesigned PAVE 100 study would have involved testing the VRC vaccine in 2,400 rather than 8,500 and would have been conducted only in U.S.-based, circumcised men who have sex with men and who lack preexisting neutralizing antibodies to Ad5. The redesigned study would have tested the vaccine's effect on viral load, provided additional safety information about the product, and examined in detail immune responses to the vaccine and their impact on viral load. After numerous consultations with stakeholders, NIH decided that the VRC vaccine regimen did not warrant a trial of this size and scope and PAVE 100 would not proceed, even in its redesigned form. However, because the vaccine is scientifically intriguing and sufficiently different from previously tested HIV vaccine candidates, a smaller, more focused clinical study will be considered. This is likely to be initiated in 2009.

Advances or Other Highlights

When the STEP trial was stopped, numerous consultations were held to discuss the future directions of vaccine research efforts. In March 2008, the NIH convened a summit on HIV vaccine research and development to garner input from experts in the field regarding the most appropriate balance between vaccine discovery and development. During the summit, panels of experts facilitated discussion within three broad areas: vaccine-related basic

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Below is a list of the clinical trials that were initiated, completed or stopped during FY 2008.

- Many ancillary studies have been initiated in the HVTN to better understand the results of the STEP and Phambili trials.
- Four studies were initiated:
  1. HVTN 070 – a phase I study of the safety and immunogenicity of a DNA vaccine (gag/ pol/env) given alone or with one of two cytokine plasmid adjuvants (IL-12 or IL-15)
  2. HVTN 404 – an observational study of HIV trial participants who become infected after participated in a vaccine study
  3. HVTN 802 – an observational study of HIV trial participants on antiretroviral therapy who were enrolled in a vaccine efficacy study
  4. A phase I study to evaluate the safety and immunogenecity of an adenoviral vector (Ad26) for the delivery of HIV genes as an HIV vaccine – funded via an individual grant (D. Barouch, Harvard University)

- Vaccinations in four studies were stopped as a result of the data from the STEP study, but participant follow-up continues.
  1. HVTN 071 – a phase IB open-label study designed to characterize the immune response, particularly the T-cell response, to a 3-dose regimen of the Merck adenovirus-based HIV gag/pol/nef vaccine in HIV-uninfected adults
  2. HVTN 503 – the Phambili trial, which was a companion study to the STEP study
  3. HVTN 069 – a phase I trial comparing the safety, tolerability and immunogenecity of 3 regimens of 3 DNA primes and 1 Ad5 boost vaccines
  4. HVTN 072 – a phase IB trial intended to assess the VRC Ad5 vaccine in combination with a VRC DNA or VRC Ad5 vaccine

- Planned participant follow-up was completed in 5 HVTN trials.
  1. HVTN 055 – a phase I study of four vaccines candidates, each of which is a poxvirus vector with an HIV gene insert
  2. HVTN 060 – a phase I study to test a DNA-based vaccine with a modified gene insert
  3. HVTN 064 – a phase I study of two different products, EP 1043, a protein vaccine, and EP HIV-1090, DNA vaccine
  4. HVTN 067 – a phase I study of two vaccines candidates, a DNA vaccine and an modified vaccinia Ankara (MVA) vaccine. This study did not proceed to its second stage because a lack of immunogenecity was seen in the first stage.
  5. HVTN 204 – a phase II clinical trial evaluating the safety and immunogenecity of the VRC's multiclade HIV 6 plasmid DNA vaccine followed by the VRC's multiclade HIV-1 Ad5 in HIV uninfected adults (follow-up of participants is being extended).

Three studies (HVTN 204, RV 172, and IAVI 001, the Triad) evaluating safety and immunogenicity of the VRC DNA prime and adenovirus boost in healthy volunteers completed their first phase of follow-up in Africa and the Americas and participants have been unblinded to their vaccine assignment (i.e., either vaccine candidate or placebo). The studies provided expanded safety and immunogenicity data to support efficacy evaluation of the VRC vaccine if a smaller, more focused HVTN trial (HVTN 505) is implementated. Several public presentations of data from these Triad studies have occurred at international meetings during the year.

In addition, several studies funded by the NIH and conducted in collaboration with the USMHRP were still underway during FY 2008. These include:

- RV 144 – a Phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (vCP1521) priming with VaxGen gp120 B/E (AIDSVAX® B/E) boosting in HIV-uninfected Thai adults. Following an interim analysis in July 2008, the Data and Safety Monitoring Board (DSMB) recommended that the study continue to its completion in July 2009.
- RV 156A – an amended version of a previous study in Uganda, RV 156, in which 15 subjects were randomized to receive the VRC DNA vaccine and 16 were randomized to receive placebo. In RV 156A, this subset of eligible subjects from RV 156 were

boosted with the VRC Ad5 vaccine.

- RV 172 – a Phase I/II clinical trial evaluating the safety and immunogenicity of NIH-VRC's Ad5 vaccine alone and in combination with another NIH-VRC's 6-plasmid DNA vaccine in HIV-l uninfected adults. The study has enrolled 326 participants at USMHRP vaccine sites in Kenya, Tanzania and Uganda. RV 172 was harmonized with the HVTN 204 and IAVI 001 studies to prepare for advanced phase studies of these vaccines.

In the past year, data from several preclinical and clinical HIV vaccine studies have been published that will help inform and further HIV vaccine research efforts.

- The first comprehensive immunologic analysis of the vaccine-induced responses in the STEP trial and an article describing the results of the study (in press).
- A study showing that antigen persistence is the cause rather than the consequence of the functional impairment of T cell responses observed during chronic HIV infection
- A study of novel recombinant adenovirus vaccines showed promise in rhesus monkeys
- A study elucidating the structure of the epitope recognized by one of the monoclonal antibodies (4E10). A number of broadly reactive neutralizing antibodies have been identified that target a specific region of the HIV envelope protein known as the membrane proximal external region (MPER). Scientists have been unable to induce such antibodies using immunogens designed to simulate the MPER region. The study found that the 4E10 epitope is embedded in the lipid envelope of the virus, suggesting that immunogens designed to elicit these types of antibodies may need a lipid component.
- A study using mathematical modeling found that most clade B HIV infections are established by a single virus, suggesting a small window of potential HIV vulnerability to vaccine-elicited immune responses

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 a major research focus. These efforts have been limited by the difficulties inherent to the genetic study of complex disorders. However, advances in the development of new technologies such as single nucleotide polymorphism (SNP) 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 the catechol-O-methyltransferase (COMT) gene has also been linked to several psychiatric disorders such as alcoholism, schizophrenia, and anxiety.

Recently, the development of high density SNP technologies have been applied to Genome-wide Association Studies (GWAS) to identify novel genes in individual human patient samples to complement classical family-based studies. Identifying additional genes that influence risk for substance abuse and co-occurring psychiatric disorders and understanding their functional implications will lead to the development of more effective therapies in these complex 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 (8.5% of the population age 18 and older) suffer from alcohol use disorders, i.e., alcohol abuse and alcohol dependence (alcoholism). Children also are at risk for alcohol related problems. 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 or system in the body such as the brain, cardiovascular system, liver and pancreas. Alcohol use also is linked to some kinds of cancer. Co-occurring psychiatric and other substance use disorders are associated with severity of alcohol dependence. Individuals who suffer the most severe subtype of alcohol dependence experience the highest rates of Antisocial Personality Disorder and psychiatric disorders such as depression, bipolar disorder and anxiety disorder. These individuals (9% of U.S. alcohol dependent individuals) comprise the largest proportion of alcohol dependent individuals who undergo treatment.

Rationale

Clinical assessments show that many individuals diagnosed with substance use disorders are also affected by other psychiatric disorders, suggesting the possibility that common pathways may underlie both types of disorders. Recent evidence suggests 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 psychiatric 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 and continue to be useful tools in genomic studies. The identification of gene/allelic variations associated with alcohol and other substance dependence as well as psychiatric disorders will advance understanding of the genetic influences on these disorders, provide important clues to the underlying causes 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 from high-risk family, twin, and special population studies. Studies with high risk family, twin and special populations have been instrumental in identifying the genetic determinants of alcohol dependence and other disorders. Comparisons of genetic materials from individuals with and without alcohol use disorders and comorbid psychiatric disorders from within these groups will help researchers continue to identify genetic variations that confer vulnerability to these disorders. Variations in the identified genes will be examined through the use of knockout and transgenic mice, as well as through human pharmacogenetic studies in the populations indicated above, to understand differences in addiction vulnerability across individuals with different genotypes.

In the first phase of the goal, the association of newly identified genes to alcohol use disorders and comorbid psychiatric disorders will be cross-validated by independent studies using different populations and sample sources. In the next phase, more genes and variants of genes validated during the first phase will be identified using rapid genomic technologies. Finally, in the last phase of the goal, the identified genes and variants will be studied and characterized for function. These steps may overlap as new genetic associations to alcohol dependence and co-occurring psychiatric disorders are discovered and genetic variants are identified and characterized for function.

Baseline 2008

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

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
	(MET) Replicated the genetic associations of GABRA2, ADH4, and CHRM2 to alcohol dependence in different sample sources in multiple groups.	Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek potential functional differences coming from these haplotypes.	(MET) Fine mapping studies were conducted to identify specific haplotypes of genes that influence risk for alcohol dependence. Functional differences of various haplotypes were identified.	Identify potential functional differences from fine mapping studies of specific haplotypes.	(MET) Functional differences were identified for the A118 allele of the OPRM1 gene. Research was conducted on functional differences of haplotypes in the GABRA2 gene.	Validate the functional differences identified from previous fine mapping studies.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. NIH-supported research has identified genes associated with increased risk for alcohol dependence and co-occurring disorders. At the fine mapping level, researchers have identified single nucleotide polymorphisms and sets of closely linked SNPs, i.e. haplotypes, which are specifically associated with an elevated risk for alcohol dependence in various populations. In a recent study of European American alcohol dependent subjects, those with the A118 allele who received naltrexone therapy drank less alcohol, as measured by the number of days they were abstinent while on the drug, than those without this gene variant. In previous research, the A118G allele was been found to be associated with response to treatment with the drug naltrexone. The A118G allele is a functional sequence variant in the OPRM1 gene (chromosome 6) which encodes the mu opiod receptor involved in the brain reward system.

Recent studies have shown a significant association between alcohol dependence and specific haplotypes and SNPs in a region of chromosome 4 that extends beyond GABRA2 in the direction of the adjacent gene GABRG1. Research has described a number of haplotypes in both GABRA2 and GABRG1 that confer different risks for alcoholism among individuals from Caucasian (Finnish, European American), African American and Native American populations. Taken together, the fine mapping studies suggest that there are likely to be independent, complex contributions from both GABRA2 and GABRG1 to alcoholism

vulnerability. Although functional sequence variants in GABRA2 specifically are yet to be identified, research continues to locate functional SNPs within this gene.

These results do not necessarily suggest that the sample populations are at increased risk for alcohol dependence, but rather individuals possessing these genetic variants may be more vulnerable to developing the disease. The sequence variants may be useful in the future as markers to predict risk of developing alcohol dependence and related disorders, or to predict treatment response to medications and personalize treatment regimens for affected individuals.

Advances or Other Highlights

Research was conducted on the protein NF-κB1. This protein regulates genes that interact with alcohol in the brain and its actions are enhanced by ethanol. The gene that encodes the protein, NFKB1, is located in a broad region of chromosome 4 that is linked to alcohol dependence. Therefore, NFKB1was analyzed as a candidate gene for contributing to alcohol dependence. Nineteen SNPs in this gene were studied and eight were significantly associated with alcohol dependence in high risk European American families.

In other findings, SNPs in receptor genes for the neurotransmitter Neuropeptide Y (chromosome 4) have been associated with alcohol dependence, particularly a severe subtype of alcohol dependence characterized by withdrawal symptoms, as well as comorbid alcohol and cocaine dependence, and cocaine dependence. These studies were performed with European-American subjects of alcoholic families participating in the Collaborative Studies on the Genetics of Alcoholism (COGA), a NIH-supported initiative.

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.
- Because the researchers plan to use allogeneic stem cell therapy, which uses cells from a donor rather than the patient's own cells, the immune system may react to the donor cells causing their rapid destruction. The researchers hypothesize that encapsulation will enhance cellular viability within the capsule and protect the cells from a reaction by the recipients immune system, leading to enhanced cellular survival and engraftment.
- Evaluation of the use of the cell encapsulation agent to allow stem cell imaging and tracking using X-ray CT imaging.

Baseline 2008

- (FY07) Current cellular therapies suffer from extremely low cell engraftment due to early destruction of cells.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.	(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.	(MET) A biocompatible cell encapsulation agent to facilitate cell tracking and survival has been formulated.	Demonstrate that encapsulated cells can be tracked non-invasively by X-ray computed tomography.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 Target was MET. The target was met by the production of X-ray and MRI-visible alginate microcapsules, which were used to encapsulate mesenchymal stem cells (MSCs). The viability of the encapsulated stem cells was then studied in vivo in a rabbit model. Encapsulation of the cells was shown to help maintain their viability while simultaneously providing a method to deliver and track retention of the cells in vivo using conventional fluoroscopy (X-ray imaging). The results advance the goal by providing a potential method to promote cell survival and engraftment to prevent the early destruction of the transplanted stem cells by the immune system.

Efficiency

Investigators made significant progress in development of the cell encapsulation agent, allowing the target to be met ahead of schedule.

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 may propose 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.

SUMMARY OF 2008 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, as well as long-term effects such as second cancers, 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 assigning patients to treatment based on the level of expression in the tumor of genes that are frequently associated with risk of recurrence for women with early-stage breast cancer will lead 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 approximately 700 sites in the United States, Canada, Peru and Ireland. 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. Achievement of this goal is conditional on receiving the requested levels of funding.

Baseline 2008

- (FY07) Approximately one-third of trial participants recruited.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Accrue two-thirds of the TAILORx trial participants.	(MET) The TAILORx trial accrued 3227 participants (73.5%) to the randomized study.	Complete accrual for the TAILORx trial.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target has been MET. The trial was designed to pre-register over 10,000 patients so that 4,390 patients could be accrued to the randomized trial. As of September 2008, there were 3227 subjects accrued to the randomized study. This is 73.5% of the planned accrual goal.

Advances or Other Highlights

This study is being carefully monitored by the Eastern Cooperative Oncology Group (ECOG). A review of the information received in 2008 indicated there was a non-random failure to accept treatment assignment and resultant patient drop-out, which is not unusual in trials of this type. However, noting the lack of compliance was non-random allowed for

adequate intervention in terms of increased investigator education at the participating sites and engagement of breast cancer consumer partners to assist in participant education.

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 2008

- (FY07) 247 patients enrolled in PIVENS

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) To date, greater than 91 percent of the participants in the PIVENS clinical study have been retained and outcome data collected to assess liver function.	Complete goal of evaluating the safety and efficacy of two novel treatments for NASH in adults.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. As of September 8, 2008, greater than 91 percent of the expected week 120 visits (week 120 is the end of the study) were completed. Not all of the study participants have reached week 120 because participants enter the trial at different points in time. The primary outcome of the trial is based on the liver biopsy test which is obtained at week 96. About 92 percent of the expected participants have reached week 96, and hence have been retained and provided endpoints for the study.

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.

In FY 2010, NIH-funded scientists propose to map a new locus on the human chromosome where a deafness gene resides. At present, mapping a deafness locus involves screening families whose members suffer from inherited deafness, and determining if their deafness is caused by a mutation in a region (locus) of the chromosome that is already known, or if it is caused by a mutation in a region that has not been previously identified -- a new deafness locus. Scientists also propose to screen families that suffer from deafness in order to identify one novel deafness gene.

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

SUMMARY OF 2008 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 factors which predispose complex disease, and then to investigate the interplay between genetic and environmental factors. An initial step toward understanding genetic factors, which lead to common disease, is to perform GWA studies for diseases of interest. Subsequent analysis will determine how environmental factors impact genetic factors in the course of disease.

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.

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.

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

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

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

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 was 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.

Interim analysis of the data revealed that repeated measurements of fat buildup in the blood vessels varied less than researchers had expected (when they initially estimated the number of participants that would be needed to obtain a statistically meaningful result). Because this

greater precision leads to a smaller standard error for statistical analyses, the investigators were able to decrease the sample size from 280 to 220 and complete recruitment ahead of schedule.

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 2008

- (FY06) Previous research suggests that compliance among pediatric patients receiving treatment for chronic illness can be as high as 70% due in part to factors such as family support and severity of symptoms

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) The sites implemented two strategies and achieved a rate of 81.4 percent study medication compliance, exceeding the goal of 80 percent study medication compliance.	Complete goal of determining the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. A quarterly newsletter is sent to all study staff and participants in the study. In each issue to staff, there is a compliance section which asks staff to remind patients of the importance of taking all of their medications, including the study medication, and the importance of returning all used study medication bottles. Similarly, participants are reminded in the patient issue of the newsletter to take the study medication daily and bring back any study medication bottles. Study medication compliance is met if a patient misses fewer than seven days of study medication per month. The persistence of the study staff in reminding patients to take the study medication as directed has been a successful strategy in helping to achieve a compliance rate of at least 80 percent in this trial. The frequency of newsletter distribution was increased from biannual to quarterly, in an effort to encourage

compliance. Through this action, sites were able to give study participants a newsletter at each visit, which contributed to the rate of 81.4 percent study medication compliance, which exceeded the goal of 80 percent.

An incentive plan was developed which included a token gift, related to the trial (ranging in the value of $1-8). At various study visits, patients were offered pocket planners, journals, and pens to help manage their appointments and compliance. Other token gifts included sport backpacks, lunch sacks, caps, t-shirts, water bottles, and Frisbees. In addition, a pill box/organizer was provided to patients when the study drug was initially dispensed. These token gifts encouraged patient compliance and long-term retention in the study.

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 2008

- (FY06) CMLD libraries under development.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) The four Chemical Methodologies and Library Development (CMLD) centers synthesized chemical libraries that were provided to collaborators for high-throughput biological screening.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET by the efforts of the four ongoing Chemical Methodologies and Library Development (CMLD) centers to synthesize libraries of small molecules and to develop collaborations in order to evaluate the biological properties of these libraries. The CMLD centers all have established multiple collaborations for using the libraries the centers have produced in high-throughput biological screens. Boston University and the University of Kansas cite 23 and ten screening collaborations, respectively. The University of Pittsburgh (UPCMLD) reports that more than 6,000 individual compound samples have been shipped to over 30 collaborators, including single academic investigators as well as the NIH Molecular Libraries Screening Centers Network sites, for biological evaluation. The UPCMLD also shipped 709 UPCMLD compounds the NIH Molecular Libraries Small Molecule Repository (MLSMR) in 5-10 mg quantities. Finally, the Broad Institute indicates that 9,879 structurally distinct CMLD compounds were subjected to as many as 171 small-molecule assays, yielding ~770,000 total assay measurements. These compounds included 6,615 from the Broad Institute's CMLD and 3,264 from the other three CMLDs.

Advances or Other Highlights

Among the assay measurements conducted by the Broad Institute were several large clusters of compounds exposed to common assays, yielding complete matrices of measurements.

Such matrices form the mathematical basis for describing similarity of small molecules in terms of their "multidimensional" assay performance; that is, there overall performance in a large number of assays). Analysis of clusters of similarly performing compounds reveals both clusters of compounds with structural relationships among members, and clusters of compounds with structurally distinct members (suggestive of distinct chemotypes targeting common nodes in cell circuitry). The impact of this type of analysis on synthetic planning is three-fold. It helps prioritize subsets of molecules for follow-up syntheses based on primary screening data, lending confidence to observations that might be less convincing in isolation. Second, by considering collections of related molecules, including stereochemical variants, it provides an early opportunity to learn SAR from primary screening data. Third, it provides functional connections between chemical structure classes not previously connected, providing potential starting points for new synthetic planning strategies.

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-5.5	**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 2007, approximately 70 million Americans were current users of an illicit drug or cigarettes. Epidemiology studies show 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 $534 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 presented their results and/or submitted manuscripts for publication in peer-reviewed scientific journals. For the BSFT trial patient enrollment was completed in 2007, the year long follow-up of patients is complete and data lock is scheduled for June 2008.

During FY 2008, the investigators from MET and Seeking Safety worked 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 analyzed their data, presented results to the Clinical Trials Network, and submitted their findings for publication in peer-reviewed scientific journals.
A dissemination package for MET has been prepared and is available to the public.

Baseline 2008

- Based on FY07 results.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) Research has been completed on two treatments for drug abuse (MET and Seeking Safety), and final analyses are under way on a third treatment (BSFT) developed and tested in community settings.	

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET, and the goal was ACHIEVED. Research has been completed on two treatments for drug abuse (MET and Seeking Safety). Final analyses are under way on a third treatment (BSFT) that has been developed and tested in community settings. Research on MET, Seeking Safety, and BSFT was conducted with the Clinical Trials Network which connects NIH researchers with community-based service providers to develop and test new treatment options with patients in community-level clinical practice.

The research on Motivational Enhancement Treatment (MET) was completed. Results from a multi-site clinical trial of MET in community drug abuse clinics showed sustained substance use reductions only among primary alcohol users. Other findings from the research demonstrated that: (1) training in Motivational Interviewing (MI) increases proficiency in its implementation; (2) the combination of expert-led workshops followed by program-based clinical supervision is an effective method for disseminating motivational interventions in treatment programs; (3) having active MI supervisory capacity and a champion for the intervention in the clinic increases its adoption; and (4) there are opportunities in the early stages of treatment for implementing motivational therapies to improve standard clinical practice and patient outcomes. (For a listing of papers and presentations aimed at a wide audience of researchers and practitioners see Source Validation Items #1, 2,5, 6, 7, 8) A dissemination package for MET has also been prepared and is available at http://www.drugabuse.gov/Blending/MIASTEP.html. It includes information about the protocols, training guides, recruitment brochures, demonstration interviews in Spanish, briefing materials for decision-makers, and instructions for using the package.

Research was completed in community treatment settings on the Seeking Safety protocol, an intervention developed for women with PTSD. Results were that integrated treatment for PTSD and substance use disorders had a significant impact on trauma symptoms, but did not

improve substance abuse outcomes more than the control condition. Seeking Safety also had a positive effect on sexual risk behaviors (decreased) and did not increase adverse events, such as substance use and its related consequences. The latter is important because PTSD treatment involves recollection and recounting of painful experiences, which has the potential to elicit negative outcomes. (See Source Validation Items # 4,, 9, 10, 11, 12)

The BSFT trial and its 1-year follow-up has been completed. This family-based intervention was developed and tested for preventing and treating child and adolescent behavior problems, including substance abuse, in inner city, minority families. The data are being analyzed for future publication in scientific journals, and/or presentation at national and regional meetings. Previous research using BSFT found that it was more efficacious than group intervention in reducing conduct problems, associations with anti-social peers, and substance use, and it increased engagement in treatment. Moreover it improves family function, which is associated with changes in behavioral problems among youth. Final results of the trial will help determine whether BSFT can be readily adopted by community treatment programs. (See Source Validation Items # 3)

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 (70-90% for 6-month quit rates) 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-one 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

2006, the median prevalence rate of current cigarette smoking by adults among the different states comprising the United States was 20.2%. This prevalence rate is almost double the nation's year 2010 Healthy People goal of achieving a 12 percent prevalence rate. The highest reported rate for a minority sub-group of the population in 2006 was 32.4% - or almost three 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.

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. Its Phase IIb trial 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 primary measure of outcome was eight weeks of continuous smoking abstinence from weeks 18-26 (following the first vaccination) of the study. 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.

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 2008

- Based on FY06 and FY07 results.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Four candidate medications, instead of two, have been identified for tobacco addiction, and research is continuing on these candidates.	(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.	(MET) Analysis of the Phase II nicotine vaccine trial showed that the vaccine assisted smokers to quit, supporting continuation of the project.	Complete goal of identifying at least two new medications to be further developed and tested for the treatment of tobacco addiction.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY2008 target was MET. Results were analyzed from the FY 2006 clinical trial (Phase

II) of the nicotine vaccine and determined that the project should be continued. The analysis showed that the vaccine improved the smoking quit rates, particularly in smokers who developed high antibodies levels. This effect was sustained at the 6, 9, and 12 month time points. Moreover, the analysis suggested ways to boost the efficacy of the vaccine by modifying the timing of the quit date to take advantage of the increased antibody levels according to when subjects were inoculated. Manuscripts for publication are in preparation.

Advances or Other Highlights

Additional research has been conducted on three candidate medications from FY 2007 for the treatment of tobacco addition – selegiline, a D3 dopamine antagonist called 809, and the glycine anatagonist GW468816. The selegiline trial, which was in the process of recruiting a cohort, completed enrollment. The trial is currently finishing patient follow-ups, and analyses will be conducted after follow-ups are completed. The D3 dopamine antagonist, called 809, was identified for testing as a smoking cessation medication and a protocol is under development. The compound will be tested for relapse prevention in a clinical trial. The clinical trial testing the glycine antagonist GW468816 for relapse prevention continues to recruit subjects, and is anticipated to be complete within a year.

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. Reproducibility is important because it determines the minimum change that can reliably be detected in a tissue of interest. Therefore, test-retest reproducibility will be an element of all research 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

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. This reproducibility will be rigorously tested in a pre-clinical setting where repetitive measures can be obtained on tissue-simulating phantoms. In addition, clinical trial data with duplicate testing of individual patients will be analyzed

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 would be standard, not experimental, therapy.

Scans would 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 were to receive duplicate FDG-PET scans prior to treatment, and half to receive duplicate FDG-PET scans after treatment. The duplicate scans would allow us to assess test-retest reproducibility. This trial has had significant difficulty in accruing patients as of mid-2008, due in part to a shift in the standard of care (adding Avastin to platinum-based doublet therapy).

A second ACRIN trial supports this GPRA goal. This trial is comparing FDG-PET before and after chemoradiation in non-small cell lung carcinoma to determine if the post-treatment glucose uptake as measured by FDG-PET is a useful predictor of long term clinical outcome (survival) after definitive chemoradiotherapy.

A trial to compare FDG-PET with FLT-PET for lung cancer was initiated in FY 2007. Accrual is expected to begin in 2008 with an interim analysis after one year of patient accrual.

In FY06, 07 and 08, programs to evaluate test-retest reproducibility both of available clinical data and of tissue simulating phantom were established. These are multiple and include FDG-PET CT longitudinal studies, multi-site phantom repeat studies, multi-imaging platform study using a PET CT phantom, DCE-MRI lung patient studies, DCE-MRI phantom for lung and other organs, and CT measurements of the lung. 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.

Achievement of this goal is conditional on recruiting a sufficient number of patients to conduct the required test-retest reproducibility analyses.

Baseline 2008

- (FY06) Performed preliminary analysis of test-retest repeatability data from 1st year of trial.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) FDG-PET and DCE-MRI workshops have been held. Consensus guidelines are on the Cancer Imaging Program web site: http://imaging.cancer.gov.	(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.	Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial. 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.	(MET) One lung cancer imaging trial will be completed within 6 months and interim results have been submitted for presentation. Reproducibility for two techniques has been evaluated. Another trial will open for patient accrual this fall.	Initiate accrual in FDG/FLT-PET comparison lung cancer trial.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target has been MET. The lung cancer trial comparing FDG-PET before and after chemoradiation - to determine if post-treatment glucose uptake as measured by FDG-PET is a useful predictor of long term clinical outcome (survival) after definitive chemoradiotherapy - has accrued 211 of the planned 250 subjects (http://www.clinicaltrials.gov/ct2/show/NCT00424138?term=6678&rank=1). This study is evaluating the utility of FDG-PET tumor standardized-uptake values (SUV) as a potential biomarker, examining reproducibility of the primary tumor SUV calculation between the local institution and the central review core facility at ACRIN. Pre-treatment FDG-PET scans from 55 patients and post-treatment FDG-PET scans from 40 patients were analyzed. Preliminary (interim) findings indicate there was good but imperfect correlation between institutional and centrally determined SUV for NSCLC.

The trial to compare FDG-PET with FLT-PET for lung cancer is expected to begin accrual before the end of the year. It has not yet been posted to http://clinicaltrials.gov.

Advances or Other Highlights

Research has continued on determining the variability of measurements by various imaging techniques. Subcontracts were awarded for work on reproducibility of PET/CT and CT in lung cancer, which involved both phantoms and analysis of patient cases. The final synthesis of these studies is in draft and will be posted on the RIDER gforge web site this quarter.

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. A device was incorporated into a clinical study which was funded in 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 2008

- (FY07) No clinical studies of hot flashes using user-friendly sternal skin conductance monitors exist.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) NIH initiated seven research projects.	(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.	(MET) NIH-supported researchers have initiated a clinical trial assessing the effectiveness of hypnosis in treating menopausal hot flashes.	Complete 20% of planned study subject accrual.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target is MET. NIH-supported researchers have initiated a clinical trial assessing the effectiveness of hypnosis in treating menopausal hot flashes. The clinical trial is targeting an enrollment of 180 women who experience 7 moderate-to-severe hot flashes per day, or 50 per week. The researchers will use a sternal skin conductance monitor, developed by NIH-supported small-business research, to validate if hypnosis is effective in reducing the frequency and severity of hot flashes.

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 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. Specific regions of human chromosome 8q24 have been associated with the risk of prostate cancer in African Americans. To further understand the genetic basis for the increased risk of prostate cancer in this region, high-density sequencing of the 8q24 region is underway on a study focused on prostate cancer in West Africans from Ghana. The data from the first round of replication has been analyzed and second stage replication of the remaining positive

associations (~150 SNPs) is ongoing. The second stage replication study sample set is enriched with several ethnic populations, with a particular focus on African Americans. In the future, intramural scientists will perform the second stage validation on positive genetic variants associated with increased susceptibility to prostate cancer from an extramural GWAS being planned on several ethnic groups. This group will have a particular focus on African Americans and will be carried out through an intramural/extramural collaboration. Positive findings from this study will be the focus of further investigation across the scientific community. 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. This population also has high rates of obesity. 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 2008

- (FY07) HapMap III not started

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(EXT) The pooled data with documentation and web utility were made publicly available in September 2006. Public data training is scheduled for March 2007.	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. 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) NIH 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.	(MET) HapMap III analyzed data from additional populations allele frequencies and haplotypes	Begin biologic assessment of the most likely diabetes/obesity susceptibility genes in regions of linkage/association.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. Samples from several populations were genotyped to provide data on a dense set of SNPs and structural variants across the genome; samples were also sequenced in 13 regions of the genome. These data were released publicly. Researchers genotyped 1260 samples (the original 270 HapMap samples from Utah, Yoruba from Nigeria, Han Chinese, and Japanese, another 270 samples from the same HapMap populations, and 720 samples from an additional 7 populations -- African-American, Mexican-American, Gujarati (India) from Houston, Chinese from Denver, Tuscans from Italy, and Luhya and Maasai from Kenya). Approximately 900,000 SNPs in these samples as well as data on structural variants were obtained. Researchers also sequenced ten 10 kb regions of the genome in 712 unrelated samples in this set of 1260. These data show that the original HapMap data are useful in the additional populations. The data are a valuable resource on allele frequencies and haplotypes that will be used in genome-wide association studies in these populations and other populations to improve the ability of researchers to find variants and regions of the genome that are associated with diseases. The data will be used to design platforms that are generally applicable to any population, and can assist researchers choosin choosing sets of SNPs for follow-up studies of particular regions of the genome.

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-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 purpose of this study is to determine the risk factors associated with early onset and altered puberty in girls. The study allows for in-depth observation and analysis of the progression through puberty of girls between the ages of 6 and 14 years old.

Approximately 1200 girls were 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 a 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.

Data will be collected from all active participants. However, as this study takes place over many years, some attrition is expected each year. Attrition over the whole study may reach as high as 75%. In designing this study, a 1200 girl cohort was recruited to help ensure sufficient statistical power in study results, taking into account attrition trends from previous studies.

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 2008

- (FY07) No exams or collection.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) For year 2 follow-up, over 87% of the current cohort was successfully contacted and completed questionnaires, with over 85% completing follow-up clinical exams.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. NIH completed year 2 follow-up clinical exams of over 85% of the cohort, and data collection for over 87%. The study follows up on the FY 2007 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. For year 2 follow-up, over 87% of the current cohort was successfully contacted and completed questionnaires. Various clinical exams, including pubertal stages assessment, anthropometry, and urine analysis, have also been completed on over 85% of the cohort.

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 a patient's quality of life, and ultimately, his or her health outcomes. The term "Quality of Life" refers to how a patient perceives their life and health status, and can include a patient's ability to perform daily activities or live free from pain while coping with a chronic disease. "Health Outcomes" is an umbrella category that includes the total effects of health care practices and medical/behavioral interventions on factors such as longevity, chronic disease morbidity, and physical and mental functional status. Measuring quality of life is only one part of assessing health outcomes. 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 clarifying 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 their ability to impact patient quality of life. Measuring the effectiveness of these strategies could include assessments of patients' abilities to perform activities of daily living, or of patients' pain status. 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 improve quality of life. Following these initial assessments of quality of life, further study will identify and assess the impact of promising behavioral symptom management strategies in reducing the effects of disease, disability or psychological distress on overall health outcomes. Assessments of health outcomes could include measurements of not only quality of life, but also factors such as longevity, chronic disease morbidity, and physical and mental functional status.

Baseline 2008

- (FY07) Ongoing studies are exploring behavioral strategies to enhance patient outcomes.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) An analysis of current literature was conducted to identify 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. An analysis of current literature was conducted to identify three candidate symptoms appropriate for assessment in studies of behavior-based symptom management strategies – pain, insomnia, and fatigue.

Through this analysis, pain was identified as one such candidate symptom. One study examined self-management training for older adults and its effect on levels of chronic pain. Patients who underwent training in chronic pain self-management experienced significantly decreased pain intensity post-intervention and a significant difference in physical role functioning. Health-engagement control strategies have also been found to manage pain in older adults. Pain associated with chronic and functional health declines was significantly decreased in patients who reported high levels of health-engagement control strategies. These preliminary results suggest that behavior-based pain management strategies, such as self-management training and health-engagement control, may be effective in reducing chronic pain.

A second candidate symptom for behavior-based management strategies is insomnia. One study examined the effects of home-based exercise intervention on older women who were currently receiving hormonal treatment for breast cancer. Older women are more likely to

receive hormonal treatment for breast cancer than younger patients, yet interventions designed to manage hormonal therapy-associated symptoms have been studied almost solely in these younger patients. Patients who underwent home-based exercise interventions had significantly improved sleep quality, as opposed to their control group counterparts, who experienced no difference in sleep quality. In addition, serotonin levels were significantly altered by the exercise intervention, suggesting that serotonin may be a useful biomarker for sleep disturbance assessments. This study indicates the potential usefulness of, and the need for future research into, behavior-based interventions. Home-based exercise interventions, as well as others, may be successful behavior-based insomnia management strategies.

Behavior-based strategies may also be effective in managing a third symptom, fatigue. Fatigue, along with pain and insomnia, are all common yet frequently under-managed symptoms that cancer patients may experience through the course of their disease. By examining the predictors of patterns of fatigue, potential behavioral-based strategies could be developed to produce effective mitigation of symptoms. One study observed fatigue in elderly patients in the first year after a cancer diagnosis. Researchers found that earlier patterns of fatigue were often associated with significantly increased risk of subsequent patterns, which were in turn associated with higher co-morbidity. Further research in this area may improve the understanding of patterns of fatigue and possible predictors, thus advancing the development of potential symptom management techniques. A behavior-based fatigue management strategy could be effective in moderating fatigue and associated consequences.

Future research on behavior-based symptom management strategies may lead to increased quality of life and better health outcomes for patients experiencing pain, insomnia, or fatigue.

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 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 2006 there were an estimated 22.6 million persons aged 12 or older (9.2 percent of that population) 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. In 2006 there were an estimated 24.9 million adults aged 18 or older with Serious Psychological Distress in the past year, or about 11.3 percent of all adults in the country in a given year, have a diagnosable psychological distress 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 2006, the number of persons needing treatment for an illicit drug or alcohol use problem was 23.6 million, and only 2.5 million of them received treatment at a specialty facility. In 2006, there were 5.6 million adults with serious psychological distress associated with substance dependence or abuse, and of these about half received mental health treatment or substance use treatment at a specialty facility.

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 may 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 could 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. However, the level of achievement from this goal is conditional on receiving applications of sufficient scientific merit. 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
						Test at least two compounds or medications in animal models of extinction of drug-seeking behavior.

SUMMARY OF 2008 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 substantially due to the aging of the U.S. population.

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. 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. 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 was developed that will allow investigators around the world to have a 'common language' to describe different stages and forms of macular disease.

In December 2006, NIH launched the Database of Genotype and Phenotype (dbGaP) using the dataset from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of Age-related Macular Degeneration (AMD) and cataracts. This database enables Genome-Wide Association Studies (GWAS), an analytic technique to assess how genetic variations across the entire human genome correlate with disease manifestation. Using these data, recent studies demonstrated an association of the complement system and inflammation with AMD, and linked two genes with the observed progression to advanced (or ‘wet’) AMD. In addition, the National Eye Disease Genotyping Network (EyeGENE) was created to assist in developing awareness of resources available to people affected with ocular genetic diseases, their clinicians, and researchers.

Complex diseases like AMD and glaucoma involve the interaction of multiple genetic and environmental factors. In addition, modifier genes may alter the progression or severity of a disease among affected individuals. Animal models are useful tools that allow investigators to explore complex genetic and biochemical interactions that cannot be directly tested in humans. Several candidate genes, including fibrillin-6 and Stargardt gene for AMD, and optineurin for glaucoma, have been identified in animal models. Research testing mutated forms of these genes, and other candidate genes identified in human genetics studies, is proving invaluable. Ultimately, therapies that delay, prevent, or reverse the effects of these genetic alterations in animals can be tested and may lead to studies in humans.

Also important in progress toward this goal is providing investigators with genetic material and information from well-characterized patients. Population-based resources of blood,

transformed lymphocytes, and DNA from patients with 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. Large-scale DNA collections allow geneticists to narrow in on disease-causing genes by studying haplotypes, a set of closely linked genes inherited as a unit. By using small changes in DNA called Single Nucleotide Polymorphisms (SNPs) as landmarks, geneticists can pinpoint regions of chromosomes and eventually specific genes that give rise to disease. It will also be necessary to accelerate the application of candidate gene and other genetic approaches to the study of AMD and glaucoma.

In advanced AMD, Vascular Endothelial Growth Factor (VEGF) induces abnormal neovascularization, the growth of new blood vessels, often resulting in blindness. Therapeutic strategies that block VEGF in the retina have been successfully applied to slow progression of AMD, and in some cases, reverse advanced AMD and improve vision. Recently, a genetic variant of complement factor H, important in immunity and inflammation, was shown to be associated with about half of the cases of AMD. This suggests that additional alterations of genes involved with innate immunity and vascular formation are likely to be involved in AMD. Genetic and observational studies in humans have also identified a role C-reactive protein and complement factor B, however, to date the mechanism by which inflammation impacts AMD is not well understood and few other genes have been identified and validated. Additional genetic studies using animal models might lead to new therapeutic options.

Baseline 2008

- (FY06) Twelve genes associated with glaucoma have been mapped six genes have been cloned.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Collected samples from over 4,000 well-characterized patients with either AMD or glaucoma. Created the National Eye Disease Genotyping Network (EyeGENE).	(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.	(MET) Haplotype analyses on African American populations identified key regions on chromosomes 2 and 3 associated with POAG. NIH also launched two new POAG GWAS projects in the US.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. In a linkage analysis in 142 primary open-angle glaucoma (POAG) families using over 5,000 SNPs, a novel region on human chromosome 3 and a previously identified locus of genes on chromosome 2 were highly associated with POAG. Other potential candidate risk haplotypes were found on chromosomes 1, 6, 12, and 17. Additionally, NIH supported analyses of SNPs and other genetic markers identified a new critical interval on chromosome 20 associated with juvenile-onset POAG.

Conducting haplotype analyses is useful for identifying specific regions of chromosomes containing one or more new genes associated with glaucoma. Currently 22 distinct genetic loci have been mapped on 15 different chromosomes, and seven of these loci are associated with POAG. Within these loci, eight glaucoma-associated genes have been identified - three are directly related to POAG, namely, myocilin, WDR36 and optineurin, on chromosomes 1, 5, and 10, respectively. Additional research is required to further characterize risk haplotypes in order to identify additional genes. Two new approaches are now being used to characterize risk haplotypes within these regions: genomic convergence and association mapping.

Other NIH studies started with a candidate gene approach. Haplotype analyses of the newly discovered LOXL1 gene found that while it was not associated with POAG, it was associated with psuedoexfoliation glaucoma (secondary open angle glaucoma). Similar analysis on the optic atrophy 1 gene found no risk associated with POAG. Additionally, mutations in the myocilin gene have been associated with both early-onset and adult-set POAG. NIH-funded investigators identified three distinct haplotypes associated with this mutation by studying families in the United States, Greece, India, Finland, and Australia and using data from the NIH HapMap consortium. Other research has shown that CYP1B1 may act as a modifier gene for some myocilin mutations, affecting the severity of the disease and possibly functioning in the same biochemical pathway.

Furthermore, in FY 2008, NIH initiated two new Genome Wide Association Studies (GWAS) to find POAG genes. The first project is studying cohorts of African American populations in the US and from West Africa. POAG is four to five times more common and much more severe in these populations. The other project is examining environmental and genetic interactions in POAG in US populations.

Advances or Other Highlights

Progress towards this goal was also made in identifying genetic regions associated with age-related macular degeneration (AMD) risk. NIH-funded teams discovered an association between AMD and a novel genetic variant in the complement factor 3 gene. Also, a variation near complement factor I was discovered to be associated with risk of advanced AMD. Additionally, two large-scale Genome-Wide Association Studies of AMD were completed in FY08; these data are now being analyzed.

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 2007, the prevalence of diabetes in the United States was approximately 24 million people, or 8 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 25 million Americans and can lead to kidney failure.
- The number of patients with kidney failure or end-stage renal disease (ESRD) has doubled over the past decade and now stands at nearly 500,000.
- 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 2007, the economic cost of diabetes in the United States was estimated at $174 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. In 2005, the total cost of caring for the ESRD population was $32 billion; of this Medicare covered $21.3 billion. The ESRD population consumes 7.5 percent of program expenditures despite the fact that these patients only make up 1.2 percent of the Medicare population. According to new data released by the NIH-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 putative 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. The treatment approach of intensive control of blood glucose was stopped due to safety concerns and a recommendation by the DSMB. The Blood Pressure and Lipid trials are continuing to their planned completion dates.

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). A total of 4,110 kidney transplant recipients were recruited.

Baseline 2008

- (FY07) Human clinical trials require periodic review and evaluation to assess progress.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005.	(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.	(MET) The Look AHEAD Data Safety and Monitoring Board reviewed and evaluated the raw data from the study's indicators to date, including safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends, and has made a determination that the science is progressing appropriately and the trial should continue.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. On May 22, 2008, Look AHEAD's Data Safety and Monitoring Board (DSMB), an outside panel of experts which has no vested interest in the clinical trial, evaluated the raw data from the study's indicators to date, including safety-monitoring analyses, data quality, participant retention, and emerging positive or negative outcome trends, and determined that the science is progressing appropriately and the trial should continue. The data provided to the DSMB for review needs to be kept confidential for several reasons. First, participant confidentiality must be protected. Second, the study must be protected from unintentional bias that could occur if investigators become aware of trends in study outcomes. Third, the study would be significantly diminished or ruined if participants heard about a trend in the outcome data which caused them drop out. In addition, data about drop-outs by study arm, and other similar performance data, are masked to the investigators in Look AHEAD. This serves to obviate a situation where investigators are providing different levels of incentives to different arms of the study in order to equalize retention rates.

Advances or Other Highlights

The Look AHEAD Clinical Trial published baseline results describing the proportion of recruited participants who met the American Diabetes Association targets for glycemia, blood pressure, and LDL cholesterol control in the Journal of Diabetes and Its Complications 22:1-9, 2008. The Look AHEAD Clinical Trial published baseline results describing the association of demographic, physical, and diabetes- and CVD-related measures with exercise capacity in study participants in Diabetes Care 30: 2679-2684, 2007.

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 the capability of housing relational and descriptive compendia on

toxicologically important genes, groups of genes, polymorphisms, and mutants and the 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 has:

1. sequence anchored 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. created 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. enabled 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.

Baseline 2008

- (FY07) CEBS currently does not link outcomes of searches to existing literature databases.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) Completed goal by developing CEBS3 knowledge base using a systems toxicology or toxicogenomics approach.	

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET and the goal was ACHIEVED. The Chemical Effects in Biological Systems (CEBS3) knowledge base has been completed and is available from within NIH. The CEBS Knowledge base is founded on the principal of permitting the user to apply systems toxicology / toxicogenomics through the integration of data gathered at the gene or protein level (transcriptomics / proteomics) or at the level of organ (histopathology, clinical chemistry, gross observations) or organism (behavior, clinical signs) or study (chemical name, species). Probe sets from public sequence-defined microarray platforms have been sequence anchored to respective genomes within CEBS. This capability was first implemented in CEBS2 and has been expanded in CEBS3, the development version of CEBS that is undergoing final 508 compliance testing. Once approved, the updated interface will be released as a means to access the data.

The public version of CEBS is CEBS2 (http://cebs.niehs.nih.gov). This knowledgebase was released to the public beginning in FY05, with annual improvements. In FY06 the decision was made to redesign the CEBS architecture to increase flexibility in data capture. This permits CEBS3 to capture data from an increased variety of sources, technologies, and study designs. During the changeover, CEBS2 was improved with added literature searching capability, and will continue to be available to the public until CEBS3 is approved for release. The capability was developed by integrating literature analysis via PDQ-Med to identify and visualize relationships among known gene sets. In addition, extensive study and subject search capabilities have been developed to correspond with gene expression profiles to specific study designs, subjects, and determine experimental outcomes.

Two processes have been initiated to link CEBS searches to external data: (1) from collaborative sources such as the NTP (National Toxicology Program) and the EPA

(Environmental Protection Agency), and (2) from external labs and the literature. Data for the literature are selected to have added value in CEBS3. For example, microarray data deposited in CEBS3 from GEO (Gene Expression Omnibus) can be linked directly to data previously only available from supplemental materials on the publisher's site. As part of this effort tissue atlases have been loaded from Novartis and the Iconix database of hepatotoxicants, encompassing over 7000 microarrays and supplemental data.

In addition, the path for loading data into CEBS3 has been automated. All current data has been added with a command-line data loader using the SIFT (Simple Investigation Formatted Text) format. The SIFT terms and definitions used to annotate the date are contained and defined within CEBS3 and linked to external taxonomies where appropriate. These terms also can be exported for use by collaborators. Automated data validation tools have also been developed to verify that all syntax and semantics in data files to be loaded are correct. These tools and the CEBS3 database enforce the minimum information needed for each study type.

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-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 2008

- (FY06) Limits of imaging methods have made it difficult to understand how AEs affect pulmonary physiology.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Developed and funded a program consisting of twelve studies which will examine the molecular, cellular, and genetic causes of AE.	(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.	(MET) Advanced imaging techniques such as multiple detector (MD) CT, 3He-MRI, and FDG-PET have been performed on approximately 40 subjects with AE.	Identify single nucleotide polymorphisms (SNPs) in DNA that may be associated with AE in children.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 Target was MET. Advanced imaging techniques such as multiple detector computed tomography (MDCT), hyperpolarized gas magnetic resonance imaging using helium-3 (3He-MRI), and fluoro-2-deoxy-D-glucose and positron emission tomography (FDG-PET) have been performed on approximately 40 subjects in an effort to detect functional, structural, and inflammatory changes associated with asthma exacerbation in each subject. MDCT allows researchers to identify areas of the lungs in which air becomes trapped in the alveoli (air sacs at the end of the bronchioles) preventing proper exchange of oxygen and carbon dioxide. 3He-MRI allows visualization of regions of air flow obstruction (ventilation defects) and FDG-PET identifies inflammation within the lung tissue. A recent study using both MDCT and 3He-MRI imaging modalities supports an association between regional air trapping and ventilation defects, indicating that use of the two modalities together may provide an improved method for identifying structural abnormalities in the lungs patients with asthma. The combined imaging technique provides new insights into pulmonary physiology and can be used to detect complex variation in imaging metrics in response to asthma exacerbation which may reflect differing asthma phenotypes and/or exacerbation triggers. The new technique advances the overall GPRA goal by providing an improved approach for identifying regions of disease associated with asthma exacerbations and characterizing pathways responsible for disease.

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

In the last year alone, over 2 million people died due to acquired immune deficiency syndrome (AIDS), and another 2.5 million people were newly infected with the human immunodeficiency virus (HIV), which causes AIDS. In 2007, an estimated 33.2 million of the world's population, including 2.5 million children younger than 15 years of age were living with HIV/AIDS. In the United States, newly diagnosed infections have remained relatively stable at approximately 40,000 per year; however, the disease continues to ravage many communities. Although African Americans comprise only 13% of the U.S. population, they accounted for nearly half (49%) of those newly infected in 2006. More than half (57%) of the new infections reported were in people aged 25–44.

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. The AIDS pandemic continues to destroy families and communities, and 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. Sub-Saharan Africa remains the most severely affected region of world. More than two out of three (68%) of adults and nearly 90% of children infected with HIV live in this region and more than three out of every four deaths due to AIDS globally (76%) occurred in that region. These statistics reflect inadequate access to HIV prevention and treatment programs in that region.

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 (MTCT), 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 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, more effective 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. As importantly, drug resistance is also associated with some of these regimens, particularly with the prevention of MTCT in resource-limited countries. These regimens can also induce 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 stimulate anti-HIV-specific immune function. Optimal strategies for long-term use 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 focuses its 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. The targets for the next three years are reflective of important studies targeting specific populations and/or HIV prevention and treatment and prevention strategies.

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 to explore promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk adolescents. The ATN conducts studies both independently and in collaboration with the other research networks, such as IMPAACT, ACTG, MTN, and HVTN. In addition, 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. Finally, research on HIV co-infections and comorbidities, including hepatitis C, hepatitis B, tuberculosis, cancers, neurological disorders, and organ-specific complications, also continues 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 several investigator-initiated grants, the HPTN, MTN, and IMPAACT, which collaborates with the Pediatric/Perinatal HIV Clinical Trials Network on the prevention of mother-to-child transmission (MTCT). Because more than one prevention strategy will be required, NIH will continue to initiate and conduct trials to evaluate strategies to reduce co-factors associated with increased HIV infection, such as herpes simplex virus, the development of pre-exposure prophylaxis regimen, and the treatment of injection drug use.

Microbides are another important potential prevention tool being examined. Currently, there are no licensed microbicides. 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 MTCT of HIV as well as studies aimed at optimizing the treatment of HIV-infected children. It also collaborates with the ATN to conduct HIV prevention studies in adolescents. Studies in this network will: evaluate strategies to prevent MTCT during breastfeeding; and evaluate approaches to optimize ART and reduce drug resistance in women and infants who are exposed to short-term ART to prevent MTCT. While the results of NIH-funded research have led to the dramatic reduction of MTCT, particularly in developed countries, the problem remains how to optimize maternal treatment. And, in resource-limited countries, the use of Neviripine as the standard for preventing MTCT often results in drug resistance which can compromise subsequent treatment for the mother and possibly the infant. The PHACS is also 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 AIDS disease.

Baseline 2008

- (FY07) Awards were made to 6 newly restructured HIV/AIDS clinical trials networks in FY06 to address the six highest priorities in HIV/AIDS clinical research.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Establish 140 domestic and international clinical research sites to conduct HIV prevention and therapeutic clinical trials.	(MET) NIH established 184 clinical research sites and 74 clinical research units in domestic and international locations 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET and exceeded. During FY 2008, the NIH funded 184 clinical research sites (CRSs) and 74 clinical research units (CTUs) affiliated with one or more of the NIH's six HIV/AIDS clinical trials research networks.

The CTUs are the national and international research institutions that conduct clinical HIV/AIDS research to develop safe and effective drugs, prevention strategies and HIV vaccines. Each CTU consists of a lead principal investigator, an administrative component and one or more affiliated clinical research sites, such as hospitals and clinics, where qualified medical professionals conduct clinical trial research in accordance with federal and local requirements. Each CTU is a member of one or more of the six NIH HIV/AIDS networks, which 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), the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) and the Microbicide Trials Network (MTN).

The CTUs collaborate with the network's leadership and local communities to conduct clinical trials addressing the highest priorities in HIV/AIDS research, including
• 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
• Developing new methods of HIV prevention

In the U.S., the CTUs are located in 19 states and territories: Alabama, California, Colorado, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Washington and Puerto Rico.

Outside the U.S., the CTUs are located in: Botswana, Brazil China, Dominican Republic, Haiti, India, Jamaica, Kenya, Malawi, Panama, Peru, South Africa, Switzerland, Tanzania, Thailand, Uganda, Zimbabwe, and Zambia.

In addition, NIH funded 184 CRSs, 96 of which are located in the United States and 88 outside the U.S. The CRSs will carry out the actual research and can be affiliated with more than one CTU and more than network. In the U.S. the CRSs are located in 21 states and territories, including: Alabama, California, Colorado, Florida, Illinois, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Ohio, Oregon, Pennsylvania, Rhode Island, Tennessee, Texas, Virginia, Washington, Puerto Rico and Washington D.C.

There are CRSs are located in 18 countries outside of the U.S., including: Botswana, Brazil, China, the Dominican Republic, Haiti, India, Italy, Jamaica, Kenya, Panama, Peru, South Africa, Spain, Switzerland, Tanzania, Thailand, Uganda, and Zambia.

Advances or Other Highlights

Several treatment and prevention studies conducted within some of the clinical trials networks have published results that will impact public health and clinical practices and/or guide future research efforts. These include the following:

- Results of follow-up from the study on the Strategies for Management of Anti-Retroviral Therapy (SMART) study conducted by the INSIGHT group published in FY 2008. The trial had previously showed that instead of decreasing secondary effects, intermittent use of antiretroviral therapy increased morbidity and mortality. Participants who had originally been in the episodic treatment arm, reinitiated continuous therapy and were followed to determine if there was an increased risk of opportunistic disease or death. After a year of being on therapy again there remained higher morbidity and mortality compared to the group that received continuous treatment. The study showed that there are long-term risks to stopping therapy both in terms of clinical outcome and immune status.
- An exploratory analysis from the SMART trial found no evidence that ART interruption or a higher HIV viral load were associated with an increased risk of cardiovascular disease. The reason for the higher risk of cardiovascular disease among those with episodic treatment as compared to those with continuous treatment remains unclear.
- An ACTG study (ACTG 5095) found that the risk of treatment failure did not vary by pre-treatment CD4 or viral load in Efavirenz (EFV)-based treatment regimens. These results will allow clinicians to be more confident when using EFV-based regimens, even in individuals with high viral loads or low baseline CD4 counts or both.
- The first direct comparison of EFV-containing regimens and protease inhibitor-containing regimens found that EFV-containing regimens continue to virologically outperform other regimens in treatment naïve patients (ACTG 5142).
- A randomized study of dual versus single ritonavir-enhanced protease inhibitors for protease-inhibitor experienced patients found that dual protease-inhibitor containing regimens did not significantly improve treatment outcomes in patients with highly protease-inhibitor resistant virus (ACTG 5143).

Selected studies that were ongoing or newly initiated by the clinical trials research networks during FY 2008 are listed below by area of research:

Conducting translational research for new drug development

- A pilot study to determine the effectiveness of adding raltegravir to ART therapy in further reducing viral load in HIV infected patients who have already achieved viral suppression below the level of detection of standard assays completed follow-up. (ACTG 5244)
- A pilot study of first phase viral decay rates in treatment naïve individuals treated with raltegravir and TDF/FTC opened to enrollment (ACTG 5248)
- A phase I/II dose-finding safety/activity study of AMD11070 (an oral CXCR4 entry inhibitor) completed follow-up. (ACTG 5210)
- Lot study to test whether enhancing ART treatment regimen with a fusion inhibitor known as Enfuvirtide or T-20 decreases the number of resting CD4 cells that become infected with HIV (ACTG 5173). Fusion inhibitors work by blocking HIV from entering human cells. Specifically, this study will evaluate whether treatment naïve, chronically infected individuals treated with Enfuvirtide plus emtricitabine, ritonavir, saquinavir and tenofovir disoproxil fumarate have a measurable decline in the latently infected CD4 cell reservoir.

Optimizing clinical management of HIV/AIDS, including co-infections and other HIV-related conditions:

- A pilot study to evaluate the safety and effectiveness of the protease inhibitor (PI) lopinavir/ritonavir (LPV/r) in HIV infected individuals who are failing an anti-HIV regimen that includes an non-nucleoside reverse transcriptase inhibitor (NNRTI) continues to enroll participants (ACTG 5230)
- A phase III study to determine the benefit of adding a nucleoside reverse transcriptase inhibitor (NRTI) to a new anti-HIV drug regimen for the suppression of HIV opened to enrollment (ACTG 5241)
- A phase II study of safety, tolerability and pharmacokinetic interactions of atazanavir (ATV), a protease inhibitor, and rifampicin completed follow-up (ACTG 5213). Rifampin is used for the treatment of tuberculosis and has been shown to lower concentrations and decrease the effectiveness of some anti-HIV drugs.
- A pilot study to determine the impact of the antiretroviral tenofovir on lipid levels in HIV infected adults on stable anti-HIV drug therapy completed follow-up and the primary analysis has been completed.(ACTG 5206)
- A phase II trial of immunogenecity and safety of a Human Papilloma Virus (HPV) vaccine in HIV-infected women opened to enrollment (ACTG 5240)
- A phase I/II study of safety and immunogenecity of an HPV vaccine in HIV infected men, conducted in collaboration with the AIDS Malignancy Consortium (AMC), opened to enrollment (ACTG 5246)
- A phase II/III trial to determine the effectiveness of uridine supplementation in treating HIV-infected individuals on stable ART with lipotrophy, the loss of body fat from particular areas of the body and a common side effect of ART; completed follow-up (ACTG 5229).

Developing microbicides to prevent HIV acquisition and transmission

- An observational cohort study of women who acquired HIV infection while using a topical microbide or oral antiretroviral pre-exposure prophylaxis in a previous trial continues to enroll participants (MTN 015)

- A phase I study of Tenofovir vaginal gel, an antiretroviral-based candidate microcide, continues to enroll participants. The gel is applied prior to caesarean delivery to determine the levels of tenofovir in HIV uninfected pregnant women and the degree to which the gel's active ingredient may be transferred to the fetus (MTN 002).
- A phase II study comparing adherence and pharmacokinetics of oral versus vaginal preparations of Tenofovir continues to enroll participants (MTN 001)
- A phase I study evaluating the safety and acceptability of the microbicide VivaGel in sexually active young women continues to enroll participants (MTN 004)

In addition to these ongoing microbicide trials, the HPTN has been planning for the implementation of a topical microbicide/pre-exposure prophylaxis trial using tenofovir gel and the antiretroviral truvada. The study referred to as the VOICE study or MTN 003) is expected to open to enrollment in 2009.

A phase II/IIb study (HPTN 035) comparing two topical microbicides – BufferGel and PRO 2000/5 Gel (P) – was also completed in FY 2008. Preliminary data should be available in early 2009.

Creating strategies to prevent mother-to-child HIV transmission (MTCT)

- A phase I/II pharmacokinetic and safety study of a protease inhibitor (BMS-232632, Atazanavir, ATV, Reyataz™) in combination regimens in ART-naïve and experienced HIV-infected infants, children, and adolescents continues to enroll participants (P1020A)
- A prospective cohort study to assess the effectiveness of interventions (e.g., ART and mode of delivery) at preventing MTCT and/or improving women's health continues to enroll participants (P1025)
- A study to determine what doses of anti-HIV medications are appropriate for pregnant women continues to enroll participants (P1026S)
- A phase II study comparing the effectiveness in reducing NVP resistance of 3 different anti-HIV drug regimens given to HIV infected pregnant women during and after their pregnancies completed enrollment (P1032)
- A phase III study of the safety and efficacy of three neonatal ART regimens for preventing intrapartum HIV transmission continues to enroll participants (P1043)
- A study assessing the safety and toxicity among infants born to HIV-infected women enrolled in ART treatment protocols in diverse areas of the world continues to enroll participants (P1054)
- A phase II trial to compare the effectiveness of an NNRTI-based regimen versus a protease inhibitor (PI)-based regimen in HIV infected infants who have or have not been exposed to single dose continues to enroll participants (P1060)
- A phase I/II study of safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine in HIV-infected youth continues to enroll participants (P1065)
- A phase I/II study to evaluate the safety, pharmacokinetics and antiretroviral activity of raltegravir in HIV infected children and adolescents continues to enroll participants (P1026S)
- A phase III study to evaluate the efficacy and safety of an extended regimen of NVP for prevention of mother-to-child transmission of HIV through breastmilk continues

to enroll participants. NVP treatment is extended from 6 weeks to 6 months or through cessation of breastfeeding, whichever is earliest, and compared with placebo among infants who are provided NVP for the first 6 weeks (through Day 42) of life and are HIV-uninfected at age 6 weeks (HPTN 046)

- A phase I study is continuing to enroll participants to evaluate the safety and pharmacokinetics of tenofovir disoproxil fumarate, when administered to HIV-infected pregnant women during labor and to their infants during the first week of life, to determine the optimal regimen for a subsequent efficacy trial, if indicated. (HPTN 057)

Developing new methods of HIV prevention
Ongoing trials within the HPTN include:

- A study comparing the HIV infection rates of two groups of couples where only one partner is infected with HIV, to determine whether ART can prevent the sexual transmission of HIV in HIV serodiscordant couples. Both groups will receive HIV primary care and couples counseling sessions to teach them how to reduce their risk of transmission. In one group, the HIV-infected individual will receive antiretroviral therapy upon enrollment plus HIV primary care. In the other group, the infected individual will receive HIV primary care, and antiretroviral therapy will be initiated when the participant has a CD4 cell count below a fixed threshold or develops an AIDS-defining illness. Data collected in Africa and Thailand suggest that the higher the viral load in the blood, the more likely the chance for transmission. ART reduces the viral load in the blood, as well as in genital secretions, strongly suggesting that ART may make HIV-infected people less contagious. (HPTN 052)
- A phase III randomized controlled trial that will assess the efficacy of buprenorphine/naloxone treatment in the prevention of HIV transmission among opiate-dependent injectors by reducing drug use and associated risk behaviors. Although a variety of prevention interventions have targeted injection drug users, no intervention has been as widely endorsed, nor as thoroughly examined as substance abuse treatment, specifically methadone treatment. (HPTN 058)
- A study in which communities in Africa and Thailand are being randomized to receive either a community-based HIV voluntary counseling and testing (VCT) intervention plus standard clinic-based VCT, or standard clinic-based VCT alone. This is the first international randomized controlled Phase III trial to determine the efficacy of a behavioral/social science intervention with an HIV incidence endpoint. (HPTN 043)

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 some invasive treatments that are commonly used today, such as more invasive surgical techniques. IGI techniques are potentially 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 and increase the ability to assess complete tumor resection. For diagnostic 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 less invasive, more precise, 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 potentially disruptive technologies that, in some cases, may completely replace

conventional surgery or more invasive procedures. For example, non-invasive treatments using high-intensity focused ultrasound technology, combined with image-guidance (e.g., MRI or ultrasound) may lead to substantial changes in the treatment of uterine fibroids, cancer, and other diseases. In order for these changes to occur, research is needed to develop and validate these integrated imaging and treatment systems for specific applications.

PERFORMANCE ANALYSIS

Target Context and Conditions

The development of a new drug is often characterized as an ever narrowing funnel where the testing of thousands of compounds leads to hundreds of promising compounds and, potentially, to one successful therapy. The development of an image guided intervention goes through a similar path but with significant differences in scale. Typically, tools and techniques are developed to evaluate the feasibility of tens of ideas. Ideas that are found to be feasible, often after several separate procedures or techniques have been developed and integrated, then need to be prepared for clinical use and validated in a first in human demonstration. Finally, an image guided intervention that makes it to this point needs to be further developed to make it practical, cost-effective, safe and effective.

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 image-guided intervention technologies that create minimally-invasive, image-guided procedures that may replace some traditional surgeries and more invasive techniques. This goal will be accomplished in two phases of investigator initiated research. 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.

Baseline 2008

- (FY07) Image-guided interventions are currently being tested in animal models and phantom studies.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Test at least one image-guided intervention in humans from the baseline of 17 active grants in FY07.	(MET) Two new MRI related techniques from the baseline of 17 active grants were tested in humans to assist with neurosurgery or in the treatment of uterine fibroid tumors.	Demonstrate prototype feasibility of at least two new image-guided intervention systems that have the potential to advance into new clinical applications.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Two new MRI related techniques from the baseline of 17 active grants were tested in humans to assist with neurosurgery or in the treatment of uterine fibroid tumors. In neurosurgery, presurgical images from multiple imaging modalities - MRI, PET scans, ultrasound, optical images, etc - are used to identify areas that need to be removed and critical areas that must be avoided during neurosurgery. But as the neurosurgery progresses, the brain can move within the skull and the critical areas become shifted from the locations seen in these presurgical images. NIH researchers developed and tested a new method to compensate for these movements by utilizing new developments in mathematics and high-performance computing. Using this technique, the presurgical images can again be warped and co-registered with an MRI acquired during the surgical procedure. These new mathematical and computing methods provide critical information to guide the neurosurgeon in identifying key regions during surgery in this image guided procedure.

NIH researchers tested a new MRI techniques developed to precisely monitor the heating and destruction of uterine fibroid tumors by focused ultrasound. MRI not only guides the procedure by providing anatomical information but also measures the temperature of the fibroids during treatment. Uterine fibroids are heated and destroyed non-invasively (without any surgical incision) using focused, high-intensity ultrasound while surrounding tissue is monitored to stay at a safe temperature. Prior to this, non-invasive technique uterine fibroids were removed by invasive procedures such as hysterectomy or blocking the uterine artery that feeds the tumor.

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.

In FY 2007, the available survey, clinical and image data were expanded to include baseline and 12 month clinic visits from 2,686 OAI participants. Because of outstanding performance of the centers, investigators also released baseline survey and clinical data from the remaining 2,110 participants ahead of schedule.

To accommodate requests from the research community, the OAI switched the order of its 2008 data releases. Many people who have OA exhibit significant changes that are detectable with x rays over the course of 2 years, whereas fewer show considerable changes in only 12 months. To provide researchers with the ability to enhance their studies by including the later time point, rather than giving them information from the baseline and 12 month visits of more people, the OAI decided to first release the 24 month survey and clinical data and images from the 2,686 participants for whom corresponding baseline and 12 month data and images are available.

Also in 2008, the OAI will provide funding for quantitative and semi-quantitative analysis of baseline, 12, and 24 month x ray and MR images for approximately 300 participants. The data will be posted to the Web site for use by others in the research community who are identifying and evaluating biomarkers for surrogate OA endpoints.

Additionally, biospecimens (blood, urine, and DNA) from the OAI will be made available to the research community in late FY 2008. Access to these specimens will be by application only, and data generated will be shared through the OAI Web site.

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. To that end, the NIH and private partners held a meeting in June 2008 to highlight the accomplishments of the OAI and to discuss plans for a possible extension of the follow-up of the cohort by an additional 4 years.

Baseline 2008

- (FY07) Baseline images, 12-month survey and clinical data, and 12-month images are available for 2,686 participants. Baseline survey and clinical data are available for all 4,796 participants.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
		Survey, clinical, and image data from baseline and 12-month clinic visits of 2,500 OAI participants will be available from the OAI Web site.	(MET) Researchers can access baseline survey and clinical data for all 4796 participants and baseline images, 12-month survey and clinical data, and 12-month images for 2686 participants.	Image data from baseline and 12-month clinic visits of remaining 2,110 OAI participants will be 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.	(MET) Survey, clinical, and image data are available from three clinic visits by 2,686 participants. Baseline and 12-month image data for the remaining 2,110 participants also are available.	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-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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was met. In addition to posting image data from baseline and 12-month clinic visits for the second half of the cohort, and survey and clinical data from 24-month visits for the first half, investigators released the 24-month image data for the initial 2,686 participants. Providing researchers with a full series of survey, clinical, and image data for 2,686 participants at three time points spanning 24 months will allow analyses of the data for joint changes over time to begin sooner than they would have had the 24-month image data been released in FY 2009 as originally planned. As noted above, the OAI is a resource to facilitate a range of scientifically rigorous studies by the OA research community and should aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis.

Actual numbers of participants for which certain data elements are available (and expected numbers for data elements that were not released as specified in the targets):

	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				
FY 2007	4796 (2500 expected)	2686	2686	2686		
FY 2008	4796	4796	4796	4796	2686	2686 (0 expected)

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 2008, more than 1000 researchers from 51 countries had registered to access OAI data. A total of 2,380 clinical datasets have been downloaded.

In 2008, 5 articles using OAI data were accepted for publication in peer reviewed journals. The OAI data also were featured in at least 28 posters and oral presentations at major scientific meetings such as the Osteoarthritis Research Society International meeting and the American College of Rheumatology annual meeting. The American College of Rheumatology also reserved time at its annual meeting for a session to introduce its members to OAI resources. The session, titled the NIH Osteoarthritis Initiative Public Data User Workshop, provided an overview of OAI design, subject characteristics, data and images; an introduction to the OAI Web site and the OAI data access policies; information about the image data that are available to researchers; and an opportunity for participants to ask questions.

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

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.

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. However, community tailored interventions to reduce dental caries may be feasible.

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.

NIH is 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.

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.

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 2008

- (FY07) A study is underway but not yet completed. Previous studies have determined that fluoride varnish applications once every 3 months is an effective strategy.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) Completed a clinical trial to demonstrate treatment feasibility and effectiveness among children of migrant farm workers. Over 600 children enrolled and 84% completed the 2 year follow-up.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. The FY 2009 target was MET EFFICIENTLY and the goal was ACHIEVED.

Intervention 1 (FY 2008 Target)

The NIH sponsored a clinical trial designed to test the feasibility and effectiveness of a lower frequency fluoride varnish regime to reduce early childhood caries in children of farm workers. Targeted participants in the trial were the children of farm workers residing in the Yakima Valley in Washington state. These farm workers are mostly descendants of Hispanic migrants. Previous studies supported the effectiveness of fluoride varnish for young children but questions remained about the most effective frequency and dose. In this trial, children ages 3 to 6 were randomized to one of two treatment groups to compare the efficacy of three doses of fluoride varnish in two weeks compared to two doses of the same varnish separated by six months. The primary outcome is the incidence of caries, measured annually.

The intervention was adapted to the community by networking with Head Start programs, schools, and clinics and by developing targeted communications including: parent meetings, flyers sent to homes, local radio announcements. These activities helped build support for the

intervention among the community and aided in recruiting and retaining participants. The recruitment goal of 500 children was exceeded with the study enrolled 601 children of migrant farm workers. Participant retention was 84% with 507 of the 601 enrolled children completing the 24-month annual exam. Multiple factors assisted in participant retention including widespread community support for the project, working with long-time community partners, and having access to children at school. This retention rate should allow researchers to establish the effectiveness of the intervention.

The clinical trial determined that the intervention was feasible in this underserved community. Targeted communications and other community involvement supported higher than expected participation rate and retention rates, and the creation of widespread community support. Effectiveness results have not been finalized. However, preliminary data suggests that receiving a high-frequency treatment has a similar effectiveness as the traditional treatment.

Intervention 2 – (FY 2009 Target)

The NIH also sponsored a clinical trial designed to test the feasibility of an intervention combining an antibacterial rinse (chlorhexidine) in mothers and fluoride varnish in children to reduce the incidence of dental caries. The trials recruited and enrolled pregnant Hispanic women in a dental disease management program. The trial compared oral health counseling alone to the combination of oral health counseling, chlorhexidine rinse for the mothers, and fluoride varnish for their babies. Participants began the study during their second trimester of pregnancy and were seen about every six months with their babies until the babies were three years old.

The intervention was adapted to the target audience with input of the community. Changes included developing culturally appropriate and targeted approaches to maintain contact with the participants, making the study visits convenient, providing incentives (such as grocery store vouchers, free dental cleanings, social support, and miscellaneous gifts), and making referrals for other health services. Trial recruitment of 556 participants enrolled exceeded expectations. The retention goal of 40% at the Month 4 post-partum visit was exceeded as 65% remained in the study at that time. Retention rates remained above expectations throughout the clinical trial.

The clinical trial determined that the intervention was feasible in with this underserved target audience in the community through higher than anticipated recruitment and retention, as well as the early completion of sample development. Intervention feasibility was supported through developing culturally appropriate communication, incentives, and improving access.

Goal Completion

This goal was completed by determining the feasibility of applying three tailored interventions (two in FY 2008 and one in FY 2007) designed to prevent dental caries in one or more underserved populations. In FY 2007, feasibility testing was completed on using motivational interviewing techniques in a low-income, inner city African American community. Through testing the feasibility of these tailored interventions to prevent dental caries, NIH has identified interventions that could be implemented in underserved populations.

Efficiency

As a result of higher than expected retention rates in the trial, it was possible to recruit the sample earlier than expected. This allowed the trial to be completed in FY 2008. No additional resources were needed to support the clinical trial as the experimental treatment was low cost and the factors associated with high recruitment and retention had little impact on the study budget.

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. Achievement of this goal is conditional on receiving the requested levels of funding.

Examples of program components that will be implemented during the pilot phase of the NCCCP include expansion and/or addition of integrated multi-specialty cancer care, clinical research, palliative care, and genetics and molecular testing programs; increased use of evidence-based guidelines for cancer care; enhanced linkages with NCI-designated Cancer Centers for referrals and research support; introduction of survivorship plans into initial patient care plans; increased use of navigation and outreach programs to reduce cancer health disparities; appropriate medical and administrative staffing; and assessment of infrastructure requirements for IT integration with caBIGTM and biospecimen resource compliance with the First Generation Guidelines for NCI-Supported Biorepositories.

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

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

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

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.

FY 2009 activities toward achieving the goal

Studies will continue on the interactions between osteoblasts and matrix components osteonectin, fibrillin-2, CTGF, and DMP-1. These efforts will add new information about

the molecular mechanisms underlying the interactions, and increase the chances for eventual clinical application of the discoveries.

Baseline 2008

- (FY06) Although fibrillin proteins have been studied as structural components of the matrix, it has only recently been recognized that they may influence the function of bone cells.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	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. 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.	(MET) Fibrillin-2-null mice have reduced bone formation, and the bones show significantly altered material and mechanical properties. The abnormalities reflect defects in their response to TGF-beta.	Complete goal of identifying and characterizing two molecular interactions of potential clinical significance between bone-forming cells and components of bone.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Scientists have determined the properties of bone-forming cells and bones from mice in which fibrillin-2 is absent.

When researchers examined the mechanical and chemical properties of bone from femora of mice that were genetically altered to lack fibrillin-2, the bones were found to be softer (i.e., had a significantly lower hardness) and less rigid (i.e., had a lower Young's modulus) than bones from wild-type controls. Compared with bones from normal mice, the bones also were weaker and less durable (i.e., displayed reduced measures of maximum load and total work to failure).

Researchers also demonstrated that a lack of fibrillin-2 in mice alters development of bone-forming cells called osteoblasts. Through a series of cell biology experiments in which osteoblasts were exposed to different growth factors and signaling molecules, fibrillin-2 was determined to be necessary for cells to interact correctly with a regulatory factor called

transforming growth factor beta (TGF-beta). When this interaction could not occur because fibrillin-2 was missing, the osteoblasts did not differentiate and form bone normally. This seems to be due to disruption of the local balance between antagonistic signals from TGF-beta and another well-characterized protein involved in bone formation and absorption—bone morphogenic protein 2 (BMP-2).

Advances or Other Highlights

TGF-beta is a potent regulator with important effects on many kinds of cells. Multiple components of the bone matrix appear to act together to control the exposure of bone cells to TGF-beta. A molecule called biglycan was found to be involved in the incorporation of TGF-beta into bone matrix. This suggests that fibrillin-2 and biglycan may interact functionally to modulate TGF-beta bioavailability. Now, researchers are developing a mouse model system in which the animals have reduced amounts of both fibrillin-2 and biglycan and will use the model to address whether such interaction really occurs.

Researchers determined that the low bone mass observed in mice lacking osteonectin is due in part to modulation of the effects of parathyroid hormone (PTH). Because PTH regulates the balance between bone formation and resorption under both normal and pathological conditions, the finding revealed an unsuspected role for bone matrix components in hormonal regulation of bone mass.

Progress also has been made in understanding the function of connective tissue growth factor (CTGF), identifying the specific molecular pathways that mediate the effects of TGF-beta on CTGF production. Thus, a picture is emerging of an integrated network in which multiple matrix components are involved in the regulation of bone formation and resorption, with TGF-beta a common factor in their modes of action.

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, have been 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 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 was 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 2008

- (FY06) IDeA/COBRE evaluation initiated.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) NIH has received the final report entitled "Process Evaluation of the Centers of Biomedical Research Excellence (COBRE) Program."	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. The full-scale evaluation for IDeA/COBRE was completed in September 2008. The contractor conducted a process evaluation which focused on the 19 COBREs that were initially funded near the end of FY 2000. The purpose of the evaluation was to determine if the program operations and outputs during the centers' first six years have been successful as well as the success of the junior investigators supported during this period. Some examples of the outputs that were assessed include: successful recruitment of new research faculty and technical staff, expansion of core facilities and successful implementation of 3-5 research projects. The period of performance for the 19 centers in this cohort will be FY 2001 to FY 2006.

The findings that emerged from the present process evaluation illustrate how effective this exploratory program project grant program has been in strengthening the research infrastructure of institutions located in IDeA states. Although it is too early to assess how successful each center has been in developing the state-of-the-art facilities and critical mass of investigators needed to enhance research competitiveness and become a center of excellence, the initial group has performed very well to date in achieving the program's process goals and many COBRE participants commented on how much they have benefited from the program.

A major achievement was the centers' recruitment and retention of a cohort of junior investigators who have done exceptionally well. Their success is especially noteworthy given the current research grant environment and the challenges of building a successful research career in an IDeA state. The study's findings are expected to be helpful to NIH administrators, COBRE program directors, and others interested in developing and evaluating multidisciplinary research center programs.

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 was initiated in a wide range of patients suffering chronic diseases and conditions, and enrollment was completed in March 2007. These data were analyzed in FY 2008 to determine a variety of item characteristics and psychometric properties, to select the most useful items for the final item bank and to develop the CAT system and hard copies (“short forms”). Additional data collection will be conducted in current domains, as well as new areas, to address any remaining questions about psychometric properties of the item banks.

Baseline 2008

- (FY07) More data needed from large, diverse samples of chronic disease patients using the test item pool.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Preliminary item pools to measure the chosen domains (Pain, Fatigue, Physical Functioning, Emotional Distress, and Social Role Participation) have been created based on exhaustive review of existing measures. Initial instruments and methodologies have been developed.	(MET) Administration of the PROMIS item pool to a diverse sample representing a wide range of conditions was initiated in July, 2006.	Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and social role participation.	(MET) Data analysis was initiated in April, 2007, six months ahead of schedule. Primary analyses have been completed, and additional analyses are ongoing.	Conduct primary data analyses of item responses in pain, fatigue, physical functioning, emotional distress, and social role participation domains obtained from large, diverse samples of the general population and chronic disease patients to calibrate items and refine item banks for the PROMIS instrument.	(MET) Primary data analysis has been conducted to allow release of calibrated item banks for preliminary versions of the PROMIS instrument.	Complete goal of developing 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. Analysis of item responses from testing in large and diverse populations in initial PROMIS core domains (pain, fatigue, physical functioning, emotional distress, and social role participation) has resulted in the release of psychometrically-calibrated (using item response theory-IRT) item banks for the CAT system and short forms. These analyses confirmed that the item responses fit the strong assumptions of IRT modeling including unidimensionality, local independence and monotonicity. The items therefore captured the core domains. Such psychometric properties at the item level allow for item banks that can be flexibly administered, for a wide range of diseases and disorders, and continuously refined. These PROMIS tools are available for testing and validation and will contribute directly to the development and continual improvement of the instrument as it is applied in a broad range of clinical settings including research trials, patient-physician encounters and surveys.

Advances or Other Highlights

PROMIS has initiated longitudinal clinical trials in adults with a variety of chronic illnesses (e.g., lower back pain, depression, chronic obstructive pulmonary disorder, congestive heart failure, and arthritis) to validate PROMIS domains clinically. These studies are designed to assess sensitivity to change and compare PROMIS tools to traditional patient-reported outcomes (PRO) instruments.

In addition, PROMIS will investigate the impact of different modes of administration (e.g., computer, interactive telephone voice response, personal digital assistant technology, and hard copies) on PRO reporting.

PROMIS is expanding its outreach and education efforts to the research community, to ensure ease of access and understanding of PROMIS item banks and techniques for clinical researchers and collaborators.

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 was added by the Centers for Disease Control to augment the vision component for 2005-2006, and both eye components in the survey have been extended to 2007-2008. These changes will provide better estimates of the extent and nature of vision impairment in the U.S. Knowledge about the nature and extent of visual impairment in the United States will allow public health officials to more efficiently tailor surveillance activities to identify individuals in need, health providers to better supply corrective modalities to individuals whose vision can be improved and rehabilitation services to those with uncorrected visual impairment, and health economists to allocate sufficient resources to this effort. The end result will be to provide more Americans with normal vision allowing them to more safely perform activities for which vision is required, including driving, occupational, and recreational activities.

Disease Burden

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

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

Rationale

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

The NIH collaborated with the National Center for Health Statistics (NCHS) to develop a vision component for NHANES in support of the vision objectives in Healthy People 2010. After collection of baseline data through 2004, changes were made to the 2005-2006 survey, including revised questions to capture better information on severe visual impairment, as well as extending the vision-related quality of life questions to ages 20 and older (compared to those 50 and older for NHANES 1999-2004). As a nationally represented survey of Americans with both interview and examination components, NHANES is uniquely suited to gather, in a cost effective manner, information on vision and ocular health from both a quality of life and medical perspective. Because NHANES encompasses a range of health and nutritional components, the opportunity exists to identify other health conditions that may be related in some manner to visual impairment or be experienced by individuals with visual impairment. Insights about concurrent 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 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 internal processes for deciding which components are included during each survey cycle as well as how survey data are acquired, managed and released to co-sponsoring agencies and to the public. At the end of 2008 survey period, NHANES staff will facilitate a preliminary analysis of the raw survey data: verifying the merge of individual responses into a secure, annotated database using unique survey participant identification numbers; checking for errors and inconsistencies; applying statistical weights based on sampling methodology; and, cross-validating data items across survey response

categories. At the completion of this preliminary analysis in late 2009, co-sponsoring agencies, such as NIH, will take receipt of data for an additional quality control review of the consolidated data file and its related data documentation and will have 60 calendar days to report any issues back to NHANES staff. Vision data and related documentation from the 2007-2008 NHANES survey are expected to be publicly released by NCHS in 2010 and, once in the public domain, will be used to develop national estimates of visual impairment.

Baseline 2008

- (FY07) Approximately 3,500 people surveyed in FY 2007.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) NHANES has conducted over 6,700 vision exams, sufficient to maintain the power of the study.	Complete preliminary analyses of the data to prepare national estimates of visual impairment.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. NHANES Survey 2007-2008 recruited participants at the anticipated rate, and conducted an estimated 6,728 examinations in total: 3,224 examinations in 2007; an estimated 3,504 examinations in 2008. This response level will provide sufficient power for the creation of stable national 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). These participants are then invited to participate in the examination portion of the survey and are asked to report to a mobile examination center. The vision exam is one of many examinations included in this second portion of the survey. As of 9/30/08 (21 months into the 24-month survey period), 6,405 survey participants reported to Mobile Examination Centers and of these 6,027 (94%) had vision exams. At this rate, NHANES staff estimated that an additional 701 people would have had vision exams between October and December 2008, when the survey cycle ends.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The baseline is slightly lower than estimated last year. Instead of 3,400 participants in 2007, the actual total was 3,224 (95% of the estimated rate). When supplemented with totals from 2008, the sample size is expected to be sufficient for generating stable national estimates of vision impairment.

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.

Baseline 2008

- (FY07) Approximately 15-20 studies are underway that may contribute to formation of effective implementation strategies.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Identify three (3) implementation mechanisms, strategies, or techniques to improve the uptake of effective interventions in healthcare settings.	(MET) Three mechanism, strategies, or techniques, were identified to improve the uptake of effective interventions in healthcare settings, including community-based models, evidenced-based care framework, and collaborative frameworks.	Identify and test at least three (3) key variables for measuring implementation to improve the uptake of effective interventions in healthcare settings.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Progress has been made toward the identification of implementation mechanisms, strategies and techniques to improve the uptake of effective interventions in healthcare settings, including community-based models, evidenced-based care framework, and collaborative frameworks.

A number of innovative approaches have been identified to integrate effective clinical and health services interventions into community-based settings. NIH researchers developed a community implementation model called the Communities That Care prevention operating system to stimulate the adoption of effective prevention interventions. This model provides manuals, tools, training, and technical assistance as a guide for communities to plan and implement community preventive services to reduce adolescent substance use, delinquency, and related health and behavior problems. A randomized controlled community trial was conducted to investigate the baseline comparability of the intervention and control communities in the study.

Another study uses the Center for Disease Control and Prevention's Replicating Effective Practices (REP) Framework to implement bipolar care into community-based organizations. The conceptual framework has been at the forefront of developing systematic and effective strategies to prepare HIV interventions for dissemination. Key elements of REP consist of four phases: pre-conditions (e.g., identifying need, target population, and suitable intervention), pre-implementation (e.g., intervention packaging and community input), implementation (e.g., package dissemination, training, technical assistance, and evaluation), and maintenance and evolution (e.g., preparing the intervention for sustainability). Findings demonstrated that REP is a well-suited framework for implementing health care interventions, as it specifies steps needed to maximize fidelity while allowing opportunities for flexibility (i.e., local customizing) to maximize transferability.

NIH researchers also documented the use of a collaborative model to create sustained improvements in depression care. This study uses local practice champions (PC), from sixteen practices of the American Academy of Family Physicians National Research

Network and the American College of Physicians Practice-based Research Network, to implement practice change strategies and effective depression care elements. The Patient Health Questionnaire (PHQ-9) was used for screening, diagnosis, surveillance, tracking and care management, and self-management support. A pre- and post-intervention depression care survey was gathered from all practice clinicians and qualitative data collected via interviews with PCs and field notes. The results indicate that all practices had implemented the PHQ-9 for depression case-finding and thirteen for monitoring severity; five practices had implemented tracking and care management and, 1 for self-management support. Overall, significant and measurable improvements were reported on several subscales of the clinician survey and in the uptake and diffusion of the office procedures and systems known to improve depression care.

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. A number of interventions, including foods, diets, drugs, and hormones, are tested through this program, which began in 2003.

Under this program, intervention testing is conducted in two phases. The first stage, which typically lasts 2 to 2 ½ years, is primarily a lifespan study with a few other parameters measured. Interventions that appear to increase lifespan, based on Phase I results, move on to Phase II, which involves a broader spectrum of assays.

In the Interventions Testing Program, 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, benefits to the public health would include reduced health care costs for the elderly as well as the individual benefits of maintaining one's independence. This research may also 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 FY 2008, NIH identified three compounds that are potential interventions to extend lifespan in a mouse model. In FY 2009, NIH will begin primary (Phase I) testing of those interventions. Also in 2009, Phase II studies on the most promising compound from Phase I will be designed. In 2010, Phase II testing will begin on this compound.

Baseline 2008

- (FY07) 14 interventions are currently undergoing Phase I testing.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Identify at least three potential interventions to extend lifespan in an animal model, and begin Phase I testing with these interventions.	(NOT MET) NIH identified three potential interventions but did not begin Phase I testing.	Begin Phase I testing of at least three potential interventions and design approach for the first Phase II pilot testing.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target to identify at least three potential interventions to extend lifespan in an animal model and begin Phase I testing was NOT MET. NIH did identify three compounds with the potential of extending lifespan in a mouse model. However, because the ITP is on bridge funding this year while the competitive renewals are revised and resubmitted, there are not sufficient funds to initiate any new testing, only to continue the testing that is in progress. The primary (Phase I) testing of those interventions will begin in 2009, as funds become available.

The three compounds identified in 2008 are SRT-X, MitoQ, and 17 α-estradiol. SRT-X is a compound that is related to resveratrol, but with a greatly enhanced bioavailability and stability. MitoQ is an antioxidant that is designed to accumulate in the mitochondria (the cell's energy source), potentially increasing its efficacy. 17 α-estradiol is chemically related to 17 b-estradiol, a hormone with documented neuroprotective effects. Compared to17 b-estradiol, however, the ability of 17 α-estradiol to bind to estrogen receptors in the body is greatly reduced, limiting undesirable side effects while still providing significant neuroprotection.

Advances or Other Highlights

As of 2007, 14 interventions were undergoing Phase I testing, and early results are available for the first compounds that were tested. Two addition publications are published or in press in 2008.

In addition, the interim analysis of the second cohort of mice produced some exciting preliminary results indicating that one of the compounds extended the median survival age (when 50% of the mice had died) when feeding this compound began at 20 months of age (middle age). This finding is particularly exciting because it shows that the benefit does not require life-long treatment, but can be initiated at middle age, the time that most people begin to seriously consider the health in their senior years. These results were presented at Cold Spring Harbor meeting on the Molecular Biology of Aging in September 2008 and at the Nathan Shock Center meeting on Caloric Restriction in October 2008.

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 2008

- (FY07) New methodologies may be applied to address interactions of depression with co-morbid physical disorders.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) Researchers identified at least four methodologies for examining interactions between depression and other co-morbid disorders including imagining techniques, observational studies, and animal models.	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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET. Researchers identified at least four methodologies for examining interactions between depression and other co-morbid disorders. Researchers used techniques such as imaging studies, naturalistic observational studies, and animal models to investigate the interconnections of depression with Alzheimer's disease (AD), chronic obstructive pulmonary disease, cancer, and epilepsy.

One study used brain imaging techniques with human subjects to investigate biomarkers primarily associated with AD pathology or other late-life dementia (e.g., vascular dementia) for potential relationship to late-onset depression. The study demonstrated that depression may herald the development of AD in some individuals using positron emission tomography (PET) imaging to evaluate whether symptoms of AD were present in the brains of elders who received treatment for major depression.

NIH researchers also used brain imaging techniques on human subjects to investigate depression as a risk factor for accelerated disease progression, poorer treatment response, or other negative outcomes in patients with cardiovascular disease. By analyzing magnetic resonance images (MRI), the study examined how the use of antidepressants influenced the progression of markers of cardiovascular disease. MRI findings indicated that the use of antidepressants may worsen cardiovascular disease markers.

Naturalistic studies of patients with comorbid depression and medical illnesses have used correlational analyses to disentangle effects of one disorder on the other or to identify key variables or pathways by which the two disorders may interact. NIH researchers examined the association between activities of daily living (ADL) and instrumental activities of daily living (IADL) dependence and major depression among older primary care patients with heart failure. Trained nurses and social workers interviewed and assessed patients using several instruments. For ADL dependence, patients were asked about six functions, including transferring from bed to chair, toileting, dressing, bathing, eating/feeding, and walking. For IADL dependence, patients were asked about meal preparation, ordinary housework, managing finances, managing medications, telephone use, and shopping. The findings indicate that heart failure has a modest association for depressed patients with ADL dependence and large effect for those with IADL dependence, resulting in a progressively greater likelihood of major depression as the number of IADL increases.

NIH-funded researchers created an animal model that can be used to study epilepsy and depression comorbidity Epidemiological evidence indicates that depression is the most common psychiatric disorder in patients with epilepsy, but little experimental evidence exists to explain mechanisms that contribute to this comorbidity. This study selectively bred rats for susceptibility or resistance to depression-like behaviors and assessed seizure susceptibility and severity parameters. The rats bred for susceptibility to depression-like behaviors experienced higher mortality rates from induced seizures than rats bred for resistance to depression. In addition, researchers are currently conducting genetic analyses of these rat strains to investigate the molecular links between epilepsy and depression.

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.

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. Building on a thirty-year experience with chronic disease registries at the Alaska Native Medical Center, 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.

NIH also is 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.

NIH researchers at the Stroke Disparities Program (SDP) are developing an integrated program of collaborative research in the Washington, DC area to overcome current gaps in stroke knowledge in an underserved population. The three key areas of stroke disparities under study include utilization of the intravenous (IV) clot-busting drug tissue plasminogen activator (tPA), secondary stroke prevention, and an observational study of cerebral microbleeds -- small brain bleeds that may serve as useful imaging markers of impending larger brain bleeds -- in primary intracerebral hemorrhage (ICH).

Baseline 2008

- (FY06) WHC lacks patient data needed to identify stroke risk factors, evaluate stroke prevention programs

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Established research infrastructure and advisory committees, and hired director for SPIRP.	(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.	(MET) Established a database of stroke patients; began populating database.	Recruit and train four practitioners to serve as community-based case managers in a secondary stroke prevention trial targeting African Americans and Hispanics.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. The NIH has developed web-based electronic databases for each of the 3 Stroke Disparities Program (SDP) projects. These databases are maintained by the Biostatistics and Data Management core housed at Medstar Research Institute (the research institute affiliated with Washington Hospital Center).

The purpose of Project 1 (ASPIRE) is to demonstrate whether emergency medical services-designated transport increases utilization rates of tissue plasminogen activator (tPA), a clot-busting drug, in the Washington, DC area to improve access to and delivery of acute stroke treatment in an underserved urban community. The primary outcome measure is the intravenous tPA treatment rate for acute stroke at study hospitals (five in Washington, DC and seven in Baltimore, Maryland). To date, baseline data has been collected and entered into the SDP database on a total of 808 subjects.

The purpose of Project 2 (PROTECT DC) is to demonstrate that a community health care navigator can increase recurrent stroke prevention treatment compliance compared to usual recurrent stroke prevention care in a randomized trial. To date, 20 subjects have been randomized.

Project 3 (DECIPHER) is a prospective, longitudinal MRI-based observational study of cerebral microbleeds in primary intracerebral hemorrhage (ICH). To date 48 subjects have been enrolled.

Advances or Other Highlights

The Washington Hospital Center Program/SDP has made other recent advances, in addition to initiating the data collection that was part of the FY 2008 goal. With respect to Project 3, the research team published findings in October 2008 on the prevalence and significance of brain microbleeds. The results show that racial differences exist in the prevalence of this condition, in patients presenting with ICH. ICH is linked to hypertension and previous research had indicated that this condition is more common in some populations, including blacks and Hispanics. The current study extends this finding by providing evidence that microbleeds are more prevalent in the black population as well, even when the research team adjusted for age and hypertension. The team also explored alcohol consumption as a risk factor and found that heavy alcohol use was also independently linked to these microbleeds. The results suggest that the burden of blood vessel disease is borne unevenly by the population, and that imaging may help reveal which individuals are at risk for clinically significant brain bleeding. Further research in this area should reveal intervention strategies that will prevent subsequent ICH in high-risk black populations.

The Alaska Native Stroke registry continues to meet and exceed their predefined milestone. To date 350 stroke events have been recorded in the Registry with 75 percent of those being fully extracted. Consistency and accuracy of abstractions continues to increase as staff experience increases and as a result of the completion of the Operations Manual finalized in June 2008. A manuscript on the stroke mortality of Native Alaskans was submitted to the

journal Stroke in May 2008 and a methods paper submitted to the American Journal of Epidemiology in June 2008. Study investigators regularly present information on incidence and prevalence of Stroke in Alaska Natives at key scientific meetings. The program continues to seek participation and guidance from regional tribal board leaders and has access to representatives from the most remote regions of the state. This participation provides them with an improved and up-to-date understanding of community concerns and a connection to the communities for future efforts. With the 2006 Scientific Advisory Committee (SAC; composed of the Principal Investigator, the Nurse Coordinator, and local experts assisting the project) and Program Advisory Committee (PAC; composed of national experts in stroke, epidemiological research, and NIH staff) decision to expand their scope from regional to statewide data collection and the enrollment of more cases the team is currently developing an interventional study aimed at better control or risk factors in stroke patients to prevent recurrence of stroke. The proposal for this has been discussed at the June 2008 PAC meeting and with NIH staff for further guidance.

In addition to these activities, two educational projects run by the 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; interim results from this project published in November 2007 suggest that the intervention can improve the children's 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). In addition to these activities, the NIH also continues to support research into treatments and interventions to improve cardiovascular health in minority communities.

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 2008

- (FY07) Preliminary analyses of changes of brain growth in children over time completed.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(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.	(MET) Prepared and disseminated three stages of anatomical neuroimaging scans and other data, 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 (BIRN) to enable researchers outside the project to collaborate and share information gained from subsequent analyses.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. Scientists have developed systems that can be used to guide an upper extremity robot to learn a patient's ability to complete a movement, to assist the patient in completing the movement, and to provide only the assistance needed. An adaptive controller ascertains a dynamic model of the patient's arm and develops a model of the patient's ability and effort. Based on these models, separate control algorithms for impeding and assisting movement can be developed and used.

Advances or Other Highlights

A Data Use Certification process has been developed for downloading the project data. Data downloading has a graphic user interface which allows the user to choose all or specific data fields in a range of formats. Raw structural scans have been made anonymous and are available through a free software download. Software to analyze particular features, areas, and volumes of brain scans is also available.

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 compiled the Manual of Procedures (MOP) and delivered the MOP to all hearing screening sites (FY 2007). Third, the NIH-supported scientists will initiate patient enrollment at all hearing screening sites (FY 2009). 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 2008

- (FY07) Manual of Procedures (MOP) delivered to all hearing screening sites.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
	(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.	(MET) The study was granted a clinical exemption, which allows for the collection of information from the public without the need for submission to the Office of Management and Budget (OMB).	Initiate patient enrollment at 7 hearing screening sites to enroll approximately 10,000 children.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. The NIH and the principal investigators obtained OMB approval for collection of information from the public for the CHIMES study.

According to the NIH Policy Manual section 1825 on collection of information from the public, the Paperwork Reduction Act (PRA) provides that a Federal agency shall not collect or sponsor a collection of information on identical items from 10 or more public respondents without obtaining approval from the Office of Management and Budget (OMB) for the data collection plans and instruments and for the information requirements in regulations. When the information is gathered from individuals undergoing treatment or clinical examination for a clinical condition, the information related to patient care and clinical research is clearly in the public interest. The process of approving this is called clinical exemption from public comment and OMB review and has been delegated by OMB to the NIH Clinical Exemption Review Committee (CERC). The NIH CERC includes the Clinical Exemption Coordinator (CEC), at the Office of Extramural Research (OER)'s Project Clearance Branch.

The Project Officer for the CHIMES Study Contract submitted the appropriate forms to the

NIH Project Clearance Branch. The study was granted a clinical exemption. A clinical exemption allows for the collection of information from the public without the need for submission to the Office of Management and Budget (OMB) as required by the PRA.

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 3,100 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 September 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. Achievement of this goal is conditional on obtaining approvals for initiation of the trial from the Data and Safety Monitoring Board and from all local Institutional Review Boards, as well as receiving the requested levels of funding.

Baseline 2008

- (FY07) Trial protocol and model informed consent documents developed.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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 enrollment of 470 subjects.	(EXT) This target has been extended until FY 2009.	Achieve cumulative enrollment of 888 subjects.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target has been EXTENDED.

The LOTT trial is testing the effectiveness and safety of long-term home oxygen therapy for individuals with COPD. The CMS has partnered with the NIH to provide coverage for oxygen therapy to Medicare-eligible participants in the trial. Although CMS participation is essential for study feasibility, copays for oxygen services, which are mandatory under Medicare, would differentially affect the two trial arms and threaten the scientific validity of the study. To deal with this issue, the investigators requested an opinion from the Office of Inspector General (OIG) regarding the possibility of forgoing collection of Medicare copays from trial subjects for study-related charges. An application for that opinion was submitted to OIG on July 19, 2007, and a favorable opinion was received from that office on September 17, 2008. Because of the importance of the copay issue to the validity of trial results, the study was delayed pending receipt of the OIG opinion. Final preparations for enrollment of subjects are now underway, including obtaining IRB approvals for modifications of informed consent documents required for consistency with the OIG opinion.

Consistent with an additional delay of 3 months, the 2009 target will be reduced to enrollment of 444 participants. The 2010 target will remain enrollment of 1776 participants. To compensate for the change in 2009, an additional 444 subjects will be added at the end of the recruitment period (in approximately FY2011-FY2012).

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 partnered 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 was 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 also participated.

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.

NIH will develop abstracts on the development and the delivery of the national Back to Sleep program and mechanisms that can be employed to spread the infant safe sleep message. The abstracts will be submitted to professional meetings attended by nurses, pharmacists, physicians and/or community health workers. Examples of organizations' annual meetings that will be targeted are the National Association of Boards of Pharmacy and the Centers for Disease Control and Prevention. Presentations to these audiences will allow for further dissemination of the SIDS risk reduction message to unreached African American populations.

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 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. Grant recipients were selected and awards made in FY08. 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 2008

- (FY07) There are no known efforts to systematically distribute "Back to Sleep" materials at a statewide campaign level in Arkansas.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) NIH distributed over 47,000 special "Back to Sleep" campaign materials targeting African American communities in collaboration with the Arkansas Department of Health for their statewide 'Back to Sleep' campaign.	Conduct a continuing education program for approximately 500 pharmacists in the DC metro area.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target was MET EFFICIENTLY. Arkansas has SIDS rates that are higher than the national average. The NIH partnered 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, over 47,000 special Back to Sleep campaign materials were distributed statewide through the Arkansas Hospital Association (AHA) to the 45 Arkansas Hospital Association members who have obstetrical and/or maternity services, the 84 ADH Local Health Units, and to the 73 Hometown Health Improvement Coalitions. The 'Back to Sleep Campaign Kits' that were distributed to across the state in each of the five regions included brochures, refrigerator magnets, door hangers, and trainer resource kits. The partnership and statewide campaign was kicked-off with a demonstration event at the Child Development Center in Little Rock, Arkansas. Future presentations on the disparity of SIDS in African American communities are planned for 'Grand Rounds' with health professionals from the ADH.

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 2008, over 2,287 nurses 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.

The Mississippi SIDS African American Outreach Project continues to be successful. NIH has worked with new partners in the Mississippi Delta and on the Mississippi Gulf Coast to improve coordination and delivery of SIDS risk-reduction materials. Fourteen train-the-trainer sessions were conducted in all nine health districts across the state. NIH continues to assist partners with community health projects including health fairs, 'baby showers', local mall events, health walks, SIDS Sunday events, press releases, and mail-outs.

Efficiency

It was originally planned to distribute approximately 43,000 special *Back to Sleep* campaign materials to African American Communities across Arkansas, but to due to high demand and need, NIH distributed an additional 4,000 to better get the SIDS risk-reduction message out to all of the communities.

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 year period, by the end of FY 08, a minimum of three programs were 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 2008

- Target 2: Piloted assistance programs (i.e., CAP, Niche, etc.)
- Target 3: Pilot programs converted to program implementation.
- Target 4: Results of pilot programs converted to program implementation

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1				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) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at an investment forum.	(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.	(MET) With the implementation of the first year of the Manufacturing Assistance Program (MAP), a full menu of three technical assistance programs was completed. Initiation of the second year trans-NIH Manufacturing Assistance Program includes an additional 25 SBIR awardees.	
3	Report critical elements to assess advances of each technical assistance program Pilot programs converted to program implementation.	(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.	(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.	Target 3: 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.	(MET) All 75 participants in the third trans-NIH Niche Assessment Program received their TNA™ reports from the contractor. Twenty-five participants enrolled in the first year Manufacturing Assistance Program.	
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.					Complete goal	(MET) 708 SBIR awardees used three assistance programs to advance commercialization of their SBIR-developed products/services.	

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 2

The FY 08 target for implementing effective piloted programs to create a menu of technical assistance programs was MET. With the implementation of the first year of the Manufacturing Assistance Program (MAP), a full menu of three technical assistance programs was completed. These included the Commercialization Assistance Program (CAP), the Niche Assessment Program (NAP), and the Manufacturing Assistance Program (MAP). The SBIR program was scheduled to expire September 30, 2008. Congress was not able to complete the reauthorization in time, but instead temporarily extended it through March 20, 2009. The extension provides NIH the opportunity to initiate a second year trans-NIH MAP program to enroll an additional 25 companies in the program.

Target 3

The FY 08 target for reporting critical elements to assess advances of each technical assistance program was MET.

3rd year Niche – Seventy-five NIH FY 2007 and 2008 SBIR Phase I awardees received Technology Niche Analyses™ from an NIH contractor. The contractor 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, and a market-entry strategy. Possible partners and/or investors were identified for consideration. All 75 participants received their reports in FY 2008. Feedback is still being collected, however, of the 43 respondents so far, 41 felt they have a more realistic understanding of their target markets.

1st year Manufacturing – After assessing the feedback from the pilot Manufacturing Assistance Program (MAP), outreach materials were developed to inform NIH's SBIR Phase II awardees of the opportunity to participate in the first trans-NIH SBIR Manufacturing Assistance Program. A scope of work was developed for each participant that detailed the tasks to be performed with the assistance of the National Institute of Standards and Technology (NIST) Manufacturing Extension Partnership (MEP) centers. Twenty-one (21) companies' projects have been completed and all improved at least one level on the manufacturing readiness level scale. Although feedback is still being collected, of the 18 who have responded so far, 17 indicated the program had a major or valuable impact on their manufacturing efforts.

2nd year CAP update: Feedback for the first nine months following completion of the second year of the CAP program was provided in the November 2007 report. Seventy-six participants for the second nine month interval provided feedback, a 70% response rate. Analysis of the data showed that more companies are now seeking partnerships rather than venture capital financing which was the case for previous CAP programs. Of the 76 responding companies, 80% (61 companies) indicated commercialization progress in the partnership and deal related activities area. Progress is defined as having participated in at least one of the following activities: (1) contact with investor/partner, (2) meeting with investor/partner, (3) Confidentiality Disclosure Agreement signed, (4) negotiation with investor/partner, (5) initial proposal and term sheet, and (6) a signed deal. Sixty-seven (67%)

of responding companies showed revenue growth. The highest reported was $17 million by ABIOMED Inc. followed by $12.2 million by Kumetrix Inc, and $10.8 million by Clever Sys Inc.

3rd year CAP update: Baseline feedback at the completion of the third year of the CAP program was provided in the November 2007 report. Ninety-one participants provided feedback, a 74% response rate. When compared to the previous year's participant baseline data, the number of deals for this group (34) is a significant increase when compared to 15 for the 2nd year group and 23 for the 1st year group. Venture capital accounted for the largest source of equity funding (37%) followed by angel funding (31%) and then strategic investors (30%). Two percent (2%) was "friends and family" funding. Four mergers and acquisitions were reported for the 3rd year CAP participants: two for technologies, and two company acquisitions.

Target 4: **Goal Achievement**
NIH has achieved the goal to increase the percentage of SBIR awardees successfully identifying resources and/or partners to help with commercializing SBIR-developed products and bringing them either closer to or into the marketplace. For the past 4 years, 708 companies have used three SBIR technical assistance programs offered by NIH to identify the resources and partners needed to advance 952 SBIR-developed products toward commercialization. These three programs, Commercialization Assistance Program (CAP), Niche Assessment Program, and Manufacturing Assistance Program (MAP), were developed to facilitate the transition of SBIR innovation into commercially viable products that will have social benefits.

The Commercialization Assistance Program is NIH's flagship Technical Assistance Program. A total of 391 SBIR Phase II awardees with 426 projects have participated. Working one-on-one with a principal advisor provided by the NIH contractor, Larta Institute, these companies developed their commercialization strategies and the tools necessary to begin implementing their plans. These tools consisted of road show presentations to be used at investor-partnering events, business case presentations to be used in private investor-partnering meetings, 18-month plans for post-CAP action, and virtual showcase materials for posting on the NIH website. If appropriate and if the companies were ready, they were given the opportunity to present their business presentation to a targeted group of potential investors and partners at Larta's Annual Venture Forum. In the pasts four years, 212 companies presented. To date, one hundred one (101) CAP participants have reported raising over $326 M which is approximately a 4 to 1 return on NIH's investments. There have also been four company and two technology acquisitions.

Over the past four years, NIH's Niche Assessment Program had a total of 418 companies participate for which 476 projects received Technology Niche Analyses™ reports from Foresight Science and Technologies. The reports assessed the potential uses of the technologies and after contacting potential end-users, the report addressed their needs, the current and emerging competing technologies, the market dynamics, and the technology's competitive advantage. Of those providing feedback for the past three years, 85% indicated their reports helped them identify resources and/or partners necessary to commercialize their SBIR projects.

The third and most recent NIH SBIR Technical Assistance Program offered is the Manufacturing Assistance Program. In the past two years, fifty (50) SBIR Phase II awardees have participated. In partnership with NIST's MEP program, manufacturing technical support was provided by MEP's nationwide network of non-profit centers. The support was quite broad in scope and had no real boundaries other than the manufacturing issues addressed must be related to an NIH SBIR-developed product. This included such topics as method of scale up, cost estimation, prototyping, design for manufacturability, and vendor identification and selection for supplying compounds for clinical trials. Seventy percent (70%) of the pilot program respondents felt the program has helped them, or will help them to improve the quality of their product or process. All participants who said yes, they expect to change their manufacturing program as a result of the pilot program, also said they expect those changes to lead to an improved product or process. Of those participating in the first year trans-NIH MAP, 94% indicated the program had a major or valuable impact on their manufacturing efforts.

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.

Baseline 2008

- (FY07) 110 minutes per title

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Reduce cataloging time by 7 minutes per title and realize a savings of 0.10 FTE.	(MET) The time to catalog an item has been reduced by 7 minutes from 110 minutes to 103 minutes and a savings of 0.10 FTE has been realized.	Reduce cataloging time by 8 minutes per title and realize an additional savings of 0.10 FTE.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. The number of minutes to catalog an item has been reduced by 7 minutes from 110 minutes to 103 minutes. This has saved 0.10 FTE time to catalog records. The time reduction in serials cataloging is the outcome of several new procedures. Catalogers no longer need to supply translations of Chinese, Japanese and Korean titles. Title abbreviations are now created from the data used by the ISSN (International Standard Serial Number) Centre, rather than looking up each word in the title to find the appropriate abbreviation. Serial cataloging guidelines have been revised to simplify the decision making process and eliminate redundancies in transcription.

CTR-7	**By 2010, establish the feasibility of sharing information from already-conducted scientific studies of warfarin (coumadin®) 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 ensured 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.

Baseline 2008

- (FY07) 13 participating groups of PharmGKB have agreed on the critical column headings for depositing data (e.g., genotypes, INR phenotypes, BMI, etc.).

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
				Begin standardizing datasets in PharmGKB to prepare for the FY09 meta-analysis.	(MET) The participating groups began 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was MET. The participating groups began standardizing datasets in PharmGKB to prepare for the FY09 meta-analysis. The participating groups collected data in categories including demographic data, primary indication for warfarin treatment, stable therapeutic warfarin dose, treatment INR, target INR, use of concomitant drugs, and genotype variants. A standardized template defined by the PharmGKB including meta-definitions was used by all participants. This data was pooled based on the phenotypic measurement (International Normalized Ratio, INR) which is used world-wide and reliable and the availability of reliable genotypes. Research groups from 9 countries and 4 continents contributed clinical and genetic data for a total of 5,700 warfarin-treated patients.

CTR-8	**By 2012, increase communication efforts and enhance centralized 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 implement a broad communications strategy for centralized grant-related communications, 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 realigned staff, roles and responsibilities to realize efficiencies of scale and improve message consistency. This group is 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.

In an effort to reach a large and diverse audience, NIH will take advantage of emerging technologies that can be used to explain the NIH grants process. This could include webcasts, streaming video, Web 2.0 technologies, podcasts, interactive training and on-line dialog. At least one new technology will be utilized by 2010.

Baseline 2008

- Multiple groups focused on grant-related, extramural communications.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) Final staff realignment completed in July 2008.	Provide a single source of information on grants policy and process to integrate and synchronize related communications efforts across NIH.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target to realign staff centrally to support the execution of a comprehensive communications strategy was MET.

The final staff alignment of the NIH Office of Extramural Research (OER) Office of Planning and Communication's (OPC) Division of Communications and Outreach (DCO) was completed in July 2008. DCO is organizationally aligned through OPC with the OER Immediate Office of the Director. The creation of DCO centralized communications and

planning activities that had previously been widely distributed across OER. DCO coordinates dissemination of OER and NIH information to external and internal customers, manages major OER communication and information distribution activities including Grants Information and the OER Web Pages and coordinates internal OER communications. DCO ensures that OER programs are understood and accessible and speak with one voice. DCO directs, guides, and maintains working groups across OER to implement consistent NIH and HHS standards for electronic Grants Information and Web Services and manages internal communications and workflow by knowing the wealth of activities ongoing in OER. Besides being responsible for the NIH OER Web site, the NIH OER Intranet Web site, and the NIH OER Staff Intranet Web site, DCO oversees the NIH Nexus, which is electronically disseminated to over 37,000 readers and which contains an Insider component specifically for NIH staff. It also coordinates internal OER communications to assure that requests for information and for work product are coordinated centrally, tracks the status of projects ongoing in OER and, when necessary, establishes temporary teams of OER and NIH employees to address efforts in specified areas that need attention, and to maintain a project management and/or workflow tracking system to manage and monitor activities and projects undertaken within the Division.

Advances or Other Highlights

DCO allows for increased coordination of NIH's trans-NIH grants process and policy related communications and more coordinated communications campaigns on these topic areas including public access, the use of animals in research, and financial conflicts of interest. With the final staff alignment of DCO, OER has in place a communications hub that increases consistency in OER and NIH communications and creates staff efficiencies by reducing potential for duplicative communications efforts in different OER organizations.

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 http://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 2008

- Target 1: The baseline is the estimated average difference in the proportion of former NRSA pre-doctoral trainees and fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 10%.
- Target 2: The baseline is the estimated average difference in the proportion of former NRSA post-doctoral fellows applying for and receiving subsequent NIH support relative to comparison groups. This number currently is 12%.

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

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY 2008 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 1987 through 1997 were more than 4 times as 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.

To determine the outcome of this target, predoctoral researchers trained under NIH NRSA funding are compared to those not trained under NIH NRSA funding. In FY 2008, NIH predoctoral trainees and fellows were 14% more likely to remain active in biomedical research than non-NIH trainees and fellows; this exceeded the annual target of 12%. The results demonstrate that former trainees and fellows funded by NIH are more likely to remain in research careers and are better able to compete for funding ten years past their degree. Data for this analysis were obtained from the NIH IMPAC II system and the national Survey of Earned Doctorates.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Trainees and Fellows	31.5% (6,619/20,997)	18.7% (3,925/20,997)
Comparison Group A	8.1% (7,233/88,783)	4% (3,565/88,783)
Comparison Group B	6.3% (1,212/19,184)	2.5% (486/19,184)

Target 2

The FY 2008 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 1987 through 1997 were more than 1½ times as 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.

To determine the outcome of this target, postdoctoral researchers trained under NIH NRSA funding are compared to those not trained under NIH NRSA funding. In FY 2008, NIH postdoctoral fellows were 13% more likely to remain active in biomedical research than non-NIH fellows; this exceeded the annual target of 12%. The results demonstrate former postdoctoral fellows funded by NIH are more likely to remain in research careers and are better able to compete for funding ten years past their training. Data for this analysis were obtained from the NIH IMPAC II system.

Group	Percent Applying for NIH Research Awards	Percent Receiving NIH Research Awards
Former NRSA Fellows	46.3% (4,539/9,814)	30.1% (2,957/9,814)
Other Postdoctoral Fellows	28.6% (3,252/11,370)	16.9% (1,920/11,370)

Advances or Other Highlights

NIH issued more than 50 new or updated education, research training, and career development funding opportunity announcements in FY 2008. Over the course of the year, NIH also continued its efforts to foster new investigators through awards designed to foster their career transition and reward innovation. In FY 2008, NIH made more than 200 career transition awards to newly independent scientists and more than 40 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 1,580 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 2014, 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 improve internal controls, require accountability, and 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 can provide NIH financial data necessary to HHS to support the NIH/HHS Consolidated Financial Statement.

PERFORMANCE ANALYSIS

Target Context and Conditions

The NBS Implementation is a phased approach, as recommended by FSIO (previously JFMIP), to incorporate individual modules as they are completed. Modules of the NBS will serve similar functions to the legacy Administrative Database System (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.

From FY 2005 through present reporting period, NBS implementation and deployment activities that the functional, technical and change management teams have undertaken include the ongoing design, configuration, and testing of the baseline system and the system at the integration phase and follow-on deployment of individual modules as they are finalized and accepted. 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 users for role based processes;
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 GovTrip. NIH requested an extension until FY 2010 to complete its migration to GovTrip. This migration is contingent upon Northrop Grumman providing NIH the same level of functionality that currently exists in its travel system. Predeployment activities associated with Phase 1 of a graduated deployment for GovTrip have been completed in FY 2008.

The NBS roll-out phase supports NBS migration activities in relation to compatible functionality. The goal will be revised during the FY 2009 planning process to better reflect business practices. Changes will appear in the FY 2011 document.

Baseline 2008

- Target 3: (FY04) NBS performance with General Ledger and Travel Modules deployed
- Target 5: (FY06) NBS without the UFMS migration
- Target 6: (FY06) No NBS post deployment support currently exist

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules.	(EXT) The program steps a-g 'Integration' is being re-planned. Extended to 2006.	(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.	(EXT) The program steps a-g 'Integration' deployment for service and supply fund modules are being extended to 2008.	(EXT) The program steps h-I 'Final review' is being extended to FY 2009.					
3	Report critical elements of General Ledger and Travel Module performance.		(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	(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 1,3 and 4
4	NBS roll-out and post deployment support.			NBS deployment	(MET) NBS was deployed.			

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
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	(MET) Commencement of NBS/UFMS migration activities have been initiated in relation to functionality.	
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	(MET) Provided NBS post deployment support for property and contracts/acquisition/accounts payable and receivable/supply modules.	Continue to provide NBS post deployment support
7	Continuation of NBS/UFMS migration activities.							Continue NBS/UFMS migration
8	Post deployment support for GovTrip travel module.							
9	(Target 9) Initiate development of NIH Grants Interface Module.							

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 3

The FY2008 target to report critical elements of General Ledger (Track 1), Travel Module (Track 2), Supply and Payable/Receivable (Track 3), and Contracts/Acquisitions/Property and Payable/Receivable (Track 4) performance was MET. Critical elements of General Ledger and Travel Module performance were reported in FY 2008 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 Other measurable NBS performance elements that are associated with finance, travel, and acquisitions include: the total number of documents created and dollars associated with acquisition, travel, and finance actions.

The NBS Travel module is used daily by all NIH Travel administrative personnel. Approximately 628,567 records have been processed in the NBS Travel module since deploying for FY 2004. For FY 2008, approximately 153,644 travel authorizations and voucher transactions were entered online in real time.

The NBS Management Center (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 24,115 patient trips were processed by the Clinical Center Travel Office during FY 2008.

The GovTrip eTravel application (Phase I) was deployed in late FY 2008 for use by approximately 1655 potential travelers in the NIH Office of Management. Over forty users were trained and began entering documents for the remainder of FY 2008. For FY 2008 64 travel authorizations, vouchers and local vouchers were entered on-line in real time. Nine vouchers were paid from the NBS Financial System.

Target 5

The FY2008 target to commence with NBS/UFMS migration activities has been MET and is now transitioned to continual activities associated with the system functionality. Commencement of NBS/UFMS migration activities were initiated in relation to functionality in FY2007 and FY2008. 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.

During FY 2008, NBS has met with the HHS Consolidated Acquisition Solution (HCAS) Team to identify and discuss common areas of concern and to share particular design solutions. The Oracle-PRISM vendor merge function was the topic of the initial meeting with HCAS.

NBS representatives participated in a series of meetings with DHHS representatives in order to explore the feasibility of establishing a DHHS-wide enterprise Compusearch PRISM license, and associated maintenance and support.

Target 6

FY2008 post deployment support of Tracks 3 and 4 has been MET and has been expanded to full user support which includes: NBS Management Center direct support for users via electronic and telephone responses to user request for assistance on functionality; mass support efforts via communication forums to NIH user staff; onsite support with subject matter experts; supplemental training offerings to NIH users; mass electronic communication efforts regarding system functionality; targeted user group information sessions and forums; support hotline teleconferences meetings; development of key performance indicators to recognize and address trends; and supplemented targeted contract support.

Post-deployment support has also included a more structured process involving NBS knowledge transition to the NIH Training Center. Collaborative efforts were initiated to ensure a sustainable training strategy for NBS functionality that will reinforce desired user behavior and allow the NIH end-user community to keep abreast of system changes.

Post deployment onsite user support has been provided through an Inventory/Warehouse Management consultant for the Gaither Distribution Center (GDC), Division of Logistics

Services, Office of Acquisition Management and Logistics. This support included, but was not limited to: on-going training of Inventory and Warehouse staff on existing and new NBS functionality supporting the supply operations; performing an analysis of the impact of new functionality on GDC operations; and, troubleshooting and resolving issues reported by GDC Inventory Managers, interface issues related to the Self-Service Stores, and issues pertaining to the standing order process.

Advances or Other Highlights

The NBS Management Center (NMC) supports the deployed NBS modules by employing standard escalation protocols for assisting users who are experiencing difficulty. In FY 2008 the NBS saw a 30% reduction in the number of user call assistance tickets from a comparable period of FY 2007 after the deployment of the Acquisitions, Property, and Supply modules. This can be largely attributed to system stability, continued user comfort with the system, and NBS education outreach efforts that include emails as well a supplementary training seminars. Topics were derived from trend analysis from monitoring NBS user call assistance tickets as well as direct user feedback.

FY 2008 realized an evolution from the "project" mode to NBS Program Management Office. Internally, standardized Program Practices have been implemented to provide consistent guidance to NBS Program staff in support of a matrix organizational structure. Practices include areas such as status reporting, risk and issue identification and tracking, action item monitoring, software control management, project staffing and management, and human resources practices. An NIH community governance model has been implemented to foster full engagement of the NIH Business Owners and their respective stakeholder groups. This governance includes an internal and external infrastructure to support software configuration and control management and decision-making.

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 completing the move of internal work flows from paper-based business processes to electronic processes. The electronic submission and receipt of grant applications through Grants.gov is an intense effort and has already succeeded with the vast majority of the grant applications received by NIH. When completed this undertaking 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. In fact, since most aspects of the grant administration process have now been automated, resulting in improved process efficiencies and lower managerial and administrative 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 all 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 in the near term. eRA continues to map electronic processes to existing business models, but as these continue to change, eRA efforts will require greater adaptability. Additionally, as eRA acquires the grants management automation of other agencies, additional flexibility will need to be developed. These unknowns make it difficult to commit to a specific schedule for total completion of paperless processing. Each year the NIH expects the capability for paperless processing to expand, and this progress will be reported. Note that continued progress in these areas is contingent upon the availability of funds necessary to support this work.

Baseline 2008

- (FY07) 55% of business processes being done electronically

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	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.	(MET) 100% of the eligible HHS OPDIVs (AHRQ, CDC, FDA, and SAMHSA) are using eRA for administration of research grants.					
2	By the end of FY 2007 complete migration of existing client/server applications to Web-based technology.	(MET) 60%of the code has been converted. This efficiency was accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.	(MET) The target was met and exceeded. 100% of the code was converted before the end of FY06, and all of the Web-based applications were deployed by the end of FY06					
3	Continue conversion of business processes: 95% of convertible business processes being done electronically by FY 2012.	(MET) Approximately, 33% of business processes & financial status reports are done electronically.	(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 (FY08); projected to increase in 5% increments annually from FY08 through FY12.	(MET) Approximately 75% of the transactions in the business processes are now being done electronically.	80% electronic business processing; projected to increase in 5% increments annually from FY09 through FY12.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 7

The FY08 target goal of 75% of the business processes being conducted electronically was MET. The proportion of competing grant applications received electronically increased from 80% to 83% during the past fiscal year. NIH remains dependent upon Grants.gov in its efforts to provide electronic application forms for all grant mechanisms. Electronic applications forms for several mechanisms (U34, SC1-SC3, and UH2-UH3) were added this year. In addition, eRA has worked with Grants.gov to achieve the transition from PureEdge to Adobe forms.

The grant applications received electronically through Grants.gov are being processed more rapidly than paper predecessors. During the past several years, application processing speed has increased by a factor of five. At the Receipt & Referral stage, the Automated Referral Workflow System (ARWS) debuted in FY 08, is making it possible to reduce cycle times within the Center for Scientific Review. ARWS relies upon data mining techniques and a machine learning algorithm to generate initial application review assignments. At the Peer Review stage, several business processes were automated in 2008, replacing long-established manual processes. Reviewer conflict of interest screening, enhancements to the process of assembling summary statements, and live (real-time) Internet-Assisted-Review final scoring are now electronically supported.

The use of electronic notification continued to expand in FY08, with further increases in the percentage of progress reports submitted electronically. (By the end of FY 07, all financial status reports (FSRs) were being submitted electronically.) For Kirschstein-NRSA training grantees, xTrain functionality deployed in FY 08 allows users to process the required paperwork electronically for the first time. Among other enhancements designed to streamline administrative processing, financial conflict of interest screening and provisions to assure institutional compliance with public access policy requirements were both automated. Within the grants management community, reliance upon electronic processing has increased significantly. More than 80% of NIH's Institutes & Centers are now relying exclusively upon electronic grant files to administer their grants, double the frequency reported just one year ago.

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.

CBRR-6	**By 2012, 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 2008

- (Target 1) Number of projects completed: (FY07) 89
- (Target 2) Number of biocontainment facilities completed: (FY07) 2

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Complete 153 construction or renovation of biomedical research infrastructures in order to build the capacity to conduct the proposed research.		(MET) 43 of the 44 construction grants were completed either early or on time. One site was unable to begin construction due to unforeseen circumstances, and NIH is seeking a legal opinion regarding final disposition of the funds.	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 authorized for occupancy until the entire institutional construction project is completed.	30 to be completed	(NOT MET) 26 of the 30 construction grants were completed either early or on time. Two sites are part of larger institution construction projects and can not be completed and authorized for occupancy until the entire institutional construction project is completed. Two sites experienced delays and requested and was granted an extension from NIH.	22 to be 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	(MET) NIH completed construction of five extramural biocontainment facilities.	Complete 7 facilities.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target was not met. Twenty-six of the 30 construction grants were completed either early or on time. Two of the construction projects are part of larger institutional construction projects. The NIH funded only a portion of these projects and authorization for occupancy can not be granted until the entire institution construction project is completed. The other two construction projects experienced construction delays and were granted extensions from NIH.

The FY08 target was MET and exceeded. NIH completed construction of five extramural 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 following universities: University of Texas Medical Branch, Galveston; Colorado State University, Fort Collins; University of Alabama at Birmingham; University of Chicago; and University of Medicine and Dentistry of New Jersey.

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 2008

- (FY08) 707 expiring grants eligible for renewal/recompetition

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(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.	(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.	(MET) 100% of the 707 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 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/strategicplan/), to efficiently conduct a trans-NIH portfolio analysis of 100 percent of the 707 grants eligible for renewal or recompetition. This portfolio analysis was conducted in concert with the ICs and a panel of outside experts.

Approximately 35 percent (250 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 at the time of award, these grants 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 2008, 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 participating students and postdoctorates, 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 has developed 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 can 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.

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, as necessary, in response to feedback from its users.

PERFORMANCE ANALYSIS

Target Context and Conditions

In December 2007 and January 2008, NIH pilot tested the newly-developed xTrain system with trainees, training grant directors, university administrators, and NIH grants

management specialists involved in more than 80 institutional research training grants at nine universities. At the conclusion of the pilot, the xTrain design and development team sought feedback from testers and honed the system's workings in preparation for broader release.

In June 2008, NIH invited the 100-plus institutions participating in the Federal Demonstration Partnership to begin using the system. By the end of FY 2008, 20 universities had submitted research training appointments through xTrain.

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. Achievement of this goal depends on the continuing commitment and involvement of a sizeable team of staff, including systems analysts and developers, technical writers, grants management specialists, and policy experts.

Baseline 2008

- (FY07) 0% processed electronically

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	By 2012, ensure that 100% of trainee appointment forms are processed electronically.					5%	(MET) 5.4% of trainee appointment forms were submitted electronically.	25%

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target to process 5 percent of research training appointments electronically was MET. After xTrain became available for use in June 2008, twenty universities began to use the system, and submitted 307 FY 2008 NRSA research training appointments electronically. Ultimately, electronic research training appointments represented 5.4% percent of the 5,722 FY 2008 research training appointments processed.

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-9	**By 2012, 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 2008

- Proposed annual costs: (FY08) $36,419 per grant

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

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

NIH achieved an average annual cost of managing construction grants of $36,419 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
						Establish repository of 300,000 compounds

SUMMARY OF 2008 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 employees tools needed 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 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 2008

- Target 1: Performance indicators are based on FY 2007 results
- Target 2: Performance indicators are based on FY 2007 results
- Target 3: Performance indicators are based on FY 2007 results

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Methods were implemented that addressed recruitment, retention and succession planning for key IRP positions. (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.	(MET) Recommendations developed for improving the effectiveness of recruitment, retention and succession planning for key ERP positions. (MET) Implemented leadership training for tenure-track and senior investigators and assessed the impact of utilizing adopted methods through surveys.	(Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.) (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.	(MET) Assessed the impact of utilizing adopted methods and processes for recruitment, development, and succession 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.	(Target 1) Evaluate and modify performance indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program. (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.	(MET) Indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Programs were evaluated and modified. (MET) Continued performing and reporting on performance indicators related to recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program. (MET) Assessed 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.	

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY 2008 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), in collaboration with its Office of Intramural Training and Education (OITE), developed a modified version of the course "Influence, Self-Promotion and Negotiation for Women in Leadership Roles", which was so successful in 2007 that it was offered to all postdoctoral fellows and graduate students in February 2008. It was rated very highly and perceived as extremely useful. As a result, staff in OITE are being trained so that OIR/OITE will be able to offer the course, with appropriate modifications reflecting the level of the audience, to staff scientists, staff clinicians, postdoctoral fellows, graduate students and postbaccalaureate trainees. OIR continues to offer the course "How to Succeed as a PI at the NIH" to new tenure-track investigators – in recognition of its value, the SDs now require that

all new investigators take it.

Target 2
The FY 2008 Target to implement methods to improve the effectiveness of recruitment, development and succession planning for key scientific positions within the Intramural Research Programs has been MET. The Office of Intramural Research (OIR) has expanded its efforts to attract a diverse pool of highly qualified applicants for its tenure-track and tenured research positions by hiring a new Assistant Director to coordinate recruitment efforts; to expand the network of contacts with which job ads are shared; to post all ads to a wide variety of job sites; and to work with search committees to ensure that they perform appropriate outreach and identify all qualified candidates.

Target 3
The FY08 Target to 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 has been MET. To date, NIH ICs have submitted over 500 existing and new positions for Title 42 designation review by the NIH Extramural/Office of the Director Title 42 Committee (ETFC). Using the position criteria established in FY-2007, approved positions were placed into one of 3 scientific categories, depending on the type of duties and responsibilities required. The three categories are: Scientific Executive, Senior Scientific Officer, and Science Policy/Program Leader.

Advances or Other Highlights
The Office of Intramural Research (OIR) has created the Scientific Director's Orientation Guide, to be used in orientation of new Scientific Directors, and is putting it online so that the information is accessible to all interested new scientific staff.

The NIH has partnered with 18 institutions in the Maryland – Virginia – DC area to establish the Mid-Atlantic Higher Education Recruitment Consortium (HERC), which maintains a regional web-based search engine of all job listings at member institutions and thereby offers an enhanced mechanism to facilitate dual career/partner job searches.

In March, 2008, the new Extramural/Office of the Director Title 42 compensation model was finalized and fully implemented. As part of this effort, the NIH Deputy Directors conducted a consolidated pay review of all scientists in positions designated for Title 42 by the ETFC. ICs submitted salary recommendation packages that addressed specific pay components in the model, crediting the experience and expertise brought to the position by the incumbent. As part of the model, total compensation limits were also determined for each scientific position category. Final approval of all salary recommendations was made by the NIH Director.

Future pay adjustments will be considered in accordance with the provisions of the new Extramural/OD Title 42 Pay Model. All compensation for Scientific Executives (e.g., base pay, performance bonuses, cash awards, etc.) will continue to be reviewed by the NIH Deputy Directors with final approval by the NIH Director. In addition to mandatory peer review for new hires and conversions to Title 42(f), peer review is also required for current extramural/OD Title 42(f) scientists moving to a different Title 42(f) professional designation (e.g., from Science Policy/Program Leader to Scientific Executive.)

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 and number of FTEs to be reviewed. Subsets of the identified

functional areas that are deemed appropriate for review and undergo a competition. 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. NIH has been viewed as the most competitive/effective in the free-market place; therefore, retained the following MEO awards:

Year	Reviews	Awards Retained	Areas of Streamlined Review
2004	9	8	• IT Telecommunications • NIEHS Logistics • Clinical Center Materials Management • Freight Forwarding • RML Logistics • RML Visual and Medical Arts • IT Help Desk • IT Data Center
2005	11	3	• IT systems administration • Food services • Patient care unit clerk
2006	4	4	• EEO Administrative Support • Clinical Center Administrative Support • IT Network Support • IT End User Support/Technical Writers
2007	2	2	• IT Systems Development • IT Administrative Support
2008	5	TBD	• HR Administrative Support • HR Strategic Programs Divisions • HR Classification and Recruitment • Equal Employment Opportunity and Diversity Management Program • Facilities Services

Baseline 2008

- Preplanning initiated for identifying functional areas
- Functional areas identified as appropriate for review

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Identify annually commercial activities for competitive sourcing comparison.	(MET) Thirteen streamlined and one standard studies conducted in FY 2005.	(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	(MET) Three functional areas were identified for reviews and announced for competitions.	
2	Evaluate transition services provided to employees.	(MET) Evaluation conducted during FY 2005.						
3	Implement transition services for employees annually displaced due to prior year's competitive sourcing.	(MET) Career transition services were provided to employees displaced.						
4	Complete negotiated competitive sourcing reviews annually.	(MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.	(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	(MET) The five studies under three functional areas identified for review were announced for competition in FY 2008.	Complete negotiated competitive sourcing reviews annually

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

FY 2008 target 'Identify annually commercial activities for competitive sourcing comparison' was MET. For FY 2008, the pre-planning step identified three functional areas for review - Human Resource function, Equal Employment Opportunity and Diversity Management Program functions, and Facilities Services function. These reviews were deemed appropriate for streamlined studies each with a Most Efficient Organization (MEO). IT E-mail Services - was granted a delay until FY 2009 due to a reorganization that is occuring at the HHS level.

Target 2

The FY 2008 target 'Complete negotiated competitive sourcing reviews annually' was MET. Five studies (HR Administrative Support, HR Strategic Programs Divisions, HR Classification and Recruitment, Equal Employment Opportunity and Diversity Management Program, Faciltities Services Functions) under three functional areas(Human Resource, Equal Employment Opportunity and Diversity Management Program, and Facilities Services) identified for review were announced for competition in FY 2008. These reviews

were deemed appropriate for streamlined studies each with a Most Efficient Organization (MEO).

The Department approved the delay of the E-mail Services, Finance and Accounting, and HR Benefits reviews until FY 2009.

In addition, in FY 2008 NIH completed and won two reviews that were announced in FY 2007. These reviews were: IT Administrative Support Services and IT Systems Development and Programming Services.

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, OHR is 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 on users own MyPage of content relevant to individual needs. Instead of relying on static websites, OHR is 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 n 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 each individual's 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. The relevance, currency and appropriate placement of the applications 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 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 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 the elements. 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.

In FY07, new pages were added to the HR Community in 2007, for HR Professionals, Career Development and Training, Clinical Center Employees, Senior Executives Services (SES) Members, Administrators/Managers, Title 5 Compensation, Title 42 at NIH, HR Calendar, HHS Careers for HR, USAJOBS, and Alphabetical HR Search. These corrective strategies were implemented to improve usability and quality of HR information.

SPD began to monitor the success of the corrective strategies plan compared to the established baselines. The monitoring will be continued into FY08, FY09 and FY10 as SPD continues to monitor satisfaction and usage of human resources content on the NIH Portal.

The HR Portal has proven to be a useful resource for the NIH community. The data below shows the number of hits, visits, and unique users that accessed the HR Community Portal.

	3rd Quarter 2007	4th Quarter 2007	Jan 1st - Feb 26th 2008
Hits	8,927	25,678	18,844
Visits	6,359	14,465	19,938
Users	1,551	3,327	2,698

Baseline 2008

- Quality management plan established.

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Developed HR Community on the NIH Portal as primary site for accessing HR information and resources (MET) The critical elements identified were, freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools.	(MET) Baselines were established for the HR critical elements: freshness of human 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.	(Target 5) Implement corrective strategies with subject matter experts and customers.	(MET) Implemented a corrective strategies plan to 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.	(Target 6) Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline.	(MET) Implemented a corrective strategies plan to 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.	(Target 6) Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baseline.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY08 target to Continuously monitor satisfaction and usage of human resources content on the NIH Portal against the established baselines was MET.

- Quarterly meetings with Content Managers from throughout the NIH Office of Human Resources (OHR) 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.

Highlights for continuously monitoring satisfaction and usage of human resources content on the NIH Portal against the established baselines in FY08 included:

- HR Professionals Community - http://hr.od.nih.gov/hrprofcommunity.htm
  - Created an HR A-76 page accessible only to OHR staff that explains provides information to OHR employees under A-76 review.
- Human Resources (HR) Community - http://hr.od.nih.gov/hrcommunity.htm
  - Portlets - Created new portlets for the HR Community:
  * Deployed the Performance Management Portlet on the HR Community.
  * Deployed the WiTS Tutorial portlet on the HR Community.
  * Redesigned the HR Systems Spotlight Newsletter Portlet.
  - Pages - Added new pages to the HR Community.
  * Developed a Workforce Evolution (WE) page for a joint initiative with the OHR and the National Cancer Institute (NCI) to allow them to collaborate and develop new HR processes to use with NCI.
  - Admin/Manager Page - http://hr.od.nih.gov/admincommunity.htm.
  * Developed and released the HHS Careers Training Tutorial Portlet on the Admin/Manager Page and the Hiring Resources for Managers page.
- Interns and Fellows Community.
  - Created and launched the new Interns and Fellows Community on the NIH Portal as a space where all NIH Interns and Fellows can collaborate and receive program information.
- HR Metrics Community.
  - Created and launched the HR Metrics Community to OHR employees that highlights the accomplishments of the Office of Human Resources at the NIH.
- Online Training. Developed and released new Portal Online Training called "HR Portal – Features" - http://intrahr.od.nih.gov/tutorials/portal/features/player.html
- 508 Compliance. Began the process of making all OHR information and content 508-compliant. 508 compliance means making our information available to individuals with disabilities who use screen readers or other technology to read and access our information. In FY2008, we revised and archived approximately 500 OHR documents.
- HR Portal Community Map (shows all HR Communities, Pages & Portlets) - http://hr.od.nih.gov/HRSystems/Portal/map.htm

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 the employees tools needed 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Examine key area to enhance leadership skills.							Leadership programs identified and/or linked to competencies.
2	Implement recommendation from prior year assessments							Develop an implementation plan to act on the recommended programs.
3	Assess results of implementation							N/A

SUMMARY OF 2008 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 or varied 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Examine key area to enhance recruitment							Develop an NIH recruitment brand, create a reengineering communication plan/strategy, and establish a standard operating procedure to improve hiring efficiency through global recruitment strategies and sharing of certificates
2	Implement recommendation from prior year assessments							N/A
3	Assess results of implementation							N/A

SUMMARY OF 2008 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 employee 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 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Examine key area to enhance retention							Increase knowledge about teleworking by developing a communication plan
2	Implement recommendation from prior year assessments							Implement Telework Communications Plan
3	Assess results of implementation							Results from telework communication plan implementation

SUMMARY OF 2008 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-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 2008

- Obligate 43% of eligible service contracting dollars through PBC

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
(MET) Obligated 44% of eligible service contracting dollars through performance-based contracting.	(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.	(MET) Obligated 43% of eligible service contracting dollars through performance-based contracting.	Obligate the FY2009 OMB/OFPP goal of eligible service contracting dollars to PBC

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 target to obligate OMB/OFPP goal of 43% eligible service contracting dollars through performance-based contracting was MET. Forty-three percent (43%) of the total eligible service contracting dollars was obligated to PBC service contracts. This information was reported in the Departmental Contract Information System (DCIS). These obligations were reported throughout the fiscal year as funds were committed to various contracts throughout NIH.

Advances or Other Highlights

PBC activity is tracked monthly through reports of funding activity obtained from the DCIS. Training opportunities continue to be offered to the acquisition and program community to ensure that they are properly trained in the use of PBC. Information about Government and industry sponsored events focused on PBC is regularly disseminate

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 now permits more than one PI on an NIH funded research project. This change in policy not only encourages the development of interdisciplinary approaches, it allows 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. As implemented by NIH, it is now possible for more than one PI to share the responsibility for a research grant. Grant applications identify all PIs involved with a particular project. All the PIs are listed on the notice of grant award and in reports related to that particular grant. Adapting to multiple PIs required 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.

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. As of the end of FY 08, NIH has transitioned 83% of grant applications from a paper-based submission process to electronic submission though Grants.gov. This reflects 100% of NIH's grant programs that Grants.gov can currently accommodate. NIH will continue to work with Grants.gov to develop forms and systems to allow additional grant programs to move to electronic submission.

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. The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central within a year of publication. 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.

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 was completed in FY08.

Baseline 2008

- Target 1: Prior to FY 04 all research grants has only one Principal Investigator
- Target 2: (FY04) Paper grant applications currently received.
- Target 4: (FY07) Peak receipt dates involving up to 8,000 applications.

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(MET) The data structure of the system was modified to maintain data for multiple Principal Investigators (PIs) for a single application and grant in the spring of 2006. Both paper and electronic applications involving multiple PIs were received and processed by NIH.	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 principal investigator applications have been accepted since the policy has been in effect.	Modify program and procedures to refine Multiple Principal Investigators Implementation to better serve end users.	(MET) Project to extend multi-PI support capability throughout the grants management life cycle (from application receipt through grant closeout) completed on schedule in June.	
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.	(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.	(MET) Reduced the correction window from 5 days to 2 days effective 1/08, allowing applications to be assigned to review groups more quickly.	
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.	(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	(MET) Receipt dates realigned in spring & fall of 2007 with NOT-OD-07-001, NOT-OD-07-053, and NOT-OD-07-083.	
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.
6	Complete goal of enhancing NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems.							

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY 08 target to refine the implementation of previously-introduced Multiple Principal Investigators functionality so as to better serve end users was accomplished by means of three additional releases implementing required modifications to CRISP, the Grants Closeout Module, and eRA's DataMart, respectively.

Target 2

The FY 08 target to refine the electronic submission of research grant applications to maximize process efficiency for grant applicants was achieved by reducing the correction window from 5 days to 2 days, streamlining the receipt and referral process and making it possible to assign applications to review groups more quickly.

Target 4

The FY 08 target to implement changes to standing application receipt dates was achieved by means of a policy directive spreading application due dates for various grant mechanisms across a broader range of receipt dates, resulting in a more balanced inflow of applications. In addition, NIH undertook a pilot study to explore the feasibility of allowing new investigators to resubmit or submit an amended R01 application in consecutive review cycles, potentially reducing application cycle time by four months.

POI-6 Provide responsible stewardship over existing federally owned real property assets.

BACKGROUND

Responsible stewardship over federally owned real property assets addresses maximizing facility investments to reduce the potential risks of deferred maintenance. Deferred maintenance compromises the life safety and health of the occupants and the public served 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 reduce the intrinsic and market value of real estate assets.

Facility Condition Index (FCI) is an industry best practice for assessing and measuring the state of an individual building or an entire facilities portfolio using engineering tools to objectively analyze and quantify deferred maintenance and non-compliance with recognized codes, guidelines and applicable standards. The FCI is defined as the ratio of the cost of deferred maintenance to the capital replacement value of a facility or portfolio of facilities. A related measure is Condition Index (CI) which converts the FCI, which is a fraction, to a number from 0 to 100.

FCI = (DM/RC), where DM = deferred maintenance and RC = replacement cost in current dollars;
CI = 1 - (DM/RC) x100

Rationale

For NIH to ensure 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 to plan, budget and monitor the capital maintenance and repair program. The FCI is a recognized benchmark and is one of the required performance 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

The R&I Program is essential to supporting the NIH mission by sustaining and improving the CI of its facilities. Key to the CI is an effective Facility Assessment program, which NIH has put into place and continues to improve. To enhance the accuracy of the condition of the facilities in NIH's portfolio, facility condition assessments are performed on a five-year cycle to identify and prioritize the necessary short and long-term maintenance and repair requirements. This provides the ability to forecast and prioritize the replacement of major components in buildings and ensure optimized allocation of funding resources. Monitoring in-between planned reviews is performed to assess facility performance and condition. As better information is made available, modifications are made to the corresponding CI data. Lessons-learned from the past four (4) years of assessments were used to improve the methodology for review and assignment of CIs.

In 2002, NIH adopted the facility condition assessment protocol to determine the condition of its real estate assets and estimate deferred maintenance based on actual identified deficiencies. Surveys of the Research Triangle Park, North Carolina, and Hamilton, Montana campuses were completed in 2003. The FCI baseline was completed in 2004 when the detailed evaluative survey that underpins the facility assessment program was completed for the Bethesda, Poolesville, and Frederick, Maryland campuses. To provide responsible stewardship, NIH annually:

- Update the facility condition assessment data
- Modify prior year's capital repair plan to reflect actual funds appropriated
- Execute projects included in 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 assessment process, NIH enhances it's knowledge of the condition of facilities and their systems, its ability to prioritize repairs, and its ability to request adequate funding to improve the condition of NIH portfolio.

NIH's Condition Index goal is for 100% of its owned buildings maintain the condition of the portfolio so the average CIwa = 85* by 2017. The original CI targets were established based on 2004 CI data and expected funding streams. Since that time, the accuracy of the CI data has been reviewed and improved to better reflect current conditions. This process improvement effectively lowered the aggregate CI of the portfolio. Chiefly, the CI for the Clinical Center Complex (Building 10) was lowered from a CI of 80 to a CI of 20. This had the immediate effect of drastically reducing the amount of gross square footage that achieved a CI of 65 or more, which entails the need for a longer timeframe to achieve the established goals. In addition, building usage and time increases the backlog of maintenance and projects associated with its aging facilities portfolio along with an increase in facilities-related risk and decrease in mission readiness. The targeted CI achievement is heavily dependent on the levels of available repair and improvement (R&I) resources.

An effective governance structure has been implemented to ensure that facility deficiencies are packaged into manageable projects. NIH has made changes to the facility condition assessment process to improve the incorporation of existing studies results and of NIH in-house subject matter expert knowledge into the assessment process. To further enhance the paradigm used for scoring project priorities of projects will be re-evaluated based on their contribution to reaching scheduled CI goals.

Baseline 2008

- Target 1: (FY07) CIwa = 72
- Target 2: (FY07) 67.5%

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Maintain the condition of the portfolio so the average CIwa = 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.	(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	(NOT MET) The condition of the portfolio reached CIwa of 73.4 in FY08.	CIwa = 85
2	By 2016, no less than 95% of occupied GSF will have a CI greater than 65	(MET) 87% of the occupied space had a CI greater than 65.	(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%	(NOT MET) The FY08 target of or 91.5% of occupied GSF was not achieved. Only 71.3% of the occupied space reached a CI > 65.	73.8%

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY08 target to maintain the condition of the portfolio so the average CIwa =85 was NOT MET. NIH achieved an average CIwa of 73.4 in FY2008. This represented a 1.9% improvement in the facility condition compared to FY2007. The improvement projects performed in the fiscal year were offset by new deficiencies generated as building systems reached the end of its useful life expectancy. NIH fully implemented management initiatives to include in-house subject matter experts (maintenance staff, facility managers, and engineers and architects knowledgeable about our facilities) in the Facility Condition Assessment review and documentation process. The benefits of this process improvement will be realized during review of the new wave of facility assessments currently underway.

Target 2

The FY2008 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 FY2008, 71.3% of NIH facilities reached a CI > 65. This represented a 5.6% improvement compared to FY2007.

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. NIH fully implemented management initiatives to include in-house Subject Matter Experts (SMEs) in the Facility Condition Assessment review and documentation process consistent with the OMB PART evaluation. This management initiative will improve the quality of information in the facility assessment database and support future year CI target goal projections.

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, often imprecise, and vulnerable to many outside influences including codes, standards, guidelines, weather, material shortages, and market forces. Thus, managing the 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 management plans for each project that will include as a minimum:

- Acquisition Planning
- 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
- Use of Earned Value Management to assess risk and variance and to help ensure completion of projects on schedule and within budget
- Construction management and quality assurance programs
- Commissioning to validate that the facility is fully operational for the intended use

Criteria for optimal performance (to be assessed as annual targets):

- Manage all B&F reportable line item projects so it is 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 authorized budget.
- 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 2008

- Target 1: (FY07) 23 active projects
- Target 2: (FY07) 23 active projects / 10% ≤ 2

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 Target/ Estimate
1	Manage all B&F reportable projects so it is completed within 100% of the final approved total project cost.	(MET) All twenty-one (21) projects were managed within the approved budget.	(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.	29 active projects	(NOT MET) 28 of the 29 active projects were managed within the approved budget. One project scope was expanded using DHHS Facility Project Approval Authorization process and reprogramming actions.	23 active projects
2	No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope.	(MET) All projects were managed within the approved scope.	(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.	29 active projects / 10% ≤ 2	(MET) Twenty-eight of the projects were managed within the approved scope. 1 or 3.4% of the 29 active projects experienced a scope increase related to increased security requirements.	23 active projects / 10% ≤ 2

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY 2008 target was Not Met. Of the 29 B&F reportable projects scheduled to be completed within 100% of the final approved total project cost in 2008; 28 or 96.6% of the portfolio Fully Met this objective. For the 29th project, the scope was expanded to include additional space to house subjects with infectious diseases resulting in additional funding requirements to support this and excessive construction material costs. The request for the additional scope was approved and an increase in total project budget was authorized. The effort to complete the 28 project items on target was made possible in part by the Pre-project Planning Process (PPP) and 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 FY2008 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-nine (29) 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 3.4% 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 2015, 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 is working 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 2008

- (Target 1) (FY08) 21 grantees
- (Target 2) No. of Projects occupied in past 20 years: (FY08) 164 prjs

#	Key Outputs	FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.	(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 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	(MET) 100% of projects under construction have approved design and construction documents and ensured the Notice of Federal Interest has been recorded.	0 expected grantees
2	Through 2015, 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.	(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	(MET) 95% of the extramural construction projects were in compliance with the post award 20 year usage requirement.	95% of 179 projects are in compliance

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

Target 1

The FY08 target was MET. During FY 2008, 100% of the 21 grantees took the necessary actions to provide the construction designs documents and the Notice of Federal Interest (NFI).

Target 2

The FY08 target was MET. During FY 2008, 95% 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 2015, 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 2008

- BSCs reviewed about 300 P.I.s. (of total of about 900 tenured and 300 tenure-track) for quality and accomplishments

FY 2005 Actual	FY 2006 Actual	FY 2007 Target/ Estimate	FY 2007 Actual	FY 2008 Target/ Estimate	FY 2008 Actual	FY 2009 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.

SUMMARY OF 2008 PERFORMANCE RESULTS

Target

The FY 2008 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 30, 2008 to discuss issues relating to the BSC reviews. The discussions included intramural budgets, recruitment and retention issues, trends in tenure and tenure-track appointments, trans-NIH intramural research initiatives, clinical research and specific issues from BSC chairs. The Director, NIH and DDIR, NIH attends the meeting and presents current intramural issues.

The annual cost savings realized in FY 2007 was $3,338,002; this amount was reallocated within the Intramural Research Programs in FY 2007. Annual cost savings for FY 2008 will be available in 2009.

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.

NIH SUPPORT FOR HHS STRATEGIC PLAN

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.

NIH Link to HHS Strategic Goal 4 and Objectives

NIH Scientific Research Outcomes (SRO) GPRA Goals (1 of 3)	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-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 corticotrophin-releasing hormone antagonist antalarmin.			X	
SRO-1.3: By 2010, develop an experimental robotic exoskeleton that can be tested for clinical rehabilitation of upper extremity movement.			X	
SRO-1.4: By 2012, identify signatures of gene expression in peripheral tissues that are associated with alcohol-induced disorders.		X		
SRO-2.1: By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.			X	
SRO-2.2: By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.			X	
SRO-2.4: By 2009, the Laboratory of Symptom Management will develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress, to reduce related symptom burden and to increase functional status and quality of life.			X	
SRO-2.5: By 2011, conduct early phase trials for 5 novel molecular-targeted interventions for early diagnosis, detection, and therapy for multiple cancers.		X		
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.		X		
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.			X	
SRO-2.8: By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.		X		
SRO-3.1: By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).			X	
SRO-3.2: By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		X		
SRO-3.3: By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.			X	
SRO-3.4: By 2010, develop an HIV/AIDS vaccine.			X	

NIH Scientific Research Outcomes (SRO) GPRA Goals (2 of 3)	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-3.5: By 2013, identify and characterize at least 2 human candidate genes that mutually influence risk for substance use disorders and risk for comorbid psychiatric disorders using high-risk family, twin, and special population studies.		X		
SRO-3.6: By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.		X		
SRO-3.7: By 2019, develop one or more improved therapies for at least one immune-mediated disease.		X		
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.			X	
SRO-4.3: By 2009, evaluate the safety and efficacy of two new treatments for nonalcoholic steatohepatitis (NASH) in adults.			X	
SRO-4.4: By 2011, identify or study additional genes involved in communication disorders in humans and animal models.		X		
SRO-4.5: By 2011, identify genetic and environmental factors which predispose to three complex diseases.		X		
SRO-5.2: By 2009, determine the efficacy of statins in preventing the progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).			X	
SRO-5.3: By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.		X		
SRO-5.5: By 2008, develop and test new evidence-based treatment approaches for drug abuse in community settings.			X	
SRO-5.6: By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.		X		
SRO-5.7: By 2010, validate and compare 4 imaging methods of assessing lung cancer response to therapy.		X		
SRO-5.8: By 2012, improve device(s) to measure hot flashes and test device(s) in clinical trials.			X	
SRO-5.9: By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.		X		
SRO-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.			X	
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.			X	
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.		X		
SRO-6.1: By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.		X		
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.			X	
SRO-6.3: By 2008, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.		X		
SRO-6.4: By 2014, identify and characterize two molecular pathways of potential clinical significance to serve as the basis for discovering new medications for preventing and treating asthma exacerbations.		X		
SRO-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.			X	
SRO-6.6: By 2015, provide at least one new or significantly improved minimally-invasive treatment for patients using image-guided interventions.		X		
SRO-7.4: By 2009, create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for osteoarthritis.		X		
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.			X	
SRO-7.7: By 2011, assess community-based methods for facilitating cancer research and providing patients access to optimal cancer care.			X	
SRO-8.2: By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.		X		
SRO-8.4: By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.		X		
SRO-8.5: By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.			X	

NIH Scientific Research Outcomes (SRO) GPRA Goals (3 of 3)	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-8.6: By 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).		X		
SRO-8.7: 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.			X	
SRO-8.8: By 2012, identify at least one candidate intervention that extends median lifespan in an animal model.		X		
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).			X	
SRO-9.2: By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.			X	
SRO-9.3: By 2011, create a database and analytical software that illustrates the progression of normal MRI measurement of brain development in a nationally representative sample of children in the United States.		X		
SRO-9.4: By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life.		X		
SRO-9.5: By 2014, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia.			X	

NIH Communication and Transfer of Results (CTR) GPRA Goals	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-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).				X
CTR-4: By 2008, increase the percentage of Small Business Innovation Research (SBIR) Program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.				X
CTR-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.				X
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.				X
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.				X

NIH Capacity Building and Research Resources (CBRR) GPRA Goals	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.
CBRR-1: By 2012, recruit, train, and retain a diverse population of highly trained scientists in biomedical, behavioral, and clinical research using research training grants, fellowships, career development awards, and student loan repayment programs.	X			
CBRR-2: Promote data sharing and provide information in real time by implementing the NIH Business System.			X	
CBRR-4: By 2013, provide greater functionality and more streamlined processes in grants administration by continuing to develop the NIH electronic research administration (eRA).			X	
CBRR-6: By 2012, build capacity to conduct research by constructing or renovating extramural facilities to meet the biomedical and behavioral research, research training or research support needs.			X	
CBRR-7: By 2010, utilize enhanced ARIS database to more efficiently conduct portfolio analysis to invest in priority AIDS research.			X	
CBRR-8: By 2012, ensure that 100% of trainee appointment forms are processed electronically, to enhance program management.	X			
CBRR-9: By 2012, achieve average annual cost savings of managing construction grants by expanding the use of electronic project management tools that enhance oversight and 20 year usage monitoring.			X	
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.				X

NIH Strategic Management of Human Capital (SMHC) GPRA Goals	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.
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.	X			
SMHC-4: Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the Agency's commercial inventory.	X			
SMHC-5: Improve and monitor the use of human resource services by providing real-time access to tools via the NIH Portal.	X			
SMHC-6: Provide opportunities for enhanced leadership skills to meet the challenges of workforce management and/or individual advancements. (Ongoing)	X			
SMHC-7: Address diverse workforce recruitment needs to ascertain highly qualified staff to conduct or support biomedical research. (Ongoing)	X			
SHMC-8: Address areas to facilitate retention of highly qualified staff to conduct or support biomedical research. (Ongoing)	X			

NIH Program Oversight and Improvement (POI) GPRA Goals	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.
POI-2: Expand the use of Performance-Based Contracting (PBC).	X			
POI-5: By 2010, enhance NIH's ability to demonstrate benefits for extramural research investments through changes to policy and information systems.				X
POI-6: Provide responsible stewardship over existing federally owned real property assets.			X	
POI-7: Manage design and construction of capital facility projects funded by the building and facilities appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the appropriate budget.			X	
POI-8: By 2015, protect NIH's interest in real property supported under the extramural construction grant program by ensuring compliance with construction and 20 year usage requirements			X	
POI-9: By 2015, reallocation of laboratory resources based on external reviews by Boards of Scientific Counselors	X			

SUMMARY OF FINDINGS AND RECOMMENDATIONS FROM PROGRAM EVALUATIONS

A summary of the findings and recommendations from NIH program evaluations completed during FY 2008 can be found in the HHS Performance Improvement Database (http://aspe.hhs.gov/pic/performance/). Below are a few examples of summaries of findings and recommendations from evaluations completed in FY 2008, taken from the HHS Performance Improvement Database.

How Effective is the Collaborative Network of Infectious Disease Models in Assisting the Nation Prepare for Outbreaks?

The Models of Infectious Disease Agent Study (MIDAS) managed by the National Institute of General Medical Sciences (NIGMS), is a consortium of researchers who develop mathematical and computational tools to assist policymakers and public health professionals in preparing the nation for outbreaks of infectious diseases. A process evaluation was conducted to determine if the program was operating as intended and whether any necessary modifications; in preparation for issuing the 2007 Request for Applications. The evaluation focused on three aspects of the program: adequacy and appropriateness of policies and infrastructure; effectiveness of internal and external collaborations and communications; and perceived value of outputs. Data for the evaluation were gathered by interviewing Principal Investigators, collaborators, federal and state government, and outside academic scientist. In addition to the interviews, extent program materials such as publications, the MIDAS web portal, solicitations, and policy documents, were reviewed. Based on the evaluation findings, recommendations were made to strengthen and better align the MIDAS program with its goals. Findings from the study were reported to the NIH staff and revisions were made based on their input.

What Impact have the Udall Centers of Excellence had on Parkinson's Disease Research Discoveries?

This study assessed 11 Udall Parkinson's Disease Research Centers, to evaluate their operations in terms of their scientific productivity, collaborations, and training. The study also provided additional insight on the reasons some of the centers were more successful than others in achieving the program's goals. There has been increasing pressure from the Parkinson's Disease (PD) voluntary community and the National Advisory Council, to evaluate the Udall Centers Program; as well as interest from many members of Congress in the Udall program, particularly in its continuation and/or expansion by The National Institute of Neurological Disorders and Stroke (NINDS). As a result of the need for prompt action to address these various constituents, NINDS conducted a full-scale evaluation of the Udall Centers of Excellence for Parkinson's Disease Research Program, designed to assess the performance of 11 Udall centers during their first five years, to assess the centers as a group, and to assess NINDS' management of the Udall Centers Program from FY 1998 to FY 2004. This study was designed to answer ten questions related to the success of the Udall Centers program, the adequacy of the NINDS management of the program, and the 'value added'. The study design involved both qualitative and quantitative approaches to assessing scientific productivity, collaboration and training; and utilized survey and interview responses as primary sources of data, publication records and progress reports as secondary data

sources. A key component of the evaluation was the involvement of an Expert Advisory Panel, comprised of scientific experts, including basic science researchers and clinicians with expertise in PD or a related research field. The primary responsibility of the Expert Panel was to assess the analyzed data and make recommendations to NINDS for further improvements in the Udall Centers program. Some of the study's key findings were that the Program significantly impacted the Parkinson's Disease research field; substantial multidisciplinary research and training occurred throughout the Udall Centers; and the selection of applications with a range of investigator backgrounds was a strength of the process. The Working Group made several recommendations specific to NINDS' operation of the Udall Centers Program, and for conducting future evaluations of programs in general.

Clinical and Translational Science Awards Program: National CTSA Process Evaluation Feasibility Study

This study designed a methodology to evaluate the operations of the Clinical and Translational Science Awards (CTSA) consortium. The National Institutes of Health's (NIH) Roadmap for Medical Research Program, launched the Clinical and Translational Science Award (CTSA) consortium to re-engineer the clinical research enterprise in the United States; by transforming the local, regional and national environment for clinical and translational science, thereby increasing the efficiency and speed of clinical and translational research. Given the ambitious goals of this consortium to transform the practice of clinical and translational science; rigorous attention must be given to evaluating the consortium. Six sources of information were used to develop a more complete understanding of the CTSA program to determine the feasibility of an evaluation, and to construct a design for the national process evaluation: (1) review of literature on clinical and translational science, evaluations of research programs, and the application of specific evaluation methodologies; (2) review of NIH evaluation studies funded by the Evaluation Set-Aside program, and interviews with NIH project directors of evaluation projects of similar magnitude and complexity; (3) interviews with representatives from biomedical professional organizations; (4) two CTSA institutional informational visits, to obtain background information on CTSA programs and identify important implementation factors; (5) review of CTSA institutional self-evaluation plans; (6) pilot data extraction from the CTSA Annual Progress Reports and the minutes of CTSA Steering Committee meetings. The results from this feasibility study highlighted the complexity of the national CTSA initiative; and raised several overarching issues that need to be considered in the design and implementation of the prospective process evaluation study, including defining key terms, transitioning from the former General Clinical Research Center (GCRC) model to the CTSA model, capturing relevant contextual variables, and determining the critical timeframes for assessing the results of program activities and their outcomes.

DATA SOURCE AND VALIDATION TABLES

Scientific Research Outcomes (SRO)

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-1.3	Wolbrecht, ET, Chan V, Reinkensmeyer DJ, Bobrow JE (2008) Optimizing compliant, model-based robotic assistance to promote neurorehabilitation, IEEE Trans Neural Syst and Rehab Eng, 16(3):286-97. http://ieeexplore.ieee.org/search/wrapper.jsp?arnumber=4451797 Rosati G, Bobrow JE, Reinkensmeyer DJ (2008) Compliant control of post-stroke rehabilitation robots: using movement-specific models to improve controller performance, Proceedings of the 2008 ASME International Mechanical Engineering Congress & Exposition Sivakumar Balasubramanian, Ruihua Wei, Mike Perez, Ben Shepard, James Koeneman, Jiping He. "RUPERT: An Exoskeleton Robot for Assisting Rehabilitation of Arm Functions." Proc. Virtual Reality and Rehabilitation 2008, Vancouver, Canada, August 25-27, 2008 Wei Ruihua, Balasubramanian S, He Jiping. "Adaptive Iterative learning control for RUPERT" Proc. BioRobot 2008. Spencer SJ, Klein J, Minakata K, Le V, Bobrow JE, Reinkensmeyer DJ (2008) A low cost parallel robot and trajectory optimization method for wrist and forearm rehabilitation using the Wii, Proceedings of the 2008 IEEE Conference on Biorobotics Klein J, Spencer SJ, Allington J, Minakata K, Wolbrecht ET, Smith R, Bobrow JE, Reinkensmeyer DJ (2008) Biomimetic orthosis for the neurorehabilitation of the elbow and shoulder (BONES), Proceedings of the 2008 IEEE Conference on Biorobotics Duff M, Attygalle S, Jiping He, and Rikakis T. "A Portable, Low-cost Assessment Device for Reaching Times," Proc. IEEE EMBS 2008, Vancouver, Canada, August 20-24 2008 Kexin Xing, Qi Xu, Jiping He, Yongji Wang, Zhongwei Liu, Xiaolin Huang. "A Wearable Device for Repetitive Hand Therapy," Proc. Virtual Reality and Rehabilitation 2008, Vancouver, Canada, August 25-27, 2008
SRO-2.1	Patients can find out if they are eligible to participate in a CIT Consortium clinical trial at http://www.CITisletstudy.org. More information on six 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 being performed in Sweden, 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.

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-2.2	Confirmation of the completion of the POUNDS Lost interventions can be found on clinicaltrials.gov at: http://clinicaltrials.gov/ct2/show/NCT00072995?term=POUNDS+Lost&rank=1 Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Loria CM, Obarzanek E, Williamson DA. Randomized trial comparing fat, protein, and carbohydrate composition of diets for weight loss for 2 years. NEJM in press Svetkey LP et al. for the Weight Loss Maintenance Collaborative Research Group. Comparison of strategies for Sustaining Weight Loss: Main results of the Weight Loss Maintenance Trial. JAMA 2008 299(10):1139-48. http://jama.ama-assn.org/cgi/content/full/299/10/1139 Hollis JF for the Weight Loss Maintenance Collaborative Research Group. Weight Loss During the Initial Intensive Intervention Phase of the Weight Loss Maintenance Trial. Am J Prev Med. 2008 35(2):118-26. http://www.ncbi.nlm.nih.gov/pubmed/18617080?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum Rosenbaum M et al. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J. Clin. Invest. 118:2583-2591 (2008). http://www.jci.org/articles/view/35055
SRO-2.4	Wang X.M., Hamza M., Wahl S.M., Dionne R.A. (2008). COX-inhibitors down regulate PDE4D expression in a clinical model of acute inflammatory pain. Clin Pharmacol Therap, 84: 39-42. http://www.ncbi.nlm.nih.gov/pubmed/18288087 Kim H., Ramsay E., Lee H., Wahl S. Dionne R.A. (2009). Genome-wide association study of acute post-surgical pain in humans. Pharmacogenomics, In Press (Accepted for publication).
SRO-2.5	Nagarajan M, et al. Synthesis and biological evaluation of bisindenoisoquinolines as topoisomerase I inhibitors. J. Med. Chem. 49: 5129-40, 2006. PMID: 16913702 Xu, H., et al. Design, Synthesis, and Characterization of a Dual Modality Positron Emission Tomography and Fluorescence Imaging Agent for Monoclonal Antibody Tumor-Targeted Imaging. J Med Chem, 2007. PMID: 17725340
SRO-2.6	Bang JH, Lim, SH, Park, E, Suslick, KS. Chemically Responsive Nanoporous Pigments: Colorimetric Sensor Arrays and the Identification of Aliphatic Amines. Langmuir ASAP Article, 10.1021/la802029m (epub ahead of print) http://dx.doi.org/10.1021/la802029m Sridhar, S., Schembri, F., Zeskind, J., Shah, V., Gustasfson, A.M., Steiling, K., Liu, G., DumasY.-M., Zhang, X., Brody, J.S., Lenberg, M.E., and Spria, A. Smoking-Induced Gene Expression Changes in the Bronchial Airway Are Reflected in the Nasal and Buccal Epithelium, BMC Genomics, 2008 9:259. http://www.biomedcentral.com/1471-2164/9/259 Funk, W.E., Waidyantha, S., Chaing, S.H., and Rappaport, S.M., Hemoglobin Adducts of Benzene Oxide in Neonatal and Adult Dried Blood Spots, Cancer Epidemiol Biomakers Prev., 2008 17(8); 1896. http://cebp.aacrjournals.org/cgi/content/abstract/17/8/1896 Kumaresan, P., Yang, C.J., Cronier, S.A., Blazej, R.G., and Mathies, R.A., High-throughput Single Copy DNA Amplification and Cell Analysis in Engineered Nanoliter Droplets, Anal. Chemistry, 2008, 80:3522. http://dx.doi.org/10.1021/ac800327d
SRO-2.7	Jordt U01ES015674: Sensory neural mechanisms of pulmonary agent and vesicant toxicity. Bessac et al. TRPA1 is a major oxidant sensor in murine airway sensory neurons. J Clinic Invest. 2008 May; 118(5): 1899-910. Braga U01NS058162: Efficacy of GluR5 antagonists against soman-induced seizure and neuropathology. 2007 Progress Report. Dingeldine U01NS058158: Prostanoid modulators that reduce brain injury and inflammation after seizures. 2008 Progress Report.

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-2.8	Wilton, R01NS044146: Antisense oligonucleotide suppression of non-deletion DMD causing mutations. 2009 Type 2 Application. Fletcher S, Honeyman K, et al. Morpholino Oligomer-Mediated Exon Skipping Averts the Onset of Dystrophic Pathology in the mdx Mouse. Mol Ther. 2007 Sep;15(9):1587-92. Wilton, R01NS044146: Antisense oligonucleotide suppression of non-deletion DMD causing mutations. 2009 Type 2 Application. Gurvich OL, Tuohy TM, et al. DMD pseudoexon mutations: splicing efficiency, phenotype, and potential therapy. Ann Neurol. 2008 Jan;63(1):81-9. Howard, R21NS051792: Antisense Mediated Suppression of Dystrophin Mutations. 2007 Progress Report. Henderson CM, Anderson CB, Howard MT. Antisense-induced ribosomal frameshifting. Nucleic Acid Res. 2006; 34(15):4302-10.
SRO-3.1	Munoz L. et al. A novel p38α MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an Alzheimer"s disease mouse model. Journal of Neuroscience 2007; 4:21. Published on line 09/04/07. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17784957 Information about AL-108: http://www.allontherapeutics.com/al-108.html
SRO-3.2	Submitted Meeting Abstract: Rausch, L. et al. Rodent toxicity of K777, a candidate therapeutic for treatment of Chagas' Disease. Society of Toxicology meeting, Baltimore, MD, March 2009. Submitted Meeting Abstract: Iyer, L. et al. In vitro metabolism and gender specific pharmacokinetics of K777, a novel cysteine protease inhibitor. Society of Toxicology meeting, Baltimore, MD, March 2009. NIAID Contract N01-AI-60011 Information on FabI inhibitor work found in internal NIAID documents – Please contact Dr. Susan Daniels/ NIAID for more information (301) 451-3238 or sdaniels@niaid.nih.gov. Development of Therapeutic Agents for Select Biodefense Pathogens solicitation and awards in FedBizOps: https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=9f5ae4c87de43db16623210cf66dc031&_cview=0
SRO-3.3	Reference: Salivary Proteome Knowledge Base (SPKB) website http://hspp.dent.ucla.edu/skb.html

GOAL	FY 2008 DATA SOURCE AND VALIDATION
	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. http://www3.niaid.nih.gov/news/newsreleases/2007/step_update.htm for early information concerning STEP and Phambili trials http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/advisory/avrs/avrs_may08.htm for information about the AIDS Vaccine Research Subcommittee meeting about the STEP and PAVE studies http://www3.niaid.nih.gov/news/newsreleases/2008/pave100.htm for information pertaining to NIAID's decision concerning the PAVE 100 study http://www3.niaid.nih.gov/news/events/summitHIVVaccine.htm for information on and presentations from the Summit on HIV Vaccine Research and Development http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/advisory/avrs/avrs.htm for status of NIAID Adenovirus-based vaccine studies
SRO-3.4	Identification and Characterization of Transmitted and Early Founder Virus Envelopes in Primary HIV Infection, Keele BF, et al. Proc. Natl. Acad. Sci. USA, 2008: 105(21): 75552-7557. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18490657 Magnitude and Phenotype of Cellular Immune Responses Elicited by Recombinant Adenovirus Vectors and Heterologous Prime-boost Regimens in Rhesus Monkeys, Liu, J., et al. J. Virol. 2008 Mar 12. http://jvi.asm.org/cgi/content/full/82/10/4844?view=long&pmid=18337575 HIV Broadly Neutralizing Antibody Extracts Its Epitope from a Kinked gp41 Ectodomain Region on the Viral Membrane, Sun ZY, et. al. Immunity, 2008 Jan; 28(1):52-63. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WSP-4RJK0CF-1&_user=5755111&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000000150&_version=1&_urlVersion=0&_userid=5755111&md5=071d58c799ae25015dc47500776cbaac HIV Vaccine Induced Immunity in the Test-of-Concept STEP Study, McElrath MJ, et. al., Lancet 2008. (in press) http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61592-5/fulltext The Step Study: The First Test-of-Concept Efficacy Trial of a Cell-Mediated Immunity HIV Vaccine, Buchbinder SP, et. Al., Lancet 2008 (in press) http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61591-3/fulltext Antigen Load and Viral Sequence Diversification Determine the Functional Profile of HIV-1-Specific CD8+ T Cells. PLoS Med. 2008 May 6:5(5):e100. http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050100&ct=1

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-3.5	Edenberg HJ, Xuei X, Wetherill LF, Bierut L, Bucholz K, Dick DM, Hesselbrock V, Kuperman S, Porjesz B, Schuckit MA, Tischfield JA, Almasy LA, Nurnberger JI Jr, Foroud T. Association of NFKB1, which encodes a subunit of the transcription factor NF-kappaB, with alcohol dependence. Hum Mol Genet 2008. Apr 1;17(7):963-70. Epub 2007 Dec 12 http://hmg.oxfordjournals.org/cgi/content/full/17/7/963 Enoch M-A, Hodgkinson CA, Yuan Q, Albaugh B, Virkkunen M, Goldman D. GABRG1 and GABRA2 as independent predictors for alcoholism in two populations. Neuropsychopharmacology 2008. advance online publication, 24 September 2008; doi:10.1038/npp.2008.171 http://www.nature.com/npp/journal/vaop/ncurrent/abs/npp2008171a.html Covault J, Gelernter J, Jensen K, Anton R, Kranzler HR. Markers in the 5'-region of GABRG1 associate to alcohol dependence and are in linkage disequilbrium with markers in the adjacent GABRA2 gene. Neuropsychopharmacology 2008 33: 837–848; doi:10.1038/sj.npp.1301456; published online 16 May 2007 http://www.nature.com/npp/journal/v33/n4/abs/1301456a.html Wetherill L, Schuckit MA, Hesselbrock V, Xuei X, Liang T, Dick DM, Kramer J, Nurnberger Jr JI, Tischfield JA, Porjesz B, Edenberg HJ, Foroud T. Neuropeptide Y receptor genes are associated with alcohol dependence, alcohol withdrawal phenotypes, and cocaine dependence. Alcohol Clin Exp Res 2008 Sep 25. [Epub ahead of print] http://www3.interscience.wiley.com/journal/121421805/abstract?CRETRY=1&SRETRY=0 Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, Goldman D. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008 Feb; 65:135-144. PMID: 18250251 [PubMed - indexed for MEDLINE] http://archpsyc.ama-assn.org/cgi/content/full/65/2/135
SRO-3.6	Presentations: Fu, Y. Kedziorek, D., Crisostomo, V., Gilson, W., Arepally, A., Lederman R., Lorenz, C., Sonmez, M., Ozturk, C., Bulte, J., Kraitchman, D. Multi-Modality Visible Alginate Microcapsules for Mesenchymal Stem Cell Delivery. 2008 World Molecular Imaging Congress. http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={3A27300A-99D2-4F7B-B388-02961A69BED6}&MKey={B47BAE74-CCA9-4C27-80FB-0005AFC9E5C0}&AKey={A4C6DD8F-4BF2-400D-97ED-20C14381CDBB}&SKey={278EAB60-0588-4590-A4FF-6A47832E1D98} Kedziorek, D., Walczak, P., Azene, N., Kraitchman, D. Cell Visibility and Viability Assessment with Novel Bioluminescence Assay of X-Ray-Visible Microencapsulated Mesenchymal Stem Cells. 2008 World Molecular Imaging Congress. http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={B5604733-7132-4162-8BA7-0B39EAD48C72}&MKey={B47BAE74-CCA9-4C27-80FB-0005AFC9E5C0}&AKey={A4C6DD8F-4BF2-400D-97ED-20C14381CDBB}&SKey={278EAB60-0588-4590-A4FF-6A47832E1D98}
SRO-3.8	The URL http://www.ctsu.org is a publicly available web site that tracks registrations to this trial. As of 10/21/08 this website had 5079 *registrations* (which exceeds the planned accrual goal). Please note this number is *not* accrual to the randomized trial, as the Clinical Trials Support Unit tracks all registrations. However, the accrual to the randomized study can be obtained from the ECOG members site in their November 2008 PACCT-1 trial report.
SRO-4.3	Please contact Dr. Patrick Donohue in the Office of Scientific Program and Policy Analysis, NIDDK, for a copy of the 01 September 2008 Data and Safety Monitoring Board report.
SRO-5.2	Study staff have submitted PDF versions of the quarterly newsletters. These newsletters may be obtained by contacting the Systemic Assessments Branch. Study medication compliance tables were presented to the Data and Safety Monitoring Committee.

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-5.3	Pyrimidinone-peptoid hybrid molecules with distinct effects on molecular chaperone function and cell proliferation. Bioorganic & Medicinal Chemistry, Volume 16, Issue 6, 15 March 2008, Pages 3291-3301 http://www.sciencedirect.com (DOI:10.1016/j.bmc.2007.12.014) Identification of Novel Epoxide Inhibitors of Hepatitis C Virus Replication Using a High-Throughput Screen. (DOI:10.1128/AAC.00233-07) http://aac.asm.org/cgi/content/short/AAC.00233-07v1 Studies Towards the Synthesis of Methionine Aminopeptidase Inhibitors: Diversification Utilizing a ROMP-Derived Coupling Reagent. J of Combinatorial Chemistry, 2008,10(2), 195-203. (DOI: 10.1021/cc70000869) http://pubs.acs.org Tubulin-Perturbing Naphthoquinone Spiroketals http://www3.interscience.wiley.com/cgi-bin/fulltext/119422882/PDFSTART Towards the Optimal Screening Collection: A Synthesis Strategy http://www3.interscience.wiley.com/cgi-bin/fulltext/117863472/PDFSTART Funded Research; RFA-GM-08-007 Centers of Excellence in Chemical Methodologies and Library Development (P50) http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-08-007.html

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SRO-5.5	1. Trial Progress Report, October 20, 2008, Data and Statistics Center at Duke Clinical Research Institute, Duke University Medical Center. 2. 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 3. 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 4. 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 5. Martino, Steve ; Ball, Samuel A. ; Nich, Charla ; Frankforter, Tami L. ; Carroll, Kathleen M. "Informal Discussions in Substance Abuse Treatment Sessions." Journal of Substance Abuse Treatment 2008 (in press). [DOI: 10.1016/j.jsat.2008.08.003]. 6. Martino, Steve ; Ball, Samuel A. ; Nich, Charla ; Frankforter, Tami L. ; Carroll, Kathleen M. "Community Program Therapist Adherence and Competence in Motivational Enhancement Therapy. " Drug and Alcohol Dependence 2008;96(1-2):37-48. [DOI: 10.1016/j.drugalcdep.2008.01.020]. 7. Santa Ana, Elizabeth J. ; Martino, Steve ; Ball, Samuel A. ; Nich, Charla ; Frankforter, Tami L. ; Carroll, Kathleen M. "What is Usual About "Treatment-As-Usual"? Data from Two Multisite Effectiveness Trials. Journal of Substance Abuse Treatment 2008 (in press). [DOI: 10.1016/j.jsat.2008.01.003]. 8. Guydish, Joseph R. ; Manser, Sarah Turcotte ; Jessup, Martha A. ; Tajima, Barbara M. "Adoption of Motivational Interviewing/Motivational Enhancement Therapy." Presented at the American Psychological Association (APA) Annual Convention, San Francisco, CA, August 17-20, 2007. 9. Hien, Denise A. ; Killeen, Therese ; Campbell, Aimee N. C. ; Jiang, Huiping ; Nunes, Edward V. "HIV Sex Risk Behaviors and PTSD: Secondary Findings from a NIDA Clinical Trials Network Randomized Controlled Trial of Women in Community-Based Substance Abuse Treatment." Poster presented at the College on Problems of Drug Dependence (CPDD) annual meeting, San Juan, Puerto Rico, June 14-19, 2008. 10. Killeen, Therese ; Hien, Denise A. ; Campbell, Aimee N. C. ; Brown, Chanda ; Hansen, Cheri ; Jiang, Huiping ; Kristman-Valente, Allison ; Neuenfeldt, Christine ; Rocz-de la Luz, Nicci ; Sampson, Royce ; Suarez-Morales, Lourdes ; Wells, Elizabeth A. ; Brigham, Gregory S. ; Nunes, Edward V. "Adverse Events in an Integrated Trauma-Focused Intervention for Women in Community Substance Abuse Treatment. " Journal of Substance Abuse Treatment 2008;35(3):304-311 [DOI: 10.1016/j.jsat.2007.12.001]. 11. Hien, Denise A. Presented at the American Psychological Association (APA) Annual Convention, San Francisco, CA, August 17-20, 2007. "Early Findings from NIDA"s Clinical Trials Network "Women and Trauma" Study." 12. Hien, Denise A. "CTN 0015: Preliminary Findings from the "Women and Trauma" Study". Presented at the American Academy of Addiction Psychiatry Annual Meeting and Symposium, St. Petersburg, FL, December 7-10, 2006.
SRO-5.6	Validation Contact Dr. Susan Weiss Chief of Science Policy Branch, Office of Science Policy and Communications, NIDA 301-443-6071 sweiss@nida.nih.gov

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SRO-5.7	http://gforge.nci.nih.gov/docman/?group_id=315) Shields AF, Lawhorn-Crews JM, Briston DA, Zalzala S, Gadgeel S, Douglas KA, Mangner TJ, Heilbrun LK, and Muzik O. Analysis and reproducibility of 3'deoxy-3'-[18F] fluorothymidine positron emission tomography imaging in patients with non-small cell lung cancer. Clin Cancer Res 2008, 14(14): 4463-4468. Vesselle H, Salskov A, Turcotte E, Wiens L, Schmidt R, Jordan CD, Vallieres E, and Wood DE. Relationship between non-small cell lung cancer FDG uptake at PET, tumor histology, and Ki-67 proliferation index. J Thorac Oncol. 2008, 3: 971–978. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, Einhorn LH, Suh WW, Samson D, Delbeke D, Gorman M, Shields AF. Recommendations on the Use of 18F-FDG PET in Oncology. J Nucl Med. 2008, 49(3):480-508. Epub 2008 Feb 20. Vesselle H, Freeman JD, Wiens L, Stern J, Nguyen HQ, Hawes SE, Bastian P, Salskov A, Vallières E, Wood DE. Fluorodeoxyglucose uptake of primary non-small cell lung cancer at positron emission tomography: new contrary data on prognostic role. Clin Cancer Res. 2007, 13(11):3255-63. Muzi M, Vesselle H, Grierson JR, Mankoff DA, Schmidt RA, Peterson L, Wells JM, Krohn KA. Kinetic analysis of 3"-deoxy-3"-fluorothymidine PET studies: validation studies in patients with lung cancer. J Nucl Med. 2005, 46(2):274-82.
SRO-5.8	Clinical trial is grant # U01AT004634-02 Abstract available through CRISP at http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen
SRO-5.9	Draft release 1 for HapMap 3 samples: http://www.broad.mit.edu/~debakker/p3.html Draft release 2 for HapMap 3 samples: http://www.hgsc.bcm.tmc.edu/projects/human/ The International HapMap Project: http://www.hapmap.org/
SRO-5.10	Contact: Dr. Les Reinlib Susceptability and Population Health Branch E-Mail: reinlib@niehs.nih.gov Phone: (919) 541-4998 Fax: (919) 316-4606 Refer to BCERC Project 2 Data Collection
SRO-5.11	Ersek M., Turner J., Cain K., and Kemp C. (2007). Results of a randomized controlled trial to examine the efficacy of a chronic pain self-management group for older adults. Pain, 138: 29-40. http://www.ncbi.nlm.nih.gov/pubmed/18086516 Kozachik S. and Bandeen-Roche K. (2008). Predictors of patterns of pain, fatigue, and insomnia during the first year after a cancer diagnosis in the elderly. Cancer Nursing, 31: 334-344. http://www.ncbi.nlm.nih.gov/pubmed/18772657 Payne J., Held J., Thorpe J., and Shaw H. (2008). Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncology Nursing Forum, 35: 635-642. http://www.ncbi.nlm.nih.gov/pubmed/18591167 Wrosch C. and Schulz R. (2008). Health-engagement control strategies and 2-year changes in older adult's physical health. Psychological Science, 19: 537-541. http://www.ncbi.nlm.nih.gov/pubmed/18578842

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SRO-6.1 (cont.)	8) Yoshida T, DeWan A, Zhang H, Sakamoto R, Okamoto H, Minami M, Obazawa M, Mizota A, Tanaka M, Saito Y, Takagi I, Hoh J, Iwata T: HTRA1 promoter polymorphism predisposes Japanese to age-related macular degeneration. Molecular Vision (2007) 4;13:545-8. http://www.molvis.org/molvis/v13/a58/ 9) Klein ML, Francis PJ, Rosner B, Reynolds R, Hamon SC, Schultz DW, Ott J, Seddon JM.CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmology. (2008) 115(6):1019-25. http://dx.doi.org/10.1016/j.ophtha.2008.01.036 10) Seddon JM, Reynolds R, Rosner B. Peripheral Retinal Drusen and Reticular Pigment Changes: Association with CFHY402H and CFHrs1410996 Genotypes in Family and Twin Studies of Age-Related Macular Degeneration Invest Ophthalmol Vis Sci. (2008) [Epub ahead of print] http://www.iovs.org/cgi/content/abstract/iovs.08-2514v1 11) Fagerness JA, Maller JB, Neale BM, Reynolds RC, Daly MJ, Seddon JM. Variation near complement factor I is associated with risk of advanced AMD.Eur J Hum Genet. 2008. [Epub ahead of print] http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg2008140a.html
SRO-6.2	Please contact Dr. Patrick Donohue, Office of Scientific Program and Policy Analysis, NIDDK, for access to the DSMB report.
SRO-6.3	Data Source & Validation: CEBS2: Chemical Effects in Biological Systems Knowledge Base http://cebs.niehs.nih.gov Development System - CEBS3: Chemical Effects in Biological Systems Knowledge Base http://devtools.niehs.nih.gov/cebs3/flex/ Please note the above URL is currently in development mode as the online database is reviewed for compliance with 508 guidelines and policies.
SRO-6.4	Fain, SB, Gonzalez-Fernandez,G, et al. Evaluation of Structure-Function Relationships in Asthma using Multidetector CT and Hyperpolarized He-3 MRI. Academic Radiology. 2008 15(6):753-62. Article can be found online at: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B75BK-4SHGSXG-9&_user=5755111&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=5755111&md5=a4928a4eda4fb711a91729a0bcb8e8a1
SRO-6.5	Risk for Opportunistic Disease and Death after Reinitiating Continuous Antiretroviral Therapy in Patients with HIV Previously Receiving Episodic Therapy, The SMART Study Group, Annals of Internal Medicine, 2 September 2008, Volume 149: No 5 http://www.annals.org/cgi/content/full/149/5/289 NIAID Planning and Reporting Process: HIV Prevention, Antivirals and Immune Based Therapy, Complications and Co-Infections, Pediatric AIDS and MTCT Prevention of SIV Rectal Transmission and Priming of T Cell Responses in Macaques after Local Pre-exposure Application of Tenofovir Gel, PLoS Med. 2008, Aug 5;5(8): el57. http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050157 Extended-dose Nevirapine to 6 Weeks of Age for Infants to Prevent HIV Transmission via Breastfeeding in Ethiopia, India, and Uganda: An Analysis of Three Randomised Controlled Trials. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A., et al., Lancet. 2008 Jul 26; 372(9635):300-13. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61114-9/fulltext

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SRO-6.6	McDannold N, Tempany C, Jolesz F, Hynynen K. Evaluation of referenceless thermometry in MRI-guided focused ultrasound surgery of uterine fibroids. J Magn Reson Imaging. 2008 Oct;28(4):1026-32. PMID: 18821603 http://www.ncbi.nlm.nih.gov/pubmed/18821603?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum Archip N, Clatz O, Whalen S, Dimaio SP, Black PM, Jolesz FA, Golby A, Warfield SK. Compensation of geometric distortion effects on intraoperative magnetic resonance imaging for enhanced visualization in image-guided neurosurgery. Neurosurgery. 2008 Mar;62(3 Suppl 1):209-15; discussion 215-6. PMID: 18424988 http://www.ncbi.nlm.nih.gov/pubmed/18424988?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum
SRO-7.4	**Performance target (data release) and data access** Current information about data available to researchers is available through http://www.oai.ucsf.edu/datarelease/. **Publications** Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, Nevitt M, Hellio Le Graverand MP. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative Progression Subcohort - association with sex, Body Mass Index, symptoms, and radiographic OA status. Ann Rheum Dis. 2008 Jul 7. [Epub ahead of print] PMID: 18519425. Hunter DJ, Niu J, Zhang Y, Totterman S, Tamez J, Dabrowski C, Davies R, Hellio Le Graverand MP, Luchi M, Tymofyeyev Y, Beals CR. Change in cartilage morphometry: a sample of the progression cohort of the Osteoarthritis Initiative. Ann Rheum Dis. 2008 Apr 13. [Epub ahead of print] PMID: 18408248. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage. 2008 Sep 9. [Epub ahead of print] PMID: 18786841. Schneider E, NessAiver M, White D, Purdy D, Martin L, Fanella L, Davis D, Vignone M, Wu G, Gullapalli R. The osteoarthritis initiative (OAI) magnetic resonance imaging quality assurance methods and results. Osteoarthritis Cartilage. 2008 Sep;16(9):994-1004. Epub 2008 Apr 18. PMID: 18424108. Wirth W, Hellio Le Graverand MP, Wyman BT, Maschek S, Hudelmaier M, Hitzl W, Nevitt M, Eckstein F; the OAI Investigator Group. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. Osteoarthritis Cartilage. 2008 Sep 11. [Epub ahead of print]. PMID: 18789729. **Presentations at meetings of professional societies** ***American College of Rheumatology Annual Meeting (2008) – oral presentations*** Chang A, Song J, Dunlop D, Hochberg M, Kwoh K, Eaton C, Bathon J, Jackson R, Nevitt M, Sharma L. Differences in varus and valgus thrust between African-Americans and Caucasians: Data from the Osteoarthritis Initiative (OAI). Arthritis Reum. 2008. Abstract #696. Hunter D, Li L, Zhang Y, Totterman S, Tamez J, Kwoh K, Eaton C, Hellio Le Graverand M, Beals C. Cartilage morphometry region of interest analysis; by selecting regions with denuded areas can we detect greater amounts of change? Arthritis Reum. 2008. Abstract #1992. Raducha-Grace L, Boudreau R, Hannon M, Newman A, Chu C, Nevitt M, Kwoh K. The association of osteoarthritis risk factors with different patterns of knee pain. Arthritis Reum. 2008. Abstract #698. Reichmann W, Katz J, Kessler C, Jordan J, Losina E. Differences in Health-Related Quality of Life (HRQL) in persons with radiographic knee osteoarthritis in NHANES III and OAI populations. Arthritis Reum. 2008. Abstract #737.

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SRO-7.4 **(cont.)**	***American College of Rheumatology Annual Meeting (2008) – poster presentations*** Dunlop D, Semanik P, Sharma L, Rowland W. Moving to maintain function in knee osteoarthritis. Arthritis Reum. 2008. Poster #206. Eckstein F, Benichou O, Wirth W, Nelson D, Maschek S, Hudelmaier M, Kwoh K, Guermazi A, Hunter D. Differences in femorotibial cartilage morphology of knees with and without joint space narrowing vary by region. Arthritis Reum. 2008. Poster #883. Sharma L, Song J, Hayes K, Dunlop D. Knee confidence and physical function in persons with or at risk for knee osteoarthritis: Data from the Osteoarthritis Initiative. Arthritis Reum. 2008. Poster #188. Vaduganathan M, Semanik P, Chang R, Sharma L, Dunlop D. The relationship between sitting and knee symptoms in knee osteoarthritis. Arthritis Reum. 2008. Poster # 1368. Wesseling J, Dekker J, Berg W, Bierma-Zeinstra S, Boers M, Cats H, Deckers P, Gorter K, Heuts P, Hilberdink W, Kloppenburgh M, Lafeber F, Nelissen R, Oosterveld F, Oostveen A, Roorda L, Viergever M, Wolde S, Bijlsma J. Early osteoarthritis cohorts: CHECK and OAI similarities and differences. Arthritis Reum. 2008. Poster #210. ***Osteoarthritis Research Society International 2008 Scientific Meeting – oral presentation*** Eckstein F, Benichou O, Wirth W, Nelson D, Maschek S, Hudelmaier M, Kwoh K, Guermazi A, Hunter D. Radiographic joint space narrowing predicts MR-based cartilage loss- Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S20. ***Osteoarthritis Research Society International 2008 Scientific Meeting – poster presentations*** Bae K, Park S, Shim H, Moon C-H, Kwoh K. Improved cartilage-joint contrast in double echo steady state (DESS) magnetic resonance (MR) imaging with the use of geometric-mean reconstruction of dual-echo images. Osteoarthritis and Cartilage. 2008;16:S176. Balamoody S, Waterton J, Williams T, Hodgson R, Bowes M, Hutchinson C. Regional knee cartilage thickness analysis in osteoarthritis- A multivendor MR scanner comparison study at 3.0T. Osteoarthritis and Cartilage. 2008;16:S186. Benichou O, Hunter D, Nelson D, Guermazi A, Eckstein F, Kwoh K, Duryea J. One year change in radiographic joint space width in patient with baseline unilateral joint space narrowing - Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S161. Blumenkrantz G, Carballido-Gamio J, Hyun B, Lynch J, Link T, Majumbar S. Longitudinal changes in the spatial distribution of cartilage MR T2 in a subset of patients from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2008;16:S179. Bowes M, Williams T, Taylor C, Hutchinson C, Maciewicz R, Waterton J, Holmes A, Vincent G. Statistical shape modeling reveals focal pattern of cartilage loss in OAI progression cohort. Osteoarthritis and Cartilage. 2008;16:S183. Chang A, Song J, Dunlop D, Hochberg M, Kwoh K, Eaton C, Bathon J, Jackson R, Nevitt M, Sharma L. Differences in varus and valgus thrust betwen African-Americans and Causasians: Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S152. Duryea J, Hunter D, Lynch J, Nevitt M, Beals C. Effect of sub optimal positioning and x-ray beam alignment on the measurement of radiographic joint space width: Analysis of longitudinal data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S167. Duryea J, Hunter D, Nevitt M, Beals C. Study of location specific lateral compartment radiographic joint space width for knee osteoarthritis progression: Analysis of longitudinal data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S168.

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-7.4 **(cont.)**	Eaton C, Kwoh K, McAlindon T, Roberts M, Hochberg M, Mysiw J, Jackson R, Bathon J, Nevitt M. Predictors of the development of symptomatic knee osteoarthritis in those with asymptomatic radiographic tibio-femoral osteoarthritis at baseline: One-year data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S137. Harvey W, Li L, Zhang Y, Lo G, Kwoh K, Hellio Le Graverand M, Beals C, Hunter D. Depth as well as size of bone marrow lesions may predict adjacent cartilage loss. Osteoarthritis and Cartilage. 2008;16:S185. Lacey T, Brett A, Williams T, Holmes A, Vincent G, Bowes M. Comparison of X-ray and MRI in the determination of OA progression in the knee measured at a fixed load-bearing position in the medial compartment. Osteoarthritis and Cartilage. 2008;16:S176. Nevitt M, Jackson R, Maeda J, Dunlop D, Hochberg M, Rubin S, Lo G, McAlindon T, Bathon J, Kwoh K. The relationship between knee-specific and person-based WOMAC physical function scores: Data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2008;16:S142. Niculescu T, Favors K, Sorkin J, Barlett S, Bathon J, Hochberg M. T he relationship of weight change with changes in knee pain and function in persons with symptomatic radiographic knee osteoarthritis: Data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2008;16:S136. Oka H, Akune T, Muraki S, Nakamura K, Yoshimura N, Kawaguchi H. Lateral joint space narrowing on radiographs predicts pain progression in knee osteoarthritis patients: Application of fully automatic KOACAD system to OAI Public Data. Osteoarthritis and Cartilage. 2008;16:S202. Sharma L, Song J, Hayes K, Dunlop D. Knee confidence and physical function in persons with or at risk for knee osteoarthritis: Data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage. 2008;16:S135. Shim H, Chang A, Tao C, Kwoh K, Boudreau R, Bae K. Efficiency and reproducibility of segmentation of knee cartilages on MR images from Osteoarthritis Initiative (OAI) - Comparison of semi-automated graph-cuts and manual delineation methods. Osteoarthritis and Cartilage. 2008;16:S56. Wesseling J, Dekker J, Berg W, Bierma-Zeinstra S, Boers M, Kloppenburgh M, Lafeber F, Oosterveld F, Bijlsma J. Cohort hip and cohort knee; Similarities and differences with the OAI Initiative. Osteoarthritis and Cartilage. 2008;16:S116. Wirth W, Benichou O, Kwoh K, Hunter D, Putz R, Eckstein F. The spatial distribution of cartilage loss in the medial femoral condyle varies with radiographic joint space narrowing - Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2008;16:S170.
SRO-7.5	2007 Annual Progress Report, 5R01DE014403-05. Ramos-Gomez F, Chung LH, Beristain RG, Santo W, Jue B, Weintraub J, Gansky S. Recruiting and retaining pregnant women from a community health center at the US-Mexico border for the Mothers and Youth Access clinical trial. Clinical Trials 2008; 5: 336-346. http://ctj.sagepub.com/cgi/content/abstract/5/4/336

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-8.2	Mechanical properties of bones deficient in fibrillin-2 and additional characterization of fibrillin-2-deficient mice: Kavukcuoglu NB, Denhardt DT, Guzelsu N, Mann AB. Osteopontin deficiency and aging on nanomechanics of mouse bone. J Biomed Mater Res A. 2007 Oct;83(1):136-44. PMID: 17390367. Additional information is contained 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 5R01AR042044-16, which is maintained by the NIAMS Extramural Research Program TGF-beta and bigycan: Bi Y, Stuelten CH, Kilts T, Wadhwa S, Iozzo RV, Robey PG, Chen XD, Young MF. Extracellular matrix proteoglycans control the fate of bone marrow stromal cells. J Biol Chem. 2005 Aug 26;280(34):30481-9. Epub 2005 Jun 17. PMID: 15964849. Parathyroid hormone's effects on bone mass in the absence of osteonectin: Machado do Reis L, Kessler CB, Adams DJ, Lorenzo J, Jorgetti V, Delany AM. Accentuated osteoclastic response to parathyroid hormone undermines bone mass acquisition in osteonectin-null mice. Bone. 2008 Aug;43(2):264-73. Epub 2008 Apr 13. PMID: 18499553. Influence of TGF-beta on CTGF: Arnott JA, Zhang X, Sanjay A, Owen TA, Smock SL, Rehman S, DeLong WG, Safadi FF, Popoff SN. Molecular requirements for induction of CTGF expression by TGF-beta1 in primary osteoblasts. Bone. 2008 May;42(5):871-85. Epub 2008 Jan 26. PMID: 18314002.
SRO-8.4	The final report entitled "Process Evaluation of the Centers of Biomedical Research Excellence (COBRE) Program" is located in the file room at the Office of Science Policy, NCRR. Please contact Patricia Newman at 301-435-0864 or pnewman@mail.nih.gov to obtain a copy.
SRO-8.5	Publication citations that describe the primary data analysis may be found at the following URL: http://www.nihpromis.org/Web%20Pages/Publications%20and%20Reports.aspx User registration to view the short forms and begin work with the CAT system is available at the following URL: http://www.assessmentcenter.net/ac1/
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 FAX (301) 496-2297 E-mail: mfc@nei.nih.gov
SRO-8.7	Hawkins JD, Catalano RF, Arthur MW, Egan2. E, Brown EC, Abbott RD, Murrray MD.Testing communities that care: the rationale, design and behavioral baseline equivalence of the community youth development study. Prev Sci. 2008 Sep; 9(3):178-90. Epub 2008 May 31. http://www.springerlink.com/content/87m7ln67u2w7vh06/?p=88101333fafe4e81ab441e1f9a6be8bf&pi=3 Kilbourne AM, Neumann MS, Pinchus HA, Bauer MS, Stall R. Implementing evidence-based interventions in health care: application of the replicating effective programs framework. Implement Sci. 2007 Dec 9; 2:42. http://www.implementationscience.com/content/2/1/42 Nease DE Jr, Nutting PA, Dickinson WP, Bonham AJ, Graham DG, Gallagher KM, Main DS. Inducing sustainable improvement in depression care in primary care practices. Jt Comm J Qual Patient Saf. 2008 May; 34(5):246-55. http://www.ingentaconnect.com/content/jcaho/jcjqs/2008/00000034/00000005/art00001

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SRO-9.1	Alexopoulos GS, et al. Developing an intervention for depressed, chronically medically ill elders: A model from COPD. Int J Geriatr Psychiatry, 2008 May; 23(5):447-53. http://www3.interscience.wiley.com/journal/116330199/abstract Butters MA, et al. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. Alzheimer Dis Assoc Disord, 2008 Jul-Sep; 22(3):261-8. http://ovidsp.tx.ovid.com/spa/ovidweb.cgi?&S=JFAEFPDOMBDDDNEGNCGLHDMJDGGFAA00&Abstract=S.sh.15.16.18|11|1 Friedman B, Lyness JM, Delavan RL, Chunyu Li, Barker WH. Major depression and disability in older primary care patients with heart failure. J Geriatr Psychiatry Neurol, 2008 Jun;21(2):111-22. http://jgp.sagepub.com/cgi/content/abstract/21/2/111 Steffens DC, et al. Antidepressant treatment and worsening white matter on serial cranial magnetic resonance imaging in the elderly: The Cardiovascular Health Study. Stroke, 2008 Mar; 39(3):857-62. Epub 208 Jan 31. http://stroke.ahajournals.org/cgi/content/abstract/39/3/857 Tabb et al. Rats bred for susceptibility to depression-like phenotypes have higher kainic acid-induced seizure mortality than their depression-resistant counterparts. Epilepsy Res. 2007; 74(2-3): 140-6. http://dx.doi.org/10.1016/j.eplepsyres.2007.02.006
SRO-9.2	Chelsea M. Kidwell, U54NS057405. Stroke Disparities Program Copenhaver BR, Hsia AW, Merino JG, Burgess RE, Fifi JT, Davis L, Warach S, Kidwell CS. Racial differences in microbleed prevalence in primary intracerebral hemorrhage. Neurology. 2008 Oct 7;71(15):1176-82.
SRO-9.3	NIH MRI Study of Normal Brain Development (http://www.bic.mni.mcgill.ca/nihpd/info/)
SRO-9.4	Please contact Dr. Bracie Watson of the National Institute on Deafness and Other Communication Disorders at 301-402-3458 to obtain a copy of the email from Charles McKay, PhD, Chief, Project Clearance Branch, Office of Policy for Extramural Research Administration, Office of Extramural Research, NIH.

Communication and Transfer of Results (CTR)

GOAL	FY 2008 DATA SOURCE AND VALIDATION
CTR-1	Information Resource Center Monthly Reports. To obtain a copy of the reports, please contact Shavon Artis at the Eunice Kennedy Shriver National Institute of Child Health and Human Development at (301) 435-3459.
CTR-4	Contract N01-LM45509 with Larta Institute Contract N01-LM-55510 with Foresight Science and Technology Contract N01-LM-75535 with Dawnbreaker, Inc. NIH SBIR CAP 2004/2005, 2005/2006, 2006/2007, 2007/2008 final reports
CTR-6	The internal NLM first quarter FY09 report for the Technical Services Division, Division of Library Operations, NLM will document that the cataloging serial time standards have been revised to reflect the reality that serials cataloging time has decreased due to the various efficiencies have been introduced. The NLM contact person for access to the quarterly report and for further information is Diane Boehr, Head, Cataloging Section, Technical Services Division, Division of Library Operations, NLM, phone 301-435-7059, email boehrd@mail.nlm.nih.gov .
CTR-7	Under preparation: New England Journal of Medicine article. For more information, please contact Dr. Juliana Blome at 301-594-2762.
CTR-8	NIH human resource and Office of Management Assessment records. Contact: Megan Columbus Acting Director, Division of Communications and Outreach Phone: 301-435-0937

Capacity Building and Research Resources (CBRR)

GOAL	FY 2008 DATA SOURCE AND VALIDATION
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: Brian Frantz NBS Management Center 301-451-1913
CBRR-4	System queries and reports provide the data to determine the percentage of electronic transactions in the system. Contact: Oliver 'Pete' Morton Acting 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 Managmeent 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. http://www.utmb.edu/gnl/ (See section: "Construction Update") http://www.nature.com/news/2008/081022/full/4551012a.html http://www.htrl.uchicago.edu/news.htm#18 http://ghrc.colostate.edu/index.asp?url=lab-opening http://newsinfo.colostate.edu/index.asp?url=news_item_display&news_item_id=741558160 http://njms.umdnj.edu/research/rbl/ http://njms.umdnj.edu/research/rbl/documents/RBL_Close_Out_Milestone_NJMS_110508.pdf http://main.uab.edu/show.asp?durki=61656
CBRR-7	ARIS is an internal management database. For more information, please contact Karin Lohman, Ph.D. at (301) 496-0357.
CBRR-8	xTrain performance results were calculated using reports from NIH's internal IMPAC II information management system. For more information, contact: Jennifer Sutton Research Training Coordinator Office of Extramural Programs (301) 435-2686
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) 451-3238 or Lori Mulligan, M.P.H. at (301) 435-0866.

Strategic Management of Human Capital (SMHC)

GOAL	FY 2008 DATA SOURCE AND VALIDATION
SMHC-3	OIR Website http://www1.od.nih.gov/oir/sourcebook/, Mentoring and Training Guide Contact: Sharon Ballard, Acting Director, WSDD, OHR (301-594-8777) OER Website http://grants.nih.gov/grants/oer.htm
SMHC-4	President"s Management Agenda scorecards for NIH and HHS: - NIH Scorecard 2008 1st Quarter - HHS FY08 1st Quarter - 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 2008 competitive sourcing reviews: - HR Administrative Support https://www.fbo.gov/index?s=opportunity&mode=form&id=fceba773756f5ce4327e34ea69044529&tab=core&_cview=0 - HR Strategic Programs Divisions https://www.fbo.gov/index?s=opportunity&mode=form&id=c871e95c6770e97be0617e3d68c3e940&tab=core&_cview=0 - HR Classification and Recruitment https://www.fbo.gov/index?s=opportunity&mode=form&id=de8ed60a5076550a421f8f8c7cb84707&tab=core&_cview=0 - Equal Employment Opportunity and Diversity Management Program https://www.fbo.gov/index?s=opportunity&mode=form&id=50a3b0f9c91e5cfa368c3b3367e97f72&tab=core&_cview=0 - Faciltities Services Functions https://www.fbo.gov/index?s=opportunity&mode=form&id=f4678388f8ace5237ae0728ad92ca5ee&tab=core&_cview=0
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)

GOAL	FY 2008 DATA SOURCE AND VALIDATION
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. Changes in standing receipt dates announced in the following notices: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-001.html; http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-053.html; and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-083.html.
POI-6	Vanderweil Facility Advisory (VFA) Inc. facility summary website (http://nih.vfafacility.com) for the National Institutes of Health ARCHIBUS for the National Institutes of Health Contact: Clarence Dukes Program Manager, Strategic Initiatives Programs Office of Research Facilities, Division of Technical Resources (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. The documents are located in the Grants Management Office at the respective Institute or Center or the 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 Larry Chloupek at (301) 594-3992.