Summary of Full Cost *

NATIONAL INSTITUTES OF HEALTH

(Dollars in Millions)

Performance Program Area	FY 2005	FY 2006	FY 2007
NIH Budget Authority	$28,644	$28,578	$28,578
NIH Full Cost Research Program	$28,644	$28,578	$28,578
SRO High Risk 1-3 Years	*9*	*9*	*4*
SRO High Risk 4-6 years	*1,323*	*1,445*	*1,481*
SRO High Risk 7-10 years	*321*	*431*	*429*
SRO Medium Risk 1-3 Years	*818*	*768*	*754*
SRO Medium Risk 4-6 years	*90*	*97*	*115*
SRO Medium Risk 7-10 years	*37*	*61*	*69*
SRO Low Risk 1-3 Years	*145*	*91*	*84*
SRO Low Risk 4-6 years	*351*	*351*	*342*
SRO Low Risk 7-10 years	*7*	*5*	*1*
Communication and Transfer of Results	*4*	*3*	*3*
Capacity Building and Research Resources	*1,612*	*1,623*	*1,667*
Strategic Management of Human Capital	*5*	*5*	*5*
Program Oversight and Improvement	*328*	*173*	*166*
Full Cost Total	$28,644	$28,578	$28,578

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

Methodology for Full Cost

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

Budget and Performance Crosswalk

The FY 2007 NIH budget request provides funding to support each of the core NIH programs. The following table provides a 3-year summary of funding (in millions) for NIH.[1]

	FY 2005 Enacted	FY 2006 President's Budget	FY 2007 Estimate
	Amount	Amount	Amount
NIH Budget Authority	$28,644	$28,578	$28,578
NIH Full Cost of Program	$28,644	$28,578	$28,578

The FY 2006 President's Budget and the FY 2007 Estimate are detailed by budget mechanism in the NIH Overview to the FY2007 President's Budget. The NIH Budget Mechanism table for FY 2005 is provided below.

NIH BUDGET MECHANISM	FY 2005 ENACTED (COMPARABLE)[2] (DOLLARS IN MILLIONS)
Research Project Grants	$15,484
Research Centers	2,731
Other Research	1,636
Research Training	756
Research and Development Contracts	2,641
Intramural Research	2,756
Research Management and Support	1,079
Cancer Prevention and Control	531
Construction	179
Library of Medicine	313
Office of the Director	341
Buildings and Facilities	118
VA/HUD Superfund	79
All Mechanisms	$28,644

Budget–GPRA Integration

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

[1] Every activity at NIH is carried out in support of the NIH mission: *To uncover new knowledge that will lead to better health for everyone.* Thus,

this Plan/Report is structured to reflect a single program—Research—for the purpose of planning and performance assessment.

[2] Includes Superfund; includes type 1 diabetes.

cooperative agreements, and contracts. A smaller fraction of NIH funds supports research that is conducted by NIH's own physicians and scientists—the intramural research program.

The major funding instruments used by NIH to fund extramural research are financial assistance award grants, cooperative agreement grants, and acquisition awards or contracts. Grants are the most common funding mechanism. All grants are identified as either competing (for NIH support) or non- competing continuations (receiving support previously committed during the competing grant cycle). A research project grant (RPG) provides a commitment of support for an average of four years of funding. Thus, after the competing year, the grantee receives noncompeting continuations each year for the specified length of the grant (subject to satisfactory progress as documented to the NIH each year). Nearly three-quarters of funding allocated to RPGs supports non-competing continuations. Institutes and Centers developed budget projections based on committed levels for continuation projects, both extramural and intramural. By working closely with scientific program staff, IC budget identified planned Requests for Applications, Requests for Proposals, and Program Announcements. Costs of these initiatives were also included in total estimates for each program goal. Estimates also included the number and amount of investigator-initiated grants likely to be relevant to achieving each program goal, based on historical trends.

NIH does not have an account or collection of accounts dedicated to program management. To allocate costs for program management, we selected the Research Management and Support (RMS) line item from the NIH mechanism display and Office of the Director Operations, a line item in the appropriation for the Office of the Director. Although these lines support some activities in addition to program management, they represent the majority of NIH program management activities. These totals were reduced by the direct costs of the performance goals that are funded through RMS or OD operations. This calculated level for Program Management was allocated across GPRA goals and the unsampled program on a pro-rata basis. The funding amounts devoted to each goal are included in the Program Performance Tables on pages 103-147.

NIH has one program-Research. Five functional areas categorize research and research-related support activities into similar clusters to provide a framework for presenting the entire portfolio. NIH utilizes a representative sampling approach to report on program performance progress. NIH has selected representative goals as proxies for performance of the larger research portfolio for each of the functional areas. Both performance goals and budget for these goals are representative.

To reflect the representative nature of performance in the GPRA plan and report, NIH has added a budget line titled "Unsampled Balance." This approach will report 100% of NIH's budget in the plan. It assumes that NIH is maintaining customary assessments and will continue reporting on the representative goals as proxies for the entire portfolio. Therefore, additional representative sampling is not needed.

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

Summary of Measures

Sixteen new performance goals were added to the GPRA FY 2007 performance plan. Ten of the goals are scientific research outcomes, one is communication and transfer of results, one is capacity building and research goal, and the remaining four are program oversight and improvement goals. These new goals can begin in FY 2005, FY 2006, or FY 2007. The annual targets are included later in the Detail Performance Analysis Tables and the performance goal narratives.

The new goals create a crest in the total number of goals in FY 2005. Many goals will be achieved in the next two years, and by FY 2007 the total number of goals will be back to the expected level seen in FY 2004. NIH continues to move in the direction of increasing the number of outcome goals while decreasing the number of output goals. NIH achieves a high level of "MET" measures. Every measure not met has a sound scientific justification for the extended or not met rating. Sound science is expected to have some extended and not met annual targets.

SUMMARY OF MEASURES AND RESULTS TABLE								
FY	Measures				Results			
	Long Term Performance Goals	Annual Measures	Total Measures in Plan *	% Reported	Met	Extended	Not Met	% Met
2002	40	80	80	100%	66	12	2	97%
2003	36	45	47	104%	39	8	0	100%
2004	41	54	56	104%	52	3	1	98%
2005	56	79	82 (+3 FY04 extended)	104%	77	4	1	99%
2006	53	76			Performance results will be reported in February 2007.			
2007	48	68			Performance results will be reported in February 2008.			

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

PART Efficiency Measures

YEAR	PROGRAM	EFFICIENCY MEASURE
FY05	HIV/AIDS Research	Annual Assessment of AIDS Research Portfolio Priorities for Potential Reallocation of Resources
FY06	Extramural Research	Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic research administration (eRA). (OMB approved)
FY07	Intramural Research	Reallocation of Laboratory Resources based on External Reviews by Boards of Scientific Counselors (OMB approved) Streamline business processes and automate data movement by implementing, monitoring and updating the Clinical Research

		Information System (CRIS). (OMB approved)
FY07	Buildings & Facilities	Provide responsible stewardship over existing federally owned real property assets. (OMB approved)

Detail of Performance Analysis

Comprehensive summary tables covering all the FY 2005, 2006, and 2007 goals and targets in NIH's Research Program follow. These tables provide updated information on the status of all of the program's performance targets, as well as budget and performance integration. Due to the complexities of scientific discovery, the identified targets are subject to change to facilitate the prospect of achieving the best science. Detailed narratives for each goal, including a chart summarizing the performance results for each target, can be found later in this section following the NIH GPRA Scientific Research Outcomes Goals Matrix. Data source and validation information are provided to confirm achievement of annual targets. Healthy People 2010, PMA, HHS Strategic Plan, 500-Day Plan, One HHS Top 20 Objectives, outcome, output, efficiency, and PARTed goals are noted in the cross reference row in the table.

Program Performance Tables: FY 2005, 2006, 2007 Goals

SCIENTIFIC RESEARCH OUTCOMES

SRO - 1.1	By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Prepare clinical protocol for testing rimonabant in humans.	1. (FY02) Two drugs have been approved for use in the US to treat alcohol addiction, with limited effectiveness	1. (MET) Rimonabant has been shown to reduce ethanol intake in rodent models of voluntary ethanol drinking.
2004	1. Complete a toxicologic evaluation of antalarmin.	1. (FY03) Antalarmin and rimonabant show promise in nonhuman animal models as excellent candidates for Phase I clinical trials	1. (MET) A toxicologic evaluation on antalarmin has been completed.
2005	1. Test antalarmin for relapse prevention in alcoholics.	1. (FY03) Recent studies have shown that antalarmin reduces voluntary ethanol intake in rat model of drinking	1. (EXT) For the drug antalarmin, the FDA requires further toxicology studies. Extended to 2007.
2006	1. Conduct toxicology studies of antalarmin in monkeys as required by FDA.	1. Meetings with FDA to discuss initial toxicity study results in monkeys and dogs led to a new request from FDA for additional studies in monkeys	1. Performance results will be reported in February 2007.
2007	1. Complete goal of conducting medications development using animal models and beginning to conduct Phase I and II human trials of two potential treatments for alcoholism: rimonabant and antalarmin.	1. FY06 results	1. Performance results will be reported in February 2008.
Data Source & Validation:	For information regarding the FDA requirement, please contact: Karen P. Peterson, Ph.D. Chief, Research Policy and Special Programs Branch Office of Scientific Affairs NIAAA, NIH 5635 Fishers Lane, Rm. 2013 Bethesda, MD 20892 (301)451-3883 fax: (301)443-7043 kpeterso@mail.nih.gov		
Cross Reference:	HP-26, 1HHS-05, 1HHS-19, SP-1.4, SP-4.1, Efficiency, Outcome		
SRO - 1.2	By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.		

FY	MEASURES/TARGETS	BASELINE	RESULTS
2003	1. Design and test a device (diaphragm) that responds to sound based on the ears of the parasitic fly "Ormia ochracea."	1. (FY02) Small insect model system exists and has hyperacute sound localization.	1. (MET) NIH scientists successfully completed design and testing of a novel microphone diaphragm that responds to the sound and is based on the ears of the parasitic fly "Ormia ochraca".
2004	1. Design and test the electronic circuitry to create a sound output from the diaphragm.	1. (FY03) Sound-responsive diaphragm based on an insect model system is available	1. (MET) NIH-supported scientists successfully developed the electronic output circuitry that will convert the microphone diaphragm's motion into an electronic signal.
2005	1. Combine the diaphragm and the electronic output circuitry into a directional microphone. *Previous Target:* Combine the diaphragm and the electronic output circuitry into a directional microphone that is small enough to fit into a hearing aid.	1. (FY04) Diaphragm and electronic circuitry are available.	1. (MET) NIH-supported scientists successfully combined the diaphragm and circuitry into a directional microphone.
2006	1. Complete goal of developing one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background.	1. FY05 results	1. Performance results will be reported in February 2007.
Data Source & Validation:	Abstract Accepted for Conference Proceedings: Weili Cui, Ronald N. Miles, F. Levent Degertekin, Neal Hall, Baris Bicen, "Optical Sensing in a Directional Microphone Inspired by the Ears of the Parasitoid Fly, Ormia ochracea Fabrication and Characterization of a MEMS directional microphone with Integrated Optical Readout" accepted for publications in the Proceedings of the IEEE MEMS 2006 Conference, to be held January 2006, Istanbul, Turkey. This paper describes the fabrication and characterization of a MEMS directional microphone with integrated optical readout. The result of this effort is a directional microphone that combines a biomimetic differential microphone diaphragm with inter-digitated fingers for optical detection of the motion of the diaphragm. Manuscript accepted for Journal Publication: Neal A. Hall, Baris Bicen, M. Kamran Jeelani, Wook Lee, Shakeel Qureshi, Murat Okandan, F. Levent Degertekin, Micromachined Microphones with Diffraction-Based Optical Displacement Detection, to appear in the Journal of the Acoustical Society of America. This manuscript describes a nondirectional microphone that utilizes the optical detection scheme being developed in this project. The verification of its performance in a more conventional, nondirectional microphone is an important step in validating its use for our novel directional microphone.		
Cross Reference:	HP-28, 1HHS-05, SP-4.1, SP-6.2, Outcome		

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

	evolutionary classification. Cover 45% of PubMed sequences, extended to 75% by adding first-generation alignments.		the size of the Conserved Domain Curator team. 45% of PubMed sequences covered and, with first generation alignments, an estimated 75% covered.
2006	1. Complete goal of developing methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	1. FY05 results	1. Performance results will be reported in February 2007.
Data Source & Validation:	The conserved Domain database is publicly available via the PubMed / Entrez search engine: http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi. Sequence similarity searches are also supported via the available CD-Search utility: http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi. CDD is also described in: Marchler-Bauer et al. CDD: A conserved domain database for protein classification, Nucleic Acids Res. 33D, 192-6, 2005.		
Cross Reference:	1HHS-05, SP-4.1, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$9	$9	$4

SRO - 2.2	By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify two new drug targets that can be used in screens for potentially therapeutic compounds in drug discovery projects or that could be evaluated for use as therapeutic agents for weight control.	1. (FY02) No highly effective drug therapies exist for overweight or obesity. Potential drug targets need to be identified	1. (MET) Three molecules can be characterized and screened as targets for therapeutic compounds or evaluated as potential therapeutic agents for weight control.
2004	1. Develop and launch at least two studies to test the effects of worksite interventions on weight control.	1. (FY03) No programs for weight control at the worksite have been examined in studies with valid designs to clearly evaluate if they are effective	1. (MET) More than two studies to test the effects of worksite interventions on weight control were developed and launched.
2005	1. Enroll and randomize 60 children with hyperinsulinimia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children 6 to 12 years.	1. (FY03) No clinical trials have demonstrated efficacy of any medication for overweight during childhood. Pilot data suggest metformin may be of benefit for those children with hyperinsulinemia	1. (MET) NIH scientists succeeded in enrolling 73 children in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.
2006	1. Enroll and randomize 240 predominantly minority pre-adolescent girls to test the efficacy of an after school dance program in reducing weight gain.	1. (FY04) Few effective community-based interventions are available to prevent weight gain in at risk children	1. Performance results will be reported in February 2007.
2007	1. Develop and launch at least three new clinical trials to test the effectiveness of intervention programs delivered in primary care practices to treat and/or prevent obesity in children.	1. (FY05) Few obesity intervention programs targeting children have been designed and tested to establish their effectiveness outside of small clinical settings.	1. Performance results will be reported in February 2008.
Data Source & Validation:	A description of the metformin study is available at: http://clinicalstudies.info.nih.gov/detail/A_2000-CH-0134.html Please contact Dr. Patrick Donohue in the Office of Scientific Program and Policy Analysis/NIDDK to obtain a spreadsheet that contains information on participants enrolled in the study.		
Cross Reference:	HP-19, 1HHS-05, 1HHS-19, SP-4.1, 5,000D-T1, 500D-A10, Efficiency, Outcome		
SRO - 2.3.2	By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify one molecule with a common role in bacterial and viral infections that may serve as a target for broad-spectrum antimicrobial drug development.	1. (FY02) None of the antibiotics and antiviral drugs licensed by the FDA are based on a molecule with a common role in both bacteria and viruses	1. (MET) Two different molecules with a common role in different classes of microbes were identified.
	1. Identify one molecule or mechanism that	1. (FY03) None of the antibiotics and	1. (MET) A drug/metabolite transporter

2004	is shared by a class or across different classes of microbes that may serve as a target for broad-spectrum antimicrobial drug development.	antiviral drugs licensed by the FDA are based on a molecule or mechanism that is shared by a class or across different classes of microbes.	molecule from the malarial parasite Plasmodium falciparum, that is similar to transporter molecules in other protozoa, may serve as a target for drugs to increase responsiveness to drug therapies.
2005	1. Develop a set of screening tools that will help evaluate potential compounds/classes of compounds for activity against multiple bacterial and viral infections. *Previous Target:* Develop a lead compound for one of the molecules or mechanisms identified as a potential target for broad-spectrum antimicrobial drug development.	1. (FY04) NIH does not have a complete set of screening tools that can be used to test compounds for activity against both bacterial and viral pathogens.	1. (MET) A complete set of in vitro screening tools that can be used to test compounds for activity against bacterial and viral pathogens has been developed.
2006	1. Use screening tools to evaluate potential compounds or classes of compounds for activity against multiple classes of infectious diseases.	1. (FY04) Screening tools for evaluation of potential compounds/classes of compounds for activity against multiple bacterial and viral infections developed.	1. Performance results will be reported in February 2007.
2007	1. Through medicinal and/or combinatorial chemistry, optimize several compounds for antimicrobial activity.	1. (FY05) Resources provided to the scientific community for development of medicinal and combinatorial chemistry capacity and assay optimization.	1. Performance results will be reported in February 2008.
Data Source & Validation:	NIH website describing the In vitro and Animal Model Screening Initiative and the bacterial screens that are currently available: http://www2..nih.gov/Biodefense/Research/invitro.htm#screens NIH website describing the existing NIH Preclinical Antiviral Testing Program: http://www.nih.gov/dmid/viral/ Meeting Poster: Presentation by The National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH). Pre-Clinical Antimicrobial Screening Programs BIO 2005 Innovation Corridor Annual International Convention: http://www.bio.org/events/2005/poster/posteronline/index.asp Meeting abstract: E.W. Barrow and W.W. Barrow. Development of High-Throughput Drug Screening for Bacillus anthracis. ASM Biodefense Conference 2005, abstract #1892. Barrow, EW et al. Development of colorimetric drug susceptibility assay for Bacillus anthracis. (Manuscript submitted to Journal of Antimicrobial Agents in May 2005)		
Cross Reference:	HP-14, HP-24, 1HHS-05, SP-2.1, SP-4.1, 5,000D-A4, Outcome		

SRO - 2.3.4	By 2010, develop an HIV/AIDS vaccine.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Design and develop new or improved vaccine strategies and delivery/production technologies.	1. (FY02) Existing DNA and viral-vector vaccines strategies require further evaluation	1. (MET) Four newly identified vaccine strategies increased scientific knowledge of how AIDS causes disease and the immune response to it.
2004	1. Initiate one to two multinational trials in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.	1. (FY03) HIV Vaccine Trials Network currently supports clinical trials at 12 international sites	1. (MET) Two multinational trials initiated in collaboration with private companies, academic investigators, other government agencies and scientists in resource-poor countries.
2005	1. Initiate four new Phase I or II trials of new or improved concepts and designs and expand capacity to conduct clinical trials in three international sites.	1. (FY04) NIH has conducted 68 phase I and phase II HIV vaccine trials to date	1. (MET) NIH initiated five phase I trials for new products and six phase I and one phase II trials to further assess existing products. NIH expanded clinical trial capacity into 8 new international settings.
2006	1. Initiate 1 new phase IIb trial to determine if a third generation vaccine candidate has efficacy.	1. (FY04) NIH is conducting a phase III trial of a second generation vaccine (canarypox) in Thailand	1. Performance results will be reported in February 2007.
2007	1. Initiate another Phase II/IIb trial(s) of the most promising third generation vaccine candidate.	1. (FY05) NIH is conducting Phase I trials of a second third generation candidate (6 plasmid DNA plus Adv boost).	1. Performance results will be reported in February 2008.
Data Source & Validation:	NIH FY 2007 Plan for HIV-Related Research – Vaccine Section: www.nih.gov/od/oar/public/pubs/fy2007/IV_Vaccines.pdf		

	HIV Vaccine Trials Network: www.hvtn.org Vaccine Research Center: http://www.niaid.nih.gov/vrc/ U.S. Military HIV Research Program: www.hivresearch.org Division of AIDS Vaccine Clinical Research and Vaccine Discovery and Development Scientific Areas of Interest – NIAID Planning and Report Process
Cross Reference:	HP-13, 1HHS-05, SP-1.2, SP-4.1, 5,000D-I2, Outcome

SRO - 2.4	By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Integrate multidisciplinary approaches to investigate: 1) biological mechanisms of pain, fatigue, or psychological distress or 2) related potential therapeutic intervention(s) by establishing at least one intramural collaboration.	1. (FY05) Identification of potential intramural collaborations.	1. (MET) One intramural collaboration was established.
2006	1. Contribute to the identification of potential interventions for symptom/illness burden by identifying results from one study of symptom distress/quality of life.	1. (FY05) One study of symptom distress/quality of life completed.	1. Performance results will be reported in February 2007.
2007	1. Contribute to the identification of potential interventions for treatment-related oral complications and associated pain by analyzing the results of two (2) clinical research protocols relevant to cancer treatment.	1. (FY04) Two (2) IRB approved clinical research protocols addressing cancer treatment-related oral complications and associated pain are open to accrual.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Requests for information related to the FY05 Performance Target may be addressed to Mr. Charles Sabatos, Chief, Office of Science Policy and Public Liaison, National Institute of Nursing Research, NIH.		
Cross Reference:	HP-2, HP-6, 1HHS-05, SP-1.1, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$1,323	$1,445	$1,481

SRO - 3.1	By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	1. (FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	1. (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.
2004	1. Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	1. (FY03) Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed	1. (MET) NIH initiated a preclinical toxicology program and expanded an intravenous testing program to expedite drug discovery, and identified a collaborative opportunity for pre-clinical drug development.
2005	1. Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	1. (FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression	1. (MET) The NIH launched the Alzheimer's Disease Neuroimaging Initiative in late 2004.
	1. Identify around 1,000 new late onset AD	1. (FY04) The genetics initiative has	1. Performance results will be reported in

2006	families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	identified 259 families, too few for researchers to identify the remaining risk factor genes.	February 2007.
2007	1. Identify and characterize molecular events that may prove to be targets for treating or preventing Alzheimer's disease through initiatives and projects focused on mechanistic and basic studies.	1. (FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.	1. Performance results will be reported in February 2008.
Data Source & Validation:	News item from NIA's Alzheimer's Disease Education and Referral Center: http://www.alzheimers.org/nianews/nianews70.html		
Cross Reference:	HP-18, 1HHS-05, 1HHS-19, SP-4.1, SP-6.2, Outcome		
SRO - 3.2.1	By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Recruit 12 participants for a Phase I trial to evaluate the safety of anti-CD52 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. (FY02) First trial of anti-CD52 to promote tolerance.	1. (NOT MET) Anti-CD52 was determined to be unsafe by a non-NIH supported trial of the agent in the target population. Therefore, the opening of the NIH-supported trial was cancelled.
2004	1. Recruit 8-12 participants for a Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	1. (FY03) First trial of anti-CD3 to promote tolerance.	1. (NOT MET) The Phase I trial of the anti-CD3 antibody in patients who had undergone islet cell transplantation was cancelled because the amount of anti-CD3 antibody needed for the trial could not be obtained because the pharmaceutical company that owns the agent decided to use it for other clinical trials.
2005	1. Submit response to FDA addressing safety concerns about anti-CD3 antibody. *Previous Target:* Establish the baseline success rate for islet transplantation, which may impact U.S. Food and Drug Administration (FDA) and Medicare standards of care for islet transplantation.	1. First trial of anti-CD3 to promote tolerance.	1. (MET) NIH submitted a response to the FDA addressing safety concerns about anti-CD3 antibody. The FDA removed the clinical hold on April 29, 2005.
2006	1. Establish uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs. *Previous Target*: Analyze data from phase I trial(s); initiate development of efficacy trial(s); if appropriate.	1. CIT established.	1. Performance results will be reported in February 2007.
2007	1. Develop 2 clinical protocols. *Previous Target:* Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in	1. Clinical protocols under development.	1. Performance results will be reported in February 2008.

	patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.		
Data Source & Validation:	Karin Lohman, NIAID, Office of Policy Analysis, 301-496-6752.		
Cross Reference:	HP-5, 1HHS-05, SP-4.1, Outcome		
SRO - 3.3	By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Implement at least five research projects directed at developing integrated technologies for the efficient and simultaneous detection of key molecules in human saliva.	1. (FY02) No integrated technologies to quickly and efficiently measure multiple substances in saliva	1. (MET) Seven research projects implemented to develop technology aimed at human salivary diagnostics.
2004	1. Implement research projects directed at identifying and cataloging saliva proteomes. Identification of salivary proteomes will help scientists detect changes in saliva that are associated with specific diseases or conditions.	1. (FY03) Technology available to help identify salivary proteomes	1. (MET) Three research projects implemented to identify and catalog salivary proteomes.
2005	1. Develop electronic microfluidic assay systems (e.g., microchip-based systems that are replacing large and costly instruments) that can quantify C-reactive protein (a biomarker for cardiovascular disease) in saliva.	1. (FY03) Systems to quantify C-reactive protein in saliva have not yet been developed.	1. (MET) Integrated microfluidic assay systems have been developed to measure C-reactive protein in saliva.
2006	1. Finalize the fabrication of a portable handheld diagnostic device that can detect C-reactive protein and other analytes associated with oral and/or systemic diseases, and develop methods for its quality assurance and standardization.	1. (FY04) Currently the individual components needed for a portable handheld diagnostic device are under fabrication and validation	1. Performance results will be reported in February 2007.
2007	1. Establish a common proteome database that will include data from 2 subject groups that cover over 80 percent of the salivary proteome.	1. (FY05) Three groups of researchers are currently working to catalog the salivary proteome.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Christodoulides, N., et al. "Application of Microchip Assay System for the Measurement of C-reactive Protein in Human Saliva", Lab on a Chip, 2005, 5(3), 261-269. Yang, Chu -Ya, et al. "Detection of Picomolar Levels of Interleukin-8 in Human Saliva by SPR", Lab on a Chip, 2005, 5(10), 1017-1023. Li, Yang, et al. "Salivary Transcriptome Diagnostics for Oral Cancer Detection", Clinical Cancer Research, 2004, 10, 8442-8450. Hu, Shen, et al. "Large-scale Identification of Proteins in Human Salivary Proteome by Liquid Chromatography/Mass Spectrometry and Two-Dimensional Gel Electrophoresis-Mass Spectrometry", Proteomics, 2005, 5, 1714-1728.		
Cross Reference:	1HHS-05, SP-4.1, Outcome		

SRO - 3.5	By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2006	1. Validate or replicate previously identified chromosome regions in different sample sources by one or more groups to identify genes.	1. (FY04) Regions have been previously mapped on chromosomes 1,4,7, and 15 by one or more independent groups.	1. Performance results will be reported in February 2007.
2007	1. Perform fine mapping studies to identify specific haplotypes for the most promising genes, and seek potential functional differences coming from these haplotypes.	1. (FY06) Susceptibility genes located on identified chromosomal regions have been mapped.	1. Performance results will be reported in February 2008.
Data Source & Validation:			
Cross Reference:	HP-18, 1HHS-05, SP-1.4, Outcome		

SRO - 3.6	By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate stem cell labeling strategy.	1. (FY04) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.	1. (MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.
2006	1. Complete optical imaging probe development.	1. (FY05) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.	1. Performance results will be reported in February 2007.
2007	1. Initiate validation and toxicity studies.	1. (FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Rothstein, E.C., Carroll, S.M., Combs, C.A., Jobsis, P.D., Balaban, R.S. Skeletal muscle NAD(P)H two-photon fluorescence microscopy in vivo: Topology and optical inner filters. Biophysical Journal 88(3):2165-76, 2005.		
Cross Reference:	HP-12, 1HHS-05, SP-4.1, Efficiency, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$321	$431	$429

SRO - 4.2	By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	1. (FY02) No repository with this specific housing and distribution capacity exists for PD research	1. (MET) Mouse model repository to house PD genetic models established.
2004	1. Conduct dose response studies of chronic rotenone administration in normal mice and assess resulting changes in striatal dopamine levels and the number of dopamine neurons in substantia nigra. *Previous Target:* Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD.	1. (FY03) Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown	1. (MET) Provided proof of concept in mouse model by administering rotenone and achieving 30-40% depletion of dopamine in striatal terminal fields with clear evidence of degenerating neurons.
2005	1. Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.	1. (FY03) A rotenone mouse model is not yet available	1. (MET) Used A53T missense mutation mouse in rotenone model; 100% mortality in test subjects, indicating that this transgenic mouse was probably more susceptible to rotenone than the normal (wildtype) mouse. Goal completed.
Data Source & Validation:	Betarbet et al., Program No. 425.1. 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005. Online. Goldberg et al., The Journal of Biological Chemistry, 2003, 278(44):43629-43635. Palacino et al., The Journal of Biological Chemistry, 2004, 279(18):18614-18622. Chandra et al., PNAS, 2004, 101(41):14966-14971. McNaught et al., Annals of Neurology, 2004, 56:149-162.		
Cross Reference:	HP-8, 1HHS-05, SP-4.1, SP-6.2, Outcome		

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

2007	1. Achieve goal of evaluating the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens.	1. FY06 results	1. Performance results will be reported in February 2008.
Data Source & Validation:	Chemical Database: http://chemdb.niaid.nih.gov Cell/HIV Protein Interaction Database: http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/index.html Adult ACTG Studies: http://aactg.s-3.com Pediatric ACTG Studies: http://pactg.s-3.com Comprehensive International Program of Research on AIDS (CIPRA): http://www.niaid.nih.gov/daids/cipra/ HIV Prevention Trials Network (HPTN): http://www.niaid.nih.gov/reposit/hptn.htm Community Programs for Clinical Research on AIDS: http://www.niaid.nih.gov/daids/pdatguide/cpcra.htm Division of AIDS Pediatric AIDS, Complications and Co-infections of AIDS, Therapeutics Discovery and Development, and Antiviral and Immune-Based Scientific Areas of Interest, NIAID Planning and Report Process		
Cross Reference:	HP-13, 1HHS-05, SP-4.1, 5,000D-I2, Outcome		

SRO - 4.5.4	By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	1. (FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	1. (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.
2004	1. Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	1. (FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened	1. (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.
2005	1. Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	1. (FY03) Known bioactive compounds require further evaluation of activity and improved availability	1. (MET) Compounds selected based on evaluation of properties; collection assembled for public use.
2006	1. Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	1. (FY04) SMA program established; 3 promising compounds identified in screens; SMA mouse models available	1. Performance results will be reported in February 2007.
2007	1. Complete goal of identifying 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	1. FY06 results	1. Performance results will be reported in February 2008.
Data Source & Validation:	For information about the collection of bioactive compounds, please contact: Paul A. Scott, Ph.D. Director Office of Science Policy and Planning National Institute of Neurological Disorders and Stroke National Institutes of Health 31 Center Drive, Room 8A03 Bethesda, MD 20892; MSC 2540 Phone: 301-496-9271 scottp@ninds.nih.gov		
Cross Reference:	HP-18, HP-26, 1HHS-05, SP-4.1, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$818	$768	$754

SRO - 5.2	By 2009, determine the efficacy of statins in preventing progression of atherosclerosis in children with systemic lupus erythematosus (SLE, or lupus).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	1. (FY02) Standard operating procedures are being completed but training not yet done	1. (MET) Training of all appointed sonographers has been completed.
2004	1. Launch patient enrollment in at least 10 of the 20 planned sites.	1. (FY03) Protocol for patient enrollment established	1. (MET) There are currently 16 sites actively recruiting patients into the study.
2005	1. Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	1. (FY03) One ancillary study approved to assess the effect of statins on blood cells	1. (MET) The ancillary studies are underway. One example is a study that explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus in pediatric patients.
2006	1. Complete baseline data analysis on the enrolled patients, including any adverse events.	1. (FY04) 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events	1. Performance results will be reported in February 2007.
2007	1. All clinical sites will be actively enrolling/following pediatric lupus patients, to result in an overall average recruitment rate of 3 new patients per month.	1. Number of Clinical Sites: 20	1. Performance results will be reported in February 2008.
Data Source & Validation:	A description of the APPLE study and some of the factors affecting its implementation was presented at the ACR/AHRP Annual Scientific Meeting in San Diego, CA, Nov. 12-17, 2005. Abstract 1426/202: Barriers In NIH Funded Multicenter Pediatric Trials: Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Case Study. APPLE DSMB Open Meeting Report, December 15, 2005. Records kept by NIAMS EP Clinical Coordinator, Project Officer, and staff, and by the NHLBI Contract Management Branch. All are located at 6701 Democracy Blvd. Suite 800, Bethesda, MD 20892.		
Cross Reference:	HP-12, 1HHS-05, 1HHS-09, 1HHS-19, SP-4.1, 500D-P1, Outcome		

SRO - 5.3	By 2009, expand the range of available methods used to create, analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	1. (FY02) Prior to FY 2003, only two centers existed.	1. (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.
2004	1. Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.	1. (FY03) High throughput methods for making chemical libraries for drug development are limited.	1. (MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.
2005	1. Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	1. (FY03) CMLD centers are currently being established; screening of their libraries has not yet begun.	1. (MET) Support for CMLD centers provides facilities to validate new methodologies used to synthesize chemical libraries. These new methods are being made available to the scientific

			community.
2006	1. Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	1. (FY 03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs.	1. Performance results will be reported in February 2007.
2007	1. Begin development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds.	1. (FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Park SH, Opella SJ. Tilt angle of a trans-membrane helix is determined by hydrophobic mismatch. J Mol Biol. 2005 Jul 8;350(2):310-8. Sinha N, Grant CV, Rotondi KS, Feduik-Rotondi L, Gierasch LM, Opella SJ. Peptides and the development of double- and triple-resonance solid-state NMR of aligned samples. J Pept Res. 2005 Jun;65(6):605-20. Review. Zheng H, Zhao J, Wang S, Lin CM, Chen T, Jones DH, Ma C, Opella S, Xie XQ. Biosynthesis and purification of a hydrophobic peptide from transmembrane domains of G-protein-coupled CB2 receptor. J Pept Res. 2005 Apr;65(4):450-8. De Angelis AA, Nevzorov AA, Park SH, Howell SC, Mrse AA, Opella SJ. High-resolution NMR spectroscopy of membrane proteins in aligned bicelles. J Am Chem Soc. 2004 Dec 1;126(47):15340-1. NIH 'Roadmap' Grants Will Establish Nine Screening Centers in Seven States: http://www.nimh.nih.gov/press/molecularlibraries.cfm		
Cross Reference:	1HHS-05, SP-4.1, Outcome		

SRO - 5.5	By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Adapt two treatment approaches from small-scale research settings to community-based settings for the purpose of bringing research-based treatments to communities.	1. (FY03) No randomized clinical trials have delivered BSFT and Seeking Safety to these specialized populations	1. (MET) Three treatments have been adapted for community-based settings.
2005	1. Build capacity for targeted treatments by training 90 treatment providers to: (a) participate in clinical trials to promote treatment fidelity; and (b) deliver evidenced-based behavioral treatment to target populations in community settings.	1. (FY03) Fewer than 25 treatment providers have been trained to deliver BSFT and Seeking Safety to these specialized populations in randomized clinical trials in community settings	1. (MET) The Clinical Trials Network has trained 184 providers (94 more than planned) in BSFT, MET, or Seeking Safety, which are being tested in community settings.
2006	1. Recruitment will be completed of approximately 1000 patients from specialized populations to test the efficacy of community-based treatments.	1. (FY04) Enrollment of subjects for Seeking Safety, BSFT, and MET was initiated.	1. Performance results will be reported in February 2007.
2007	1. Analyze data from completed behavioral protocols and report initial findings from data analysis.	1. Providers trained, subjects being recruited for intervention.	1. Performance results will be reported in February 2008.
Data Source & Validation:	From information from the study database emailed by Principal Investigators of the projects.		
Cross Reference:	HP-26, HP-27, 1HHS-01, 1HHS-05, 1HHS-19, SP-1.4, SP-3.4, Outcome		

SRO - 5.6	By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify 1-2 promising compounds as candidate medications for tobacco addiction.	1. (FY05) Current medications inadequate to address tobacco addiction.	1. (MET) Four candidate medications, instead of two, have been identified for tobacco addiction, and research is continuing on these candidates.
2006	1. Begin at least one clinical trial of a candidate medication for tobacco addiction.	1. (FY05) NicVAX shows promise in pre-clinical or early clinical trials.	1. Performance results will be reported in February 2007.
2007	1. Develop and test 1-2 potential new compounds for tobacco addiction in animal models.	1. To be determined by results in FY06.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Paterson NE, Froestel W, Markou A. Repeated Administration of the GABAB receptor agonist CGP44532 decreased nicotine self-administration, and acute administration decreased cue-induced reinstatement of nicotine-seeking in rats. Neuropsychopharmacology (2005) 30, 119-128. Sofuoglu M, Mouratidis M, Yoo S, Cullligan K, Kosten T. Effects of tiagabine in combination with intravenous nicotine in over night abstinent smokers. Psychopharmacology (2005) 181:504-510. George TP, Vessicchio JC, Termine A, Jatlow PI, Kosten TR, O'Malley SS. (2003) A preliminary placebo-controlled trial of selegiline hygrochloride for smoking cessation. Biol Psychiatry 53(2):136-43. Lesage MG, Keyler DE, Hieda Y, Collins G, Burroughs D, Le C, Pentel PR. (2005) Effects of a nicotine conjugate vaccine on the acquisition and maintenance of nicotine self-administration in rats. Psychomp]harmacology (Berl) Jul1;:1-8 [Epub ahead of print]		
Cross Reference:	HP-26, HP-27, 1HHS-05, 1HHS-19, SP-1.4, SP-1.5, 5,000D-T1, Outcome		

SRO - 5.7	By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Convene workshops of relevant experts on PET and MRI scanning to develop consensus standards and quantitative tools for image assessment.	1. (FY05) Workshop planned.	1. (MET) FDG-PET and DCE-MRI workshops have been held. Consensus guidelines are on the Cancer Imaging Program web site: imaging.cancer.gov.
2006	1. Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial.	1. (FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.	1. Performance results will be reported in February 2007.
2007	1. Complete accrual in lung cancer therapy trial and perform final analysis of test-retest reproducibility of functional imaging scans.	1. (FY05) Trial not complete.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Workshop reports. For copies of the reports, please contact Dr. Daniel Sullivan, Associate Director, Division of Cancer Treatment and Diagnosis, NCI, EPN, Room 6052; phone: 301-496-9531; e-mail ds274k@nih.gov .		
Cross Reference:	HP-3, 1HHS-05, Outcome		

SRO - 5.8	By 2011, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate at least 3 research projects to improve objective measures of hot flash frequency.	1. (FY04) Currently available monitors are not suitable for multiple day ambulatory studies.	1. (MET) NIH initiated seven research projects.
2006	1. Develop and validate improved devices to measure hot flash frequency.	1. (FY05) Improved devices not yet available.	1. Performance results will be reported in February 2007.
2007	1. Continue validation of at least 2 devices to measure hot flash frequency.	1. (FY06) Prototype device from FY05 target should be available for additional validation testing.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Information on these seven research projects is publicly available from CRISP, by: • querying the terms hot and flash • selecting SBIR/STTR in the 'activity' box • selecting the Institutes and Centers NCCAM, NIA, and NIBIB • searching for new projects in FY 2005		
Cross Reference:	1HHS-05, 1HHS-19, SP-4.1, 5,000D-T1, 500D-P1, Outcome		

SRO - 5.9	By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Collect a cumulative total of 5.8 million genotypes from the FUSION study.	1. (FY04) 3 million genotypes collected in the FUSION study.	1. (MET) The FUSION study collected 3.0 million genotypes, making a cumulative total of 6.0 million genotypes collected for this study of genetic variants that predispose to common type 2 diabetes. The cumulative total exceeded the projected target by 200,000 genotypes.
2006	1. Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community.	1. (FY05) No FBPP data publicly available to the scientific community.	1. Performance results will be reported in February 2007.
2007	1. Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study.	1. (FY06) Scientific infrastructure established and RFP for initial scan released.	1. Performance results will be reported in February 2008.
Data Source & Validation:	'Tag SNP Selection for Finnish Individuals based on the CEPH Utah HapMap Database' Willer et al., submitted to Genetic Epidemiology.		
Cross Reference:	1HHS-01, 1HHS-05, SP-3.4, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$90	$97	$115

SRO - 6.1	By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Expand the genomic resources available to vision researchers through NEIBank and related trans-NIH activities.	1. (FY02) 31,000 human gene sequences; 12,000 unique human eye-expressed genes	1. (MET) Genomic resources expanded to include 30% more human gene sequences, 8% more unique human eye-expressed genes, and new DNA sequence data and clones.
2004	1. Reach consensus on a descriptive manual with standards that can be used to describe the diverse retinal phenotypes found in macular degeneration.	1. (FY03) No consensus descriptions on AMD phenotypes exist	1. (MET) A consensus was reached on a manual of classification standards for use by fundus photograph and reading centers that will aide in maintaining useful classification systems to identify new phenotypes and allow for possible meta-analysis of retinal phenotype collections.

2005	1. Collect and make available to investigators genetic material and information from over 4,000 well-characterized patients with either AMD or glaucoma.	1. (FY04) DNA specimens from large numbers of well-characterized AMD or glaucoma patients are not available	1. (MET) Collected samples from over 4,000 well-characterized patients with either AMD or glaucoma. Created the National Eye Disease Genotyping Network (EyeGENE).
2006	1. Develop animal models of AMD and glaucoma that closely mimic the pathologic processes underlying these diseases in humans.	1. (FY05) Existing animal model systems for AMD and glaucoma do not closely resemble the human disease	1. Performance results will be reported in February 2007.
2007	1. Conduct studies in animal models to identify potential modifier genes.	1. (FY05) Modifier genes for AMD and glaucoma have not yet been identified.	1. Performance results will be reported in February 2008.
Data Source & Validation:	http://neibank.nei.nih.gov/index.shtml http://www.iovs.org/cgi/reprint/46/9/3081 http://www.sciencemag.org/cgi/content/full/308/5720/385 http://www.sciencemag.org/cgi/content/full/308/5720/421 http://www.sciencemag.org/cgi/content/full/308/5720/419 http://www.pnas.org/cgi/content/full/102/20/7227		
Cross Reference:	HP-28, 1HHS-05, SP-4.1, SP-6.2, Outcome		

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.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	1. (FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	1. (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.
2004	1. Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	1. (FY03) Look AHEAD had recruited about half (2,500) of its patients	1. (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.
2005	1. Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	1. (FY03) ACCORD had recruited 1,184 participants in a Vanguard phase	1. (MET) The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005.
2006	1. Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	1. (FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population	1. Performance results will be reported in February 2007.
2007	1. To complete at least 90% of the total enrollment for the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial which aims to determine whether reduction of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in atherosclerotic CVD.	1. (FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Validation of participants enrolled as of September 30, 2005, is provided in the ACCORD recruitment reporting system. The recruitment report is confidential, but verification of the completion of recruitment may be obtained		

	by contacting Dr. Stephanie Burrows in the Office of Science and Technology at the National Heart Lung and Blood Institute.
Cross Reference:	HP-4, HP-5, HP-12, 1HHS-05, SP-1.1, SP-4.1, Outcome

SRO - 6.3	By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	1. (FY02) Intramural databases and commercial software to build ProtoCEBS available	1. (MET) ProtoCEBS launched, tested, and implemented.
2004	1. Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	1. (FY03) CEBS object model to capture molecular expression data (only) designed but not tested	1. (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.
2005	1. Create and provide public access to a global molecular expression and toxicology/pathology database of both chemicals found in the environment and drugs that have an effect on biological systems (CEBS), featuring simple query download capability.	1. (FY03) CEBS version 1.0 launched in August 2003 contains only microarray data.	1. (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.
2006	1. Enhance the CEBS to allow the capture and integration of transcriptomics, proteomics, and toxicologic data for the same compound.	1. (FY04) The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound	1. Performance results will be reported in February 2007.
2007	1. Enhance electronic sharing of 'omics and biology endpoint data	1. Initial integration of microarray and toxicologic/histopatholigic data achieved	1. Performance results will be reported in February 2008.

Data Source & Validation:	The publication by Xirasagar S, Gustafson S, Merrick BA, Tomer KB, Stasiewics S, Chan DD, Yost KJ, Yates JR, Sumner S, Xiao N, and Waters MD. CEBS object model for system biology data, SysBio-OM. Bioinformatics. 2004 Sep 1; 20(13):2004-15. Epub 2004 Mar 25, provides evidence to support the statements regarding Implementation Strategy Advances. The CEBS website: http://cebs.niehs.nih.gov/ may be consulted to confirm the functionality of CEBS as required to meet the FY05 Performance Target.
Cross Reference:	HP-8, 1HHS-05, SP-4.1, Outcome

SRO - 6.4	By 2014, identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating asthma exacerbations.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Initiate study of molecular, cellular, and genetic causes in AE.	1. (FY05) Little is known about the factors that predispose asthmatics for exacerbation.	1. (MET) Developed and funded a program consisting of twelve studies which will examine the molecular, cellular, and genetic causes of AE.
2006	1. Initiate study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history.	1. (FY05) Little is known about the role glycosidase activity may play in modification of airway glycans and the promotion of virus-induced AE.	1. Performance results will be reported in February 2007.
2007	1. Analyze data from studies of molecular, cellular, and genetic causes in AE.	1. (FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.	1. Performance results will be reported in February 2008.

Data Source & Validation:	Descriptions of the twelve studies being funded are available to the public in the CRISP Database (Computer Retrieval of Information on Scientific Projects) at http://crisp.cit.nih.gov/.

	Grant Numbers for entry on CRISP query form: 1R01AI068083-01, 1R01AI068084-01, 1R01AI068085-01, 1R01AI068086-01, 1R01AI068088-01, 1R01HL080083-01, 1R01HL080258-01, 1R01HL080337-01, 1R01HL080343-01, 1R01HL080412-01, 1R01HL080414-01, 1R01HL080676-01
Cross Reference:	HP-24, 1HHS-05, 1HHS-19, SP-4.2, 5,000D-T1, Outcome

FULL COST(dollars in millions)	FY05	FY06	FY07
	$37	$61	$69

SRO - 7.2	By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Establish intramural and extramural collaborations to select and employ substrate nanotechnology fabrication techniques to enable high-throughput and highly reliable/reproducible proteomic analyses.	1. (FY02) Lack of relevant collaborations.	1. (MET) Collaborations established and work progressing on employing nanotechnology techniques to enable high-throughput proteomic analyses relevant to early detection of cancer.
2004	1. Establish a core laboratory at NIH to bring together extramural and intramural fabrication technologies with the capability to derive targets, identify the most promising applications for combined functionalized nanoparticles, and steward therapeutic nanotechnologies through validation.	1. (FY03) No current core laboratory with needed capacity	1. (MET) The national Nanotechnology Characterization Laboratory (NCL) has been established and will enable development of essential data about the profiles of nanoparticles in biological systems.
2005	1. Integrate nanosensors and nanoparticles into a platform technology for development in applied research settings.	1. (FY03) Existing nanosensors and nanoparticles not integrated into a common platform.	1. (MET) Nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings.
2006	1. Complete goal of integrating nanotechnology-based components into a system capable of detecting specific biomarkers to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption.	1. FY05 results	1. Performance results will be reported in February 2007.
Data Source & Validation:	Wojciech Lesniak, Anna U. Bielinska, Kai Sun, Katarzyna W. Janczak, Xiangyang Shi, James R. Baker Jr., and Lajos P. Balogh. Silver/Dendrimer Nanocomposites as Biomarkers: Fabrication, Characterization, in Vitro Toxicity, and Intracellular Detection. Nano Letters, Vol. 5. No. 11, 2123-2130. Chao Li, Marco Curreli, Henry Lin, Bo Lei, F. N. Ishikawa, Ram Datar, Richard J. Cote, Mark E. Thompson, and Chongwu Zhou. Complementary Detection of Prostate-Specific Antigen Using In2O3 Nanowires and Carbon Nanotubes. JACS Communications, Vol. 127. No. 36, 12484-12485. Dawn L. Nidaa, Mohammed S. Rahmana, Kristen D. Carlsona, Rebecca Richards-Kortuma, Michelle Follen. Fluorescent nanocrystals for use in early cervical cancer detection. Gynecologic Oncology (In Press). Stroh M, Zimmer JP, Duda DG, Levchenko TS, Cohen KS, Brown EB, Scadden DT, Torchilin VP, Bawendi MG, Fukumura D, Jain RK. Quantum dots spectrally distinguish multiple species within the tumor milieu in vivo. Nat Med. 2005 Jun;11(6):678-82. Epub 2005 May 8. PMID: 15880117.		
Cross Reference:	HP-3, 1HHS-05, SP-4.1, SP-4.2, Efficiency, Outcome		

SRO - 7.3	By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. For existing blood samples from U.S. residents of Western and northern European ancestry, obtain additional consent from the donors for this new use and begin genotyping 300,000 single nucleotide polymorphisms (SNPs, sites in the human genome where individuals differ by a single letter) in those samples.	1. (FY02) 90 existing samples, none of which included the necessary consent for genotyping	1. (MET) All needed consents obtained and genotyping performed on 132,000 SNPs.
2004	1. Collect samples from populations in Japan, China, and Nigeria; complete collection of additional 3 million SNPs and release in public databases.	1. (FY03) 2.4 million SNPs in database	1. (MET) Sample collection has been completed, and greater than 3 million SNPs have been released in the public database.
2005	1. Develop a first-pass draft HapMap containing 600,000 SNPs.	1. (FY03) 2.4 million SNPs in database but none of the samples genotyped to produce any part of the HapMap	1. (MET) Completed first-pass draft HapMap with 1.007 million SNPs, an increase of more than 400,000 SNPs over the projected total of 600,000. Goal completed.
Data Source & Validation:	http://www.hapmap.org/ Altshuler D, Brooks LD, Chakravarti A, Collins FS, Daly MJ, Donnelly P; International HapMap Consortium. A haplotype map of the human genome. Nature. 2005 Oct 27;437(7063):1299-320.		
Cross Reference:	1HHS-05, SP-4.1, Outcome		

SRO - 7.8.1	By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Complete the genomic sequences for at least five bacteria and two protozoa that cause infectious disease.	1. (FY02) Genome sequences for 32 bacterial pathogens, 1 protozoan parasite, and 1 insect completed.	1. (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.
2004	1. Complete the genomic sequences of at least five bacterial pathogens, two protozoa, and three fungal pathogens that cause infectious disease.	1. (FY03) Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed	1. (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.
2005	1. Complete the genomic sequences of at least five bacterial pathogens, four protozoa, two fungal pathogens that cause infectious disease.	1. (FY04) Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi and 1 insect completed	1. (MET) Genomic sequencing projects for 30 bacteria, 1 protozoan, 1 insect and 3 fungi were completed.
2006	1. Complete the genome sequence of at least six bacterial pathogens, two protozoan parasites, and one invertebrate vector of infectious diseases.	1. (FY05) Genome sequences for 63 bacterial pathogens, 12 protozoan parasites, 5 fungi, and 1 invertebrate vectors of infectious diseases completed	1. Performance results will be reported in February 2007.
2007	1. Complete goal of determining the genome sequences of 45 human pathogens and 3 invertebrate vectors	1. FY06 results.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Genbank accession numbers for each sequence provided below (for use on http://www.ncbi.nlm.nih.gov/ under the subheading "Genome Project": Aedes aegypti - AAGE00000000; Aspergillus terreus - AAJN00000000; Burkholderia mallei - AAHQ00000000; AAHO00000000; AAHM00000000; AAHP00000000; AAHN00000000; Burkholderia pseudomallei - AAHR00000000; AAHS00000000; AAHT00000000; AAHU00000000; AAHV00000000; AAHW00000000; Burkholderia thailandensis - NC_007321; Ehrlichia spp. – http://riki-lb1.vet.ohio-state.edu/ehrlichia/; accession number pending; Escherichia coli HS - AAJY00000000; Escherichia coli E24377A- AAJZ00000000; Escherichia coli 53638- AAKB00000000; Escherichia coli B7A - AAJT00000000; Escherichia coli F11- AAJU00000000; Escherichia coli E22- AAJV00000000; Escherichia coli E110019 - AAJW00000000; Escherichia coli B171- AAJX00000000; Giardia lamblia - NW-888268; Histoplasma capsulatum - http://genomeold.wustl.edu/blast/histo_client.cgi; accession number pending; Shigella boydii BS512 - AAKA00000000; Vibrio cholerae - AKF00000000; AAKG00000000; AAKH00000000; AAKI00000000; AAKJ00000000; AAKF00000000; Yersinia pestis Angola strain - AAKS00000000; Yersinia pseudotuberculosis IP31758 (Scarlet Fever isolate) -AAKT00000000		

Cross Reference:	HP-10, HP-14, HP-24, HP-25, 1HHS-05, SP-1.2, SP-2.1, SP-4.1, Efficiency, Outcome		
SRO - 7.8.3	By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA) transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Make the RefSeq Collection database available for downloading to enable commercial or academic groups to perform exhaustive analyses across the entire RefSeq Collection data set.	1. (FY02) At the end of FY02, the RefSeq collection included 446,000 proteins and was not available for FTP	1. (MET) The RefSeq collection was made available on a regular release cycle to scientists at commercial and academic sites for downloading and analysis of the entire data set.
2004	1. Develop the infrastructure to support wider access to the RefSeq Collection via the Internet to provide users with a centralized set of annotated sequence information.	1. (FY03) RefSeq collection includes sequence data from 2124 species; only a limited database is available	1. (MET) The RefSeq collection is now fully available via the online resource Entrez Gene.
2005	1. Expand the project to include outside groups to increase the amount of sequence and functional information in the database. Collaborations will provide additional reference sequence records, whole-genome annotation, functional annotation of multigene families, and expert review of single genes.	1. (FY04) About 40 collaborations in place for obtaining annotated RefSeq records and other functional data	1. (MET) The RefSeq project was expanded through the deployment of a database and web site that both tracks the submission of genome sequencing projects and supports the generation of RefSeq records from those submissions. Collaborations were established at multiple levels to support the expansion and curation of the project.
2006	1. Complete goal of building a publicly accessible RefSeq Collection to serve as the basis for medical, functional, and diversity studies	1. FY05 results	1. Performance results will be reported in February 2007.
Data Source & Validation:	Public release of the Genome Project database which includes information about the genomic RefSeq collection serves to verify that the FY2005 performance target was met. Project web site: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj Status of eukaryotic genome sequencing projects: http://www.ncbi.nlm.nih.gov/genomes/leuks.cgi Status of prokaryotic genome sequencing projects: http://www.ncbi.nlm.nih.gov/genomes/lproks.cgi The Entrez Genome Project resource was announced on NCBI web pages, and in workshops and conferences. The resource is available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj The Entrez Genome Project resource is also described in the following publication: Wheeler, D., Barrett, T., Benson, D., Bryant, S., Canese, K., Church, D., DiCuccio, M., Edgar, R., Federhen, S., Geer, L., Helmberg, W., Kapustin, Y., Kenton, D., Khovayko, O., Lipman, Dl, Madden, T., Maglott, D., Ostell, J., Pruitt, K., Schuler, G., Database Resources of the National Center for Biotechnology Information, Nucleic Acids Research, Database Issue, In press The Genome Champion project has included participation in several conference calls, conferences, and workshops including: Plant & Animal Genome Conference XIII, January 2005 Workshop title: Animal and Plant genome resources at NCBI Speakers: Tatiana Tatusova, Kim Pruitt, Melissa Landrum, Steve Pechous Web site: http://www.intl-pag.org/13/13-ncbi.html Workshop on Chicken Genomics and Development, May 2005 Cold Spring Harbor Laboratory Title: Exploring the Chicken Genome using NCBI's Map Viewer Speaker: Janet Weber Zebrafish Development & Genetics International Meeting, July, 2005 Workshop Title: Zebrafish Genome Resources Workshop		

	Speakers: Lynn Schriml, Judy Sprague, Kerstin Jekosch Web site: http://www.ncbi.nlm.nih.gov/genome/guide/zebrafish/Workshop2004/ The Genome Champion project supports a series of web pages that serve as a central point of access to organism-specific RefSeq and other data available publicly. The 'Genomic Biology' home page includes links to nineteen Genome Guide web pages that are currently available. Genome guide web sites continue to be added to this collection. Please see the Genomic Biology home page: http://www.ncbi.nlm.nih.gov/Genomes/ Conserved CDS (CCDS) was announced on NCBI web pages, in email announcement lists, and in press releases released by different members of this collaboration. The web resource is available at: http://www.ncbi.nlm.nih.gov/CCDS/
Cross Reference:	1HHS-15, SP-4.1, Efficiency, Outcome

FULL COST(dollars in millions)	FY05	FY06	FY07
	$145	$91	$84

SRO - 8.2	By 2009, identify and characterize two molecular interactions of potential clinical significance between bone-forming cells and components of bone. Such interactions are defined as those having significant impact on the accrual of bone mass or the actual mechanical performance of bone (i.e., fracture resistance) in laboratory animals.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Characterize effects of the bone protein thrombospondin-2 on the generation of bone-forming cells from precursor cells in the bone marrow and identify regions of the thrombospondin-2 molecule that are required for the effects.	1. (FY02) Information on the role of thrombospondin-2 in bone generation is incomplete.	1. (MET) Thrombospondin-2 promotes bone formation in the early stage of cell differentiation; functional elements at one end of molecule responsible for this effect.
2004	1. Identify biochemical pathways in bone-forming cells that are responsible for extended survival of cells on interaction with the bone protein osteonectin.	1. (FY03) Biochemical pathways that mediate cell survival are unknown.	1. (MET) Results suggest that the interaction of bone-forming cells with osteonectin enhances cell survival through activation of the Wnt pathway.
2005	1. Identify regions of bone and bone marrow in which thrombospondin-2 is produced under conditions of bone loss and bone formation. Generate a genetically altered mouse strain in which a fluorescent protein is produced under the control of the same genetic elements that control the production of thrombospondin-2.	1. (FY03) Information is incomplete on where thrombospondin-2 is produced; mouse model can provide this data.	1. (EXT) The FY05 target was extended to FY 2007. The stromal cells of bone marrow appear to be the key producers of thrombospondin-2. Technical difficulties have delayed construction of the fluorescent reporter mouse.
2006	1. Generate a genetically modified mouse in which only bone-forming cells are deficient in fibronectin, and identify the cell surface molecule mediating interaction between bone-forming cells and connective tissue growth factor.	1. (FY04) Mice wholly deficient in fibronectin are not viable. Molecules interacting with CTGF are unknown.	1. Performance results will be reported in February 2007.
2007	1. Determine the characteristics of the skeleton in mice deficient in dentin matrix protein 1 (DMP-1), and assess the consequences of DMP-1 deficiency for bone cell function.	1. The skeleton of a mouse lacking DMP-1 exhibits complex defects. It is unknown how this is related to bone cell function.	1. Performance results will be reported in February 2008.
Data Source & Validation:	The increase in TSP2 production by stromal cells stimulated to produce bone was reported at the 27th Annual Meeting of the American Society for Bone and Mineral Research (Abstract SA038, J. Bone Mineral Res. Vol. 20 Suppl. 1). The protection of ovariectomized TSP2-deficient mice against bone loss was reported in Matrix Biology Vol. 24, pp. 362-370. The role of fibronectin and biglycan in matrix incorporation of transforming growth factor beta was reported in J. Biol. Chem. Vol. 280, pp. 18871-80, and pp. 30481-89.		
Cross Reference:	HP-2, 1HHS-05, SP-4.1, SP-6.2, Outcome		

SRO - 8.4	By 2009, assess the impact of two major Institutional Development Award (IDeA) Programs on the development of competitive investigators and their capacities to compete for NIH research funding.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Develop a data collection and management system to allow for the retrieval of potential target indicators to evaluate the impact of the IDeA/Centers of Biomedical Research Excellence (COBRE) Program.	1. (FY02) Indictors from Pre-COBRE analysis and previous evaluations.	1. (MET) Data collection and management system in place for retrieval of potential target indicators related to evaluating impact of IDeA/Centers of Biomedical Research Excellence Program.
2004	1. Assessment Methodology for IDeA Program (Step 1): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/COBRE impact. -Develop a data collection system for BRIN.	1. (FY03) Data collection and management system to evaluate impact of IDeA/COBRE in place. (FY04) Indicators from IDeA/COBRE evaluation design.	1. (MET) The COBRE evaluation design, which includes a confirmed list of target indicators, is complete. Data collection and management system is in place for BRIN.
2005	1. Assessment Methodology for IDeA Program (Step 2): -Complete evaluation design to determine a confirmed list of target indicators to measure IDeA/BRIN impact. -Assess results of COBRE evaluation design study.	1. (FY04) Data collection and management system to evaluate impact of IDeA/BRIN in place. (FY04) COBRE evaluation design completed but not evaluated.	1. (MET) The IDeA/INBRE evaluation design was completed in September 2005 and the final report included a confirmed list of target indicators to measure INBRE impact. The results of the COBRE evaluation design study were assessed.
2006	1. Full-Scale Assessment of the IDeA Program (Step 1): - Initiate the full-scale evaluation for IDeA/COBRE.	1. (FY04) COBRE evaluation design	1. Performance results will be reported in February 2007.
2007	1. Full-Scale Assessment of the IDeA Program (Step 2): - Initiate the full-scale evaluation for IDeA/INBRE.	1. (FY05) INBRE evaluation design.	1. Performance results will be reported in February 2008.
Data Source & Validation:	In September 2005, NCRR received the final report from the contractors entitled 'Feasibility Study for the INBRE Program Evaluation, Final Report.' This report contains the methodology used as well as the confirmed list of indicators that are part of the conceptual framework for the full-scale evaluation of INBRE. A copy of this report can be obtained from the Office of Science Policy and Public Liaison, NCRR, One Democracy Plaza, 6701 Democracy Boulevard, Room 985, Bethesda, Maryland 20892-4874, tel 301-435-0866 (contact is Patricia Newman). All of the information received through the data collection and management system can be found in the Annual Progress Reports (APR) received from each INBRE grantee.		
Cross Reference:	HP-23, 1HHS-15, SP-4.3, Outcome		

SRO - 8.5	By 2009, develop an item bank and computerized adaptive testing system available to clinical researchers to improve assessment of non-specific symptoms (e.g., pain and fatigue) and other domains of health-related quality of life in chronic disease.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify specific domains to be measured, evaluate existing measures and items, and develop instrument(s) and assessment methods for use in diverse chronic disease patient samples.	1. (FY04) Highly valid, reliable, and broadly usable assessment tools are needed to enhance clinical research on patient-reported chronic disease outcomes.	1. (MET) Preliminary item pools to measure the chosen domains (Pain, Fatigue, Physical Functioning, Emotional Distress, and Social Role Participation) have been created based on exhaustive review of existing measures. Initial instruments and methodologies have been developed.
2006	1. Initiate administration of instrument(s) to a large demographically diverse patient sample representing a wide range of chronic disease type and severity.	1. (FY05) An initial item pool for assessing specified domains of symptoms and/or domains of health-related quality of life developed using FY 05 target.	1. Performance results will be reported in February 2007.
2007	1. Initiate analyses on preliminary data of pain, fatigue, physical functioning, emotional distress, and social role participation.	1. Preliminary data analyses undertaken	1. Performance results will be reported in February 2008.

Data Source & Validation:	PROMIS Steering Committee Minutes Noncompeting continuation applications for: U01 AR 52181 GUESS HARRY U01 AR 52186 WEINFURT KEVIN U01 AR 52158 FRIES JAMES U01 AR 52155 PILKONIS PAUL U01 AR 52177 CELLA DAVID U01 AR 52162 WILLIAMS DAVID U01 AR 52171 AMTMANN DAGMAR U01 AR 52170 STONE ARTHUR PROMIS Home Room (an e-room hosted by the SCC that includes information on committee and working group activities, documents, abstracts and manuscripts submitted, calendars, etc.) PROMIS website: www.nihpromis.org
Cross Reference:	PMA-4, 1HHS-05, SP-4.1, 500D-A8, Outcome

SRO - 8.6	By FY 2011, develop stable national estimates of vision impairment by extending the vision component of the National Health and Nutrition Examination Survey (NHANES).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2007	1. Extend NHANES and survey approximately 7,000 people.	1. (FY06) Very little reliable data on the prevalence of visual impairment in the U.S.	1. Performance results will be reported in February 2008.
Data Source & Validation:			
Cross Reference:	HP-28, 1HHS-05, SP-4.1, SP-4.4, Outcome		

SRO - 8.9.1	By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Identify at least one biological (gene-environment) interaction that has high probability of contributing to depression.	1. (FY02) Known that stress linked to depression but interaction not known.	1. (MET) A link was made between a specific gene-environment interaction (5-HTT and high stress) and vulnerability to depression.
2004	1. Determine whether vascular changes related to aging contribute to depression.	1. (FY03) Subcortical lesions, common in elderly with depression and in vascular disease, are being studied as potential cause of depression.	1. (MET) A strong correlation has been found between vascular changes resulting in unique lesions in the brain and depression in elderly patients.
2005	1. Determine at least four characteristics that help identify subgroups of people with depression who respond differentially to existing treatments.	1. (FY04) A series of clinical trials are currently underway that match patients' responses to different treatments.	1. (MET) Characteristics that influence the efficacy of pharmacological and behavioral treatment for depression have been identified. The characteristics range from genetic variation to psychosocial factors.
2006	1. Identify at least one effective strategy for treating depression in the elderly in a variety of settings.	1. (FY05) A number of interventions to treat depression in the elderly are currently being developed and tested.	1. Performance results will be reported in February 2007.
2007	1. Determine the relative efficacy of combined treatment strategies or sequential treatment algorithms in treating chronic depression.	1. (FY05) Studies are underway to test the efficacy of differing treatment combinations or sequences for depressed patients.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Gaynes BN, Rush AJ, Trivedi M, et al. (2005) A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. General Hospital Psychiatry 27:87- 96.		

Trivedi MH, Rush AJ, Wisniewski SR, et al. (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. Am J Psychiatry, 163:28-40.

Gildengers AG, et al. (2005) Trajectories of treatment response in late-life depression: psychosocial and clinical correlates. J Clin Psychopharmacol, 25 (4 Suppl 1):S8-13.

Kraft JB, Slager SL, McGrath PJ, and Hamilton SP. (2005) Sequence analysis of the serotonin transporter and associations with antidepressant response. Biol Psychiatry. (In press).

Leuner B, Mendolia-Loffredo S, Shors TJ. (2004) Males and females respond differently to controllability and antidepressant treatment. Biol Psychiatry 56:964-970.

Murphy, GM et al. (2004). Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry, 61:1163-1169.

Curry JF, (2005 October) Predictors and moderators of acute treatment outcomes in TADS. Paper presented at the 2005 Joint Annual Meeting of the American Academy of Child & Adolescent Psychiatry and the Canadian Academy of Child and Adolescent Psychiatry, Toronto, Canada.

Peters EJ, Slager Sl, et al. (2004) Investigation of serotonin-related genes in antidepressant response. Mol Psychiatry, 9(9): 879-89.

Serretti A and Artioli P. (2004) From molecular biology to pharmacogenetics: a review of the literature on antidepressant treatment and suggestions of possible candidate genes. Psychopharmacology, 174:490-530.

Serretti A and Artioli P. (2004) The pharmacogenomics of selective serotonin reuptake inhibitors. The Pharmacogenomics Journal, 4:233-244.

Serretti A, Artioli P and Quartesan R. (2005) Pharmacogenetics in the treatment of depression: pharmacodynamics studies. Pharmacogenetics and Genomics, 15:61-67.

Zisook S, Rush AJ, Albala A, et al (2004) Factors that differentiate early vs. later onset of major depression disorder. Psychiatry Research, 129:127-140.

Cross Reference:	HP-5, HP-12, HP-18, 1HHS-05, SP-4.1, SP-6.2, Outcome

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

Data Source & Validation:	The completion of the FY 2005 performance target is documented in the grantee's progress report; however, progress reports are not available to the public.
Cross Reference:	HP-7, HP-12, 1HHS-01, 1HHS-19, SP-1.1, SP-3.4, SP-4.1, SP-4.4, 5,000D-T1, Efficiency, Outcome

FULL COST(dollars in millions)	FY05	FY06	FY07
	$351	$351	$342

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.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Prepare and disseminate the first of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	1. (FY04) First of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.	1. (MET) Enrolled 504 children, and prepared and disseminated the first stage of scans, demographic, medical, cognitive, and behavioral data collected from 430 children, age 4.5 to 18, to the research community.
2006	1. Complete the second of three stages of neuroimaging scans and data collection of approximately 500 children across the United States.	1. (FY05) The first of three stages of scans, demographic, medical, cognitive, and behavioral data were collected from 500 children and disseminated to research community.	1. Performance results will be reported in February 2007.
2007	1. Complete preliminary analyses of changes of brain growth in children over time and share findings with research community.	1. (FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.	1. Performance results will be reported in February 2008.
Data Source & Validation:	Brain Development Cooperative Group, Evans, A. (in press) The NIH MRI study of normal brain development, NeuroImage.		
Cross Reference:	HP-16, 1HHS-05, 1HHS-15, SP-4.1, SP-4.4, 500D-A7, Efficiency, Outcome		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$7	$5	$1

COMMUNICATION AND TRANSFER OF RESULTS

CTR - 1	By 2008, reduce the disparity between African American and white infants in back sleeping by 50% to further reduce the risk of sudden infant death syndrome (SIDS).		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. In collaboration with African American organizations, community health and other local officials, and faith-based organizations, conduct regional summit meetings to train and motivate individuals who will implement SIDS risk reduction activities in their communities.	1. (FY02) No regional summit meetings were held prior to 2003	1. (MET) Over 1,000 participants were trained and motivated to reduce SIDS in African American communities during 3 regional U.S. summits.
2004	1. Conduct 250 interviews among the approximately 1,500 participants who attended the three summit meetings held in FY 2003 to determine that each summit resulted in a minimum of 50 outreach activities.	1. (FY03) No interviews have been conducted for this purpose	1. (MET) Interviews were held with participants from each summit and 150 outreach activities resulted from each of the summits.
2005	1. Continue to extend "Back to Sleep" campaign messages to African American populations through community-based collaborations/partnerships by involving a minimum of six national organizations in SIDS training and educational activities.	1. (FY03) Three participating national organizations	1. (MET) NIH extended the 'Back to Sleep' campaign messages to African American populations through community-based collaborations with eight national organizations in SIDS training and educational activities.
2006	1. Promote a continuing education module with at least six national nursing organizations serving African American communities to extend the Back to Sleep campaign messages.	1. (FY03) There are no known efforts to systematically educate the nursing community on a national level about SIDS risk reduction.	1. Performance results will be reported in February 2007.
2007	1. Extend the continuing education module for nurses in appropriate community-based clinical settings in African American communities in the Mississippi Delta region.	1. (FY05) There are no known efforts to systematically educate nurses on a community level about SIDS risk reduction.	1. Performance results will be reported in February 2008.
Data Source & Validation:	A description of the 'Back to Sleep' Campaign is available at http://www.nichd.nih.gov/sids/. Contact: Andrea Furia Back to Sleep Campaign National Institute of Child Health and Human Development (301)-435-3459		
Cross Reference:	HP-11, HP-16, 1HHS-05, 1HHS-19, SP-3.4, 5,000D-T1, 500D-P1, 500D-T3, Efficiency, Outcome		

CTR - 2	By 2006, increase awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least five communities and extending the impact of the campaign, "*Know Stroke. Know the Signs. Act in Time.*"		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Work with partners in five communities with at least 15 percent African American audiences to extend the Know Stroke campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 Know Stroke community education kits and 100,000 Know Stroke brochures (25,000 will be distributed to African American audiences).	1. (FY03) National partnerships developed; no current comprehensive local partnerships	1. (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.
2005	1. Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 Know Stroke community education kits (1,000 will be through African American partners).	1. (FY03) Five Partnerships developed in FY 2004.	1. (MET) Planned outreach programs in 5 U.S. cities. An additional 5,686 Know Stroke community education kits are being distributed (approximately 1,000 through African American partners). Distribution efforts are under budget by $142,000 and 686 kits over the projected target.
2006	1. Complete goal of increasing awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least 5 communities and extending the impact of the campaign, "*Know Stroke. Know the Signs. Act in Time.*"	1. FY05 results	1. Performance results will be reported in February 2007.
Data Source & Validation:	Validation sources for the reported distribution quantities of materials include: • NINDS Warehouse Inventory, Quarterly Cost Recovery Report • NINDS Warehouse Inventory, Quarterly Know Stroke Materials Report These reports can be obtained through Marian Emr, Director, Office of Communications and Public Liaison, NINDS, NIH, at (301)496-5924.		
Cross Reference:	HP-11, HP-12, 1HHS-19, SP-1.1, SP-4.4, 5,000D-T1, 500D-P1, 500D-T3, Output		

CTR - 3	By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	1. (FY03) No known needs assessment studies exist for developing technology TA program.	1. (MET) Developed a 'needs' assessment study for a technical assistance program.
2005	1. (Target 2) Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	1. (FY03) No personnel.	1. (MET) Personnel joined OTT to design and implement the TA program based on the results of the needs assessment study.
	2. (Target 3) Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	2. (FY03) Limited access to targeted training in developing countries.	2. (MET) OTT identified and targeted appropriate institutions in seven developing countries for participation in either an educational and technical assistance internship program (China, South Africa, India, and Brazil) or an on-site training seminar (Ghana, Zambia and Korea).
2006	1. (Target 4) Complete goal of through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.	1. FY05 results	1. Performance results will be reported in February 2007.

	Previous Target: Secure potential supporting partner(s) to support the onset of the technical assistance program		
Data Source & Validation:	(Target 1) For the list of institutions in developing countries and the inventory of international organizations, U.S. government agencies, and other stakeholders with OTT, as well as supporting documentation, please contact: Luis A. Salicrup, Ph.D., MS.M. Senior Advisor for International Technology Transfer Office of Technology Transfer (301) 435-5009 (Target 2) For supporting documents related to the recruitment of personnel to design and implement the TA program, contact: Luis A. Salicrup, Ph.D., MS.M. Senior Advisor for International Technology Transfer Office of Technology Transfer (301) 435-5009 (Target 3) For supporting documentation related to internships and training sessions, please contact: Luis A. Salicrup, Ph.D., MS.M. Senior Advisor for International Technology Transfer Office of Technology Transfer (301) 435-5009		
Cross Reference:	SP-4.4, 5,000D-I1, Output		

CTR - 4	By 2008, increase the percentage of Small Business Innovation Research (SBIR) program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing or FDA Regulatory Assistance	1. No current programs.	1. (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. (MET) Initiated trans-NIH CAP with 130 participants.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program	3. Pilot programs converted to program implementation.	3. (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.
2005	1. (Target 1) Pilot test specific TA program to support SBIR projects : Niche Assessment	1. No current program.	1. (MET) Completed pilot Niche Assessment Program with 100 participants.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. (MET) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at an investment forum.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program.	3. Pilot programs converted to program implementation.	3. (MET) Pilot CAP -- 40% of forum presenters received additional private investments or sales. Cumulative private sector funding/sales received was $37,764,520 with most received by five firms.
2006	1. (Target 1) Pilot test specific technical assistance programs to further development of SBIR projects towards commercialization. Manufaturing or FDA Regulatory Assistance.	1. No current program.	1. Performance results will be reported in February 2007.

	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. Performance results will be reported in February 2007.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program	3. TBD in FY04 CAP pilot conversion to program implementation.	3. Performance results will be reported in February 2007.
2007	1. (Target 1) Pilot test specific technical assistance programs to further development of SBIR projects towards commercialization.	1. No current program.	1. Performance results will be reported in February 2008.
	2. (Target 2) Implement effective piloted programs to create a menu of technical assistance programs.	2. Pilot Assistance Programs (i.e., CAP, Niche, etc.).	2. Performance results will be reported in February 2008.
	3. (Target 3) Report critical elements to assess advances of each technical assistance program.	3. TBD in FY04 CAP pilot conversion to program implementation.	3. Performance results will be reported in February 2008.
Data Source & Validation:	(Target 1) Pilot Niche Assessment Program: 1. Contract Number N01-LM-4-5510 with Foresight Science and Technology, Inc. 2. Foresight Science and Technology Technology Niche Analyses for 100 NIH Phase I SBIR Awardees (Target 2 & 3) CAP: 1. Contract N01-LM-4-5509 with Larta Institute 2. NIH-CAP 2004-05 Final Report, Submitted by Larta Institute, July 18, 2005		
Cross Reference:	1HHS-15, 1HHS-18, SP-4.2, SP-4.4, Outcome		

CTR - 5	By FY 2013, improve marketing and management of NIH intellectual property assets by building text mining capability.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. Identify and text mine at least four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	1. (FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.	1. (MET) Identified and text mined five relevant data sources: TechTracS, CRISP, PubMed, Science News Wire, and the USPTO's patent database (2001-present).
2006	1. Identify and text mine an additional four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	1. To be determined by results of FY05 target.	1. Performance results will be reported in February 2007.
2007	1. Establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually.	1. To be determined by results of FY06 target.	1. Performance results will be reported in February 2008.
Data Source & Validation:	The validation sources are: 1. Contract Number NJC74175 with Discovery Logic, Inc.; and 2. The tool created through text mining the five data sources, registered as GovPatents.com. It is password protected. Access may be obtained by contacting: Bonny Harbinger, Ph.D., J.D. Deputy Director, Office of Technology Transfer 6011 Executive Boulevard, Room 325 Rockville, MD 20852 (301) 594-7700		
Cross Reference:	SP-4.2, SP-4.4, SP-8.5, Efficiency, Output		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$4	$3	$3

CAPACITY BUILDING AND RESEARCH RESOURCES

CBRR - 1	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. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	1. (FY04) NRSA Group: 20.5% Comparison Group A: 7.0% Comparison Group B: 2.9%	1. (MET) Award rate to comparison groups exceeded by 12%
	2. (Target 2) Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination.	2. (FY04) NRSA Group: 34.7% Comparison Group: 20.8%	2. (MET) Award rate to comparison groups exceeded by 14%
	3. (Target 3) Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments.	3. (FY04) 556 multidisciplinary or interdisciplinary grants	3. (MET) The reported rate of multidisciplinary grants was 44%
	4. (Target 4) Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	4. (FY03-FY06) Awards granted K23 120 K24 50 K30 50	4. (MET) All annual targets achieved (K23=222, K24=50, K30=59)
	5. (Target 5) Provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity. *Previous Target:* Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	5. (FY04) 0 additional positions supported	5. (MET) The percentage of under-represented minorities rose by 2.4% in FY 2004.
	6. (Target 6) Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. (FY04) LRP applications received: 2,498 LRP contracts awarded: 1,407	6. (MET) Applicants 2,498, Awards 1,407 (56% of applicants received an award)
2005	1. (Target 1) Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	1. (FY04) NRSA Group: 20.5% Comparison Group A: 7.0% Comparison Group B: 2.9%	1. (MET) Award rate to comparison groups exceeded by at least 14%
	2. (Target 2) Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination.	2. (FY04) NRSA Group: 34.7% Comparison Group: 20.8%	2. (MET) Award rate to comparison groups exceeded by at least 13%
	3. (Target 3) Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of	3. (FY04) 556 multidisciplinary or interdisciplinary grants	3. (MET) The reported rate of multidisciplinary grants was 27%

	Training, or Discipline/Specialty Field codes or departments.		
	4. (Target 4) Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	4. (FY03-FY06) Awards granted K23 120 K24 50 K30 50	4. (MET) All annual targets achieved (K23=223, K24=76, K30=51)
	5. (Target 5) Provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity.	5. (FY04) 0 additional positions supported	5. (MET) Provided enhanced opportunities to recruit and retain underrepresented groups to biomedical research
	6. (Target 6) Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. (FY04) LRP applications received: 2,498 LRP contracts awarded: 1,407	6. (MET) Applicants 3,290, Awards 1,600 (49% of applicants received an award)
2006	1. (Target 1) Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	1. (FY04) NRSA Group: 20.5% Comparison Group A: 7.0% Comparison Group B: 2.9%	1. Performance results will be reported in February 2007.
	2. (Target 2) Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination.	2. (FY04) NRSA Group: 34.7% Comparison Group: 20.8%	2. Performance results will be reported in February 2007.
	3. (Target 3) Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments.	3. (FY04) 556 multidisciplinary or interdisciplinary grants	3. Performance results will be reported in February 2007.
	4. (Target 4) Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.	4. (FY03-FY06) Awards granted K23 120 K24 50 K30 50	4. Performance results will be reported in February 2007.
	5. (Target 5) Provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity.	5. (FY04) 0 additional positions supported	5. Performance results will be reported in February 2007.
	6. (Target 6) Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	6. (FY04) LRP applications received: 2,498 LRP contracts awarded: 1,407	6. Performance results will be reported in February 2007.
2007	1. (Target 1) Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.	1. (FY04) NRSA Group: 20.5% Comparison Group A: 7.0% Comparison Group B: 2.9%	1. Performance results will be reported in February 2008.
	2. (Target 2) Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent	2. (FY04) NRSA Group: 34.7%	2. Performance results will be reported in February 2008.

	NIH support exceeds relevant comparison groups by 10% within 10 years of termination.	Comparison Group: 20.8%	
	3. (Target 3) Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments.	3. (FY04) 556 multidisciplinary or interdisciplinary grants	3. Performance results will be reported in February 2008.
	4. (Target 5) Provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity.	4. (FY04) 0 additional positions supported	4. Performance results will be reported in February 2008.
	5. (Target 6) Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	5. (FY04) LRP applications received: 2,498 LRP contracts awarded: 1,407	5. Performance results will be reported in February 2008.
Data Source & Validation:	"Outcome Evaluation of the NIH National Research Service Award (NRSA) Postdoctoral Training Program." PO #: MZ600302. Contact: William E. McGarvey, Ph.D. Scientific Program Evaluation Specialist Office of Extramural Programs (301)435-2691		
Cross Reference:	HP-23, 1HHS-02, 1HHS-05, SP-4.3, Output		

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

	FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)		to 2008.
2006	1. (Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07)	1. (FY03) NBS without contracts/acquisition/accounts payable/supply modules	1. Performance results will be reported in February 2007.
	2. (Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	2. (FY03) NBS without service and supply fund activities module	2. Performance results will be reported in February 2007.
	3. (Target 3) Report critical elements of General Ledger and Travel Module performance.	3. (FY04) NBS performance with General Ledger and Travel Modules deployed	3. Performance results will be reported in February 2007.
2007	1. (Target 3) Report critical elements of General Ledger and Travel Module performance.	1. (FY04) NBS performance with General Ledger and Travel Modules deployed	1. Performance results will be reported in February 2008.
	2. (Target 4) NBS roll-out and post deployment support.	2. (FY05) NBS without contracts/acquisition/accounts payable and receivable /supply modules	2. Performance results will be reported in February 2008.
	3. (Target 5) Commencement of NBS/UFMS migration activities.	3. (FY06) NBS without the UFMS migration	3. Performance results will be reported in February 2008.
Data Source & Validation:	All project performance metrics and associated communications are stored in the NBS project database. Contact: Eric Cole NBS Program Management Office (301) 451-0052		
Cross Reference:	PMA-3, 1HHS-01, 1HHS-02, 1HHS-06, SP-8.4, SP-8.5, Output		

CBRR - 3	Streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS). (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. Implement a core hospital system.	1. (FY03) 28 year old legacy system	1. (MET) The core hospital system, CRIS, went live and the legacy system was retired.
2005	1. Implement a surgery and anesthesia management system.	1. (FY03) No current system exists	1. (MET) Surgery and anesthesia management system implemented; project is on task and within budget.
	2. Implement a clinical data warehouse.	2. (FY03) No trans-NIH clinical data warehouse currently exists	2. (MET) Implemented a clinical data warehouse; project is on task and within budget.
2006	1. Integrate clinical systems across the NIH Clinical Center. *Previous Target:* Integrate clinical systems across the NIH to eliminate redundancy.	1. (FY04) Multiple clinical systems exist, but information is not retrievable in a central system.	1. Performance results will be reported in February 2007.
2007	1. Integrate clinical research systems across the NIH Clinical Center. *Previous Target:* Integrate clinical care systems such as EKG, Echocardiograms.	1. (FY 05) The CRIS vision is to integrate all systems providing clinical data. Integration requires complex technical solutions based on HL7 standards.	1. Performance results will be reported in February 2008.

Data Source & Validation:	(Target 1) Full documentation of the project, including a detailed workplan, weekly progress reports, extensive background material (including existing process analyses), and change management logs are available from the DCRI Project Management Office. Contact: Elaine Ayres Center for Information Technology (301)-594-3019 (Target 2) All documents, including meeting minutes, interim reports, and the final report from the CRIS Steering Committee subcommittee to develop CRDW requirements are available from the CRIS project office. The draft RFP is also available from the CRIS project office. Contact: Elaine Ayres Center for Information Technology (301)-594-3019
Cross Reference:	PMA-4, PMA-3, 1HHS-01, 1HHS-05, SP-5.1, SP-5.2, SP-5.5, SP-8.5, 500D-A7, Output

CBRR - 4	Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic Research Administration (eRA) system. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. (Target 1) Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership[1]	1. (FY99) No institutions using electronic reporting	1. (MET) Electronic reporting available to the 65 FDP participating institutions.
	2. (Target 2) Begin pilot-testing of progress reporting for multi-project mechanisms.	2. (FY99) 14 simple competing grant applications received	2. (EXT) XML development needed. Extended to 2007.
2004	1. (Target 1) Expand availability of electronic progress reporting to all grantee institutions	1. (FY02) 145 FDP institutions given access to electronic reporting.	1. (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.
	2. (Target 2) Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	2. FY03) Need for system to conform with OMB/Federal Enterprise Architecture	2. (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.
	3. (Target 3) Develop plan to integrate OPDIV's	3. No plans in place for OPDIV Integration.	3. (MET) eRA has developed plans for adding the FDA and components of the CDC.
2005	1. (Target 1) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. Goals: FY05 – 50% of eligible HHS OPDIV's FY06 – 100% of eligible HHS OPDIV's	1. Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's AHRQ and CDC/NIOSH	1. (MET) The Target was exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) are using eRA to process new grants.
	2. (Target 2) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 – 25% electronic business processing FY06 – 40% electronic business processing FY07 – 55% electronic business processing	2. 10% of business processes being done electronically	2. (MET) Approximately, 33% of business processes & financial status reports are done electronically.
	3. (Target 3) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 – 50% code conversion FY06 – 75% code conversion FY07 – 100% code conversion	3. (FY03) Migration plan developed. Current architecture is client-server mix with web	3. (MET) 60%of the code has been converted. This efficiency was accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.
2006	1. (Target 1) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006.	1. Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIVs, AHRQ and	1. Performance results will be reported in February 2007.

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

	Goals: FY05 – 50% of eligible HHS OPDIV's FY06 – 100% of eligible HHS OPDIV's	CDC/ NIOSH	
	2. (Target 2) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 – 25% electronic business processing FY06 – 40% electronic business processing FY07 – 55% electronic business processing	2. 10% of business processes being done electronically	2. Performance results will be reported in February 2007.
	3. (Target 3) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 – 50% code conversion FY06 – 75% code conversion FY07 – 100% code conversion	3. (FY03) Migration plan developed. Current architecture is client-server mix with web	3. Performance results will be reported in February 2007.
2007	1. (Target 2) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 – 25% electronic business processing FY06 – 40% electronic business processing FY07 – 55% electronic business processing	1. 10% of business processes being done electronically	1. Performance results will be reported in February 2008.
	2. (Target 3) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 – 50% code conversion FY06 – 75% code conversion FY07 – 100% code conversion	2. (FY03) Migration plan developed. Current architecture is client-server mix with web	2. Performance results will be reported in February 2008.
Data Source & Validation:	All project performance metrics and associated communications are stored in the eRA project database. Contact: Thomas Boyce Interim eRA Program Manager Office of Extramural Research and Reports Management (301)-594-4490		
Cross Reference:	PMA-4, 1HHS-16, SP-8.5, Efficiency, Output		

CBRR - 5	By 2007, expand by 15,000 the pool of researchers and clinicians NIH has trained in biomedical informatics, bioinformatics, or computational biology.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY04) 6,134 people received short-term training in informatics or computational biology.	1. (MET) NIH provided short-term training for 8,716 people in informatics or computational biology.
	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY04) 267 trainees enrolled in pre- or post-doctoral training in informatics or computational biology.	2. (MET) NIH enrolled 365 people in pre or post-doctoral training in informatics or computational biology.
2006	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY05) Determined by FY05 results.	1. Performance results will be reported in February 2007.

	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY05) Determined by FY05 results	2. Performance results will be reported in February 2007.
2007	1. (Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	1. (FY06) Determined by FY06 results	1. Performance results will be reported in February 2008.
	2. (Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	2. (FY06) Determined by FY06 results	2. Performance results will be reported in February 2008.
Data Source & Validation:	(Target 1) Each IC compiles and tracks these activity statistics separately, as these activities are not grant projects and, hence, are not available via IMPAC. Contact: Valerie Florance, Deputy Director for Extramural Programs at the National Library of Medicine. (Target 2) There are IMPAC records for grants awarded in the F and K series. For institution based training, NIH requires funded institutions to provide annual records of the number of enrollees in each program as part of their annual progress reports. Contact: Valerie Florance, Deputy Director for Extramural Programs at the National Library of Medicine.		
Cross Reference:	HP-23, 1HHS-05, 1HHS-15, SP-4.3, Output		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$1,612	$1,623	$1,667

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

SMHC - 3	Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the agency's programmatic objectives and projected future needs. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	1. (FY01) NIH Workforce plan, June 2001	1. (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.
	2. (Target 2) Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.	2. (FY02) Administrative Restructuring Advisory Committee	2. (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.
2005	1. (Target 1) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	1. Practices related to recruitment, retention and succession planning	1. (MET) Methods were implemented that addressed recruitment, retention and succession planning for key IRP positions.
	2. (Target 2) Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	2. Practices related to recruitment, retention and succession planning	2. (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.
2006	1. (Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.	1. (FY04) Performance indicators to be determined from FY 2005 results	1. Performance results will be reported in February 2007.
	2. (Target 2) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)	2. (FY04) Performance indicators to be determined from FY 2005 results	2. Performance results will be reported in February 2007.
2007	1. (Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.)	1. (FY 04) Performance indicators to be determined from FY 2006 results	1. Performance results will be reported in February 2008.
	2. (Target 2) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program.	2. (FY 04) Performance indicators to be determined from FY 2006 results	2. Performance results will be reported in February 2008.
	3. (Target 3) Establish performance indicators with baselines related to recruitment, development and succession planning for the NIH Extramural Research Program.	3. Performance indicators to be determined from FY 2006 results	3. Performance results will be reported in February 2008.
Data Source & Validation:	Data Source & Validation: OIR Website, OIR Mentoring and Training Guide Contact: Dan Dupuis, Acting Deputy Director Office of Strategic Management Planning (301)-402-0622		
Cross Reference:	PMA-1, HP-23, 1HHS-02, SP-8.2, Output		

SMHC - 4	Ensure that NIH commercial functions are performed as efficiently and cost-effectively as possible by conducting competitive sourcing reviews on the required number of functions within the agency's commercial inventory. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.
2004	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Nine streamlined and two standard studies conducted in FY 2004.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. (MET) Career transition services provided for out-placed staff as a result of competitive assessments/studies.
2005	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. (MET) Thirteen streamlined and one standard studies conducted in FY 2005.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. (MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. (MET) Career transition services were provided to employees displaced.
	4. (Target 4) Evaluate transition services provided to employees.	4. (FY03) Career transition services provided to employees impacted by one of the FY 2003 studies	4. (MET) Evaluation conducted during FY 2005.
2006	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2007.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. Performance results will be reported in February 2007.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. Performance results will be reported in February 2007.
	4. (Target 4) Evaluate transition services provided to employees.	4. (FY03) Career transition services provided to employees impacted by one of the FY 2003 studies	4. Performance results will be reported in February 2007.
2007	1. (Target 1) Identify annually commercial activities for competitive sourcing comparison.	1. (FY02) Preplanning initiated for identifying functional areas	1. Performance results will be reported in February 2008.
	2. (Target 2) Complete negotiated competitive sourcing reviews annually.	2. (FY02) Functional areas identified as appropriate for review	2. Performance results will be reported in February 2008.
	3. (Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.	3. (FY03) Transition plans developed for employees	3. Performance results will be reported in February 2008.
	4. (Target 4) Evaluate transition services provided to employees.	4. (FY03) Career transition services provided to employees impacted by one of the FY 2003 studies	4. Performance results will be reported in February 2008.
Data Source & Validation:	The validation information is located at the website for the Federal Business Opportunities (www.fedbizopps.gov) and included in the NIH Competitive Sourcing Report that is sent to the Department of HHS on a quarterly basis. December 2005 report from the NIH Office of Strategic Management Planning.		
Cross Reference:	PMA-2, PMA-3, 1HHS-02, 1HHS-04, SP-8.3, SP-8.4, Efficiency, Output		

SMHC - 5	Improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	1. (FY04) Multiple means of access to HR systems; multiple websites for HR information and resources.	1. (MET) Developed HR Community on the NIH Portal as primary site for accessing HR information and resources
	2. (Target 2) Identify HR critical elements and tools to monitor use and quality of the HR information.	2. Inconsistent quality and currency of HR information.	2. (MET) Worked with CIT to evaluate products for measuring usage of HR information on HR Community Portal.
2006	1. (Target 3) Establish baselines for the HR critical elements to monitor over time.	1. (FY05) HR critical elements and tools identified.	1. Performance results will be reported in February 2007.
	2. (Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information.	2. (FY05) HR Community established.	2. Performance results will be reported in February 2007.
2007	1. (Target 5) Implement corrective strategies with subject matter experts and customers.	1. (FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.	1. Performance results will be reported in February 2008.
Data Source & Validation:	(Target 1) Human Resources Community on the NIH Portal – http://hr.od.nih.gov/hrcommunity.htm> (NIH Only) Informational page - http://hr.od.nih.gov/ehr/portal.htm Article for the OIT Newsletter - http://oit.od.nih.gov/pubs/crm/Spring05Newsletter.pdf (Target 2) Portal Interaction Analytics – http://my.nih.gov> Portal Info Center (NIH Only) Informational page (about the product) - http://www.plumtree.com/products/analytics/		
Cross Reference:	PMA-4, 1HHS-02, SP-8.5, Efficiency, Output		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$5	$5	$5

PROGRAM OVERSIGHT AND IMPROVEMENT

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

POI - 2	Utilize performance-based contracting (PBC). (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	1. (FY02) $207 million projected for contracted work with requirements tied to performance	1. (MET) Obligated $557 million of eligible service contracting dollars through performance-based contracting.
2004	1. Obligate 40% of eligible service contracting dollars through PBC.	1. Obligate 40% of eligible service contracting dollars through performance-based contracting	1. (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.
2005	1. Obligate 40% of eligible service contracting dollars through PBC.	1. Obligate 40% of eligible service contracting dollars through performance-based contracting	1. (MET) Obligated 44% of eligible service contracting dollars through performance-based contracting.
2006	1. Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	1. FY 2006 OMB/OFPP Goal	1. Performance results will be reported in February 2007.
2007	1. Obligate the FY 2007 OMB/OFPP goal of eligible service contracting dollars to PBC.	1. FY 2007 OMB/OFPP Goal	1. Performance results will be reported in February 2008.
Data Source & Validation:	Obligations to PBC eligible service contracts as reported in the DCIS. These obligations were reported throughout the fiscal year as monies were committed to various contracts throughout NIH. Contact: Shirley Mizzell Acting Director, Division of Acquisition Policy and Evaluation Office of Acquisition Management and Policy Phone (301)496-6014		
Cross Reference:	PMA-5, PMA-1, 1HHS-06, SP-8.4, Output		

POI - 4	By 2005, ensure proper stewardship of public funding for research.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2003	1. Conduct five proactive compliance site visits.	1. (FY02) Criteria in place for selecting institutions for site visits	1. (MET) Five proactive compliance site visits conducted.
	2. Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.	2. (FY03) Framework in place for risk assessment	2. (MET) Initial risk assessment of 35 grants administration policies performed; ten policies selected for compliance review.
	3. Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.	3. (FY02) Web site in place for grants compliance and oversight under the Office of Extramural Research	3. (MET) Internet-accessible resource information posted on enhancing institutional compliance programs.
2004	1. Begin internal compliance reviews.	1. (FY03) Ten policies selected for compliance reviews	1. (MET) Compliance reviews grants-administration policies were initiated.
2005	1. Implement recommendations from the internal compliance reviews held in 2004. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research.	1. (FY04) Completed compliance reviews	1. (MET) Recommendations from the internal compliance reviews held in 2004 were implemented.
Data Source & Validation:	Contact: Susan Kauble Asst Grant Compliance Officer Office of Policy for Extramural Research Administration Phone (301) 451-4351		
Cross Reference:	PMA-5, 1HHS-05, SP-8.2, SP-8.4, SP-8.6, Output		

POI - 5	By FY 2010, enhance NIH's ability to demonstrate benefits resulting from extramural research investments through changes to policy and information systems.		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2007 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI.	1. In FY 2004, all research grants had only one Principal Investigator	1. (MET) Addressed signature and regulatory issues, and develop plans for application forms and data systems associated with multiple PIs.
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) – Mock Pilot 424-R&R forms using "dead data" to assess utilization of common data sets. (FY06) – Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) – Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements.	2. Paper grant applications currently received	2. (MET) A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use.

	3. (Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) – Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) – Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	3. (FY 04) No mechanism exists to receive manuscripts	3. (MET) NIH developed and launched the NIHMS system was May 2, 2005.
2006	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2007 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI.	1. To be determined by FY05 results	1. Performance results will be reported in February 2007.
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) – Mock Pilot 424-R&R forms using "dead data" to assess utilization of common data sets. (FY06) – Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) – Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements.	2. To be determined by FY05 results	2. Performance results will be reported in February 2007.
	3. (Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) – Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) – Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	3. To be determined by FY05 results	3. Performance results will be reported in February 2007.
2007	1. (Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2007 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of	1. To be determined by FY06 results	1. Performance results will be reported in February 2008.

	forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI.		
	2. (Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) – Mock Pilot 424-R&R forms using "dead data" to assess utilization of common data sets. (FY06) – Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) – Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements.	2. To be determined by FY06 results	2. Performance results will be reported in February 2008.
Data Source & Validation:	The July 7, 2005 issue of Inside eRA for Partners references the NIH-Grants.gov testing (http://era.nih.gov/eranews/eRAAllArticles.cfm?newslettertype=Partner&newsletterID=1E66D925-C038-4076-AC0B8E51B327C52B) and specifically reports on the pilot. Contact: Michael Goodman 301-435-1286		
Cross Reference:	1HHS-16, SP-8.5, Output		
POI - 6	Provide responsible stewardship over existing federally owned real property assets. (Ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY04) CIwa = 85 (FY05) CIwa = 85	1. (MET) The condition of the portfolio was maintained so that the average CI was 85.
	2. (Target 2) By 2010, not less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%) FY09 (target = 93.0%) FY10 (target = 95.0%)	2. (FY04) 86.0% (FY05) 87.0%	2. (MET) 86% of occupied GSF had a CI greater than 65.
2005	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY04) CIwa = 85 (FY05) CIwa = 85	1. (MET) The condition of the portfolio improved so that the average CI for 2005 was 87 which met and exceeded the 2005 target of 85.
	2. (Target 2) By 2010, not less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%) FY09 (target = 93.0%) FY10 (target = 95.0%)	2. (FY04) 86.0% (FY05) 87.0%	2. (MET) 87% of the occupied space had a CI greater than 65.
2006	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY04) CIwa = 85 (FY05) CIwa = 85	1. Performance results will be reported in February 2007.
	2. (Target 2) By 2010, not less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%)	2. (FY04) 86.0% (FY05) 87.0%	2. Performance results will be reported in February 2007.

	FY07 (target = 90.0%) FY08 (target = 91.5%) FY09 (target = 93.0%) FY10 (target = 95.0%)		
2007	1. (Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	1. (FY04) CIwa = 85 (FY05) CIwa = 85	1. Performance results will be reported in February 2008.
	2. (Target 2) By 2010, not less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%) FY09 (target = 93.0%) FY10 (target = 95.0%)	2. (FY04) 86.0% (FY05) 87.0%	2. Performance results will be reported in February 2008.
Data Source & Validation:	Vanderweil Facility Advisory (VFA) Inc. facility summary website (http://nih.vfafacility.com) for the NIH Contact: Clarence Dukes Program Manager, Federal Programs Office of Research Facilities, Division of Policy and Program Assessment (301) 496-5078		
Cross Reference:	PMA-5, SP-8.4, Efficiency, Output		

POI - 7	Manage design and construction of capital facility projects funded by the Building and Facilities Appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the approved budget. (Ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2004	1. (Target 1) Manage all B& F line item projects so they are completed within 100% of the final approved project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) TBD active projects (FY07) TBD active projects	1. (FY04) 19 active projects (FY05) 21 active projects	1. (MET) All 19 projects were managed within the approved budget.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) TBD (FY07) TBD	2. (FY04) ≤ 2 (FY05) ≤ 2	2. (MET) No projects required scope adjustments.
2005	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21active projects (FY06)TBD active projects (FY07) TBD active projects	1. (FY04) 19 active projects (FY05) 21 active projects	1. (MET) All twenty-one (21) projects were managed within the approved budget.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) TBD (FY07) TBD	2. (FY04) ≤ 2 (FY05) ≤ 2	2. (MET) All projects were managed within the approved scope.
2006	1. (Target 1) Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21active projects (FY06)TBD active projects (FY07) TBD active projects	1. (FY04) 19 active projects (FY05) 21 active projects	1. Performance results will be reported in February 2007.
	2. (Target 2) No more than 10% of the	2. (FY04) ≤ 2	2. Performance results will be reported in

	projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) TBD (FY07) TBD	(FY05) ≤ 2	February 2007.
2007	1. Manage all B&F line item projects so they are completed within 100% of the final approved total project cost. (FY04) 19 active projects (FY05) 21active projects (FY06)TBD active projects (FY07) TBD active projects	1. (FY04) 19 active projects (FY05) 21 active projects	1. Performance results will be reported in February 2008.
	2. (Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) TBD (FY07) TBD	2. (FY04) ≤ 2 (FY05) ≤ 2	2. Performance results will be reported in February 2008.
Data Source & Validation:	GPRA Capital Portfolio Performance Reports: DPPA database Contact: Clarence Dukes Program Manager, Federal Programs Office of Research Facilities, Division of Policy and Program Assessment (301) 496-5078		
Cross Reference:	PMA-5, 1HHS-12, SP-8.4, Output		

POI - 8	Protect NIH's interest in real property supported under the extramural construction grant program throughout each phase of the project. (ongoing)		
FY	**MEASURES/TARGETS**	**BASELINE**	**RESULTS**
2005	1. (Target 1) Meet 100% of pre-award requirements for construction grants or implement corrective strategies. • Ensured the Availability of Matching Funds, when applicable • Ensured Compliance with Public Policy Requirements • Ensured Sufficient Title to Site	1. No. of Awards: (FY05) 21 issued (FY06) TBD (FY07) TBD	1. (MET) 100% of awards met the pre-award requirements or are implementing corrective strategies.
	2. (Target 2) For projects under construction, have met 100% of award requirements or implement corrective strategies. • Approved Design and Construction Documents • Ensured the Notice of Federal Interest has been Recorded	2. No. of Projects: (FY05) 35 active (FY06) TBD (FY07) TBD	2. (MET) 100% of projects under construction met the award requirements or are implementing corrective strategies.
	3. (Target 3) Meet 100% of post-award compliance measures, as defined by NIH Policies and Procedures, for completed construction grant projects or implement corrective strategies. • Ensured Adequate Protection Against Physical Destruction • Monitored the Use of Grant-supported Space	3. No. of Projects occupied in past 20 years: (FY05) 322 active (FY06) TBD (FY07) TBD	3. (MET) 100% of projects completed in the past 20 years met the post-award requirements or are implementing corrective strategies.
2006	1. (Target 1) Meet 100% of pre-award requirements for construction grants or implement corrective strategies. • Ensured the Availability of Matching Funds, when applicable • Ensured Compliance with Public Policy Requirements • Ensured Sufficient Title to Site	1. No. of Awards: (FY05) 21 issued (FY06) TBD (FY07) TBD	1. Performance results will be reported in February 2007.
	2. (Target 2) For projects under construction, have met 100% of award requirements or implement corrective strategies.	2. No. of Projects: (FY05) 35 active (FY06) TBD (FY07) TBD	2. Performance results will be reported in February 2007.

	• Approved Design and Construction Documents • Ensured the Notice of Federal Interest has been Recorded		
	3. (Target 3) Meet 100% of post-award compliance measures, as defined by NIH Policies and Procedures, for completed construction grant projects or implement corrective strategies. • Ensured Adequate Protection Against Physical Destruction • Monitored the Use of Grant-supported Space	3. No. of Projects occupied in past 20 years: (FY05) 322 active (FY06) TBD (FY07) TBD	3. Performance results will be reported in February 2007.
2007	1. (Target 1) Meet 100% of pre-award requirements for construction grants or implement corrective strategies. • Ensured the Availability of Matching Funds, when applicable • Ensured Compliance with Public Policy Requirements • Ensured Sufficient Title to Site	1. No. of Awards: (FY05) 21 issued (FY06) TBD (FY07) TBD	1. Performance results will be reported in February 2008.
	2. (Target 2) For projects under construction, have met 100% of award requirements or implement corrective strategies. • Approved Design and Construction Documents • Ensured the Notice of Federal Interest has been Recorded	2. No. of Projects: (FY05) 35 active (FY06) TBD (FY07) TBD	2. Performance results will be reported in February 2008.
	3. (Target 3) Meet 100% of post-award compliance measures, as defined by NIH Policies and Procedures, for completed construction grant projects or implement corrective strategies. • Ensured Adequate Protection Against Physical Destruction • Monitored the Use of Grant-supported Space	3. No. of Projects occupied in past 20 years: (FY05) 322 active (FY06) TBD (FY07) TBD	3. Performance results will be reported in February 2008.
Data Source & Validation:	Hardcopy documentation with signatures from grantees. Contact: Patricia Newman National Center for Research Resources Office of Science Policy & Public Liaison (301) 435-0866 PNewman@mail.nih.gov		
Cross Reference:	PMA-5, 1HHS-16, Output		

FULL COST(dollars in millions)	FY05	FY06	FY07
	$328	$173	$166

Data Limitations Affecting Performance Targeting or Reporting

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

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

- Research outcomes are challenging to predict with a high degree of accuracy, but can be captured in many cases with milestones of progress toward the goal. Although outcomes may encompass the

proposed hypothesis, unplanned results such as serendipitous discoveries and findings that narrow the avenue of the research focus (elimination discoveries) can be just as significant.

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

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

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

GPRA Performance Goal Narratives By Five Functional Areas:

SCIENTIFIC RESEARCH OUTCOMES

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

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

The vastness of the NIH portfolio presents a challenge in terms of articulation of goals. NIH has selected 28 specific, representative research goals, as proxies for performance on the larger, research portfolio. The goals were selected based on the following criteria:

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

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

NIH GPRA SCIENTIFIC RESEARCH OUTCOMES GOALS MATRIX

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
High	**1.1** By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin. **1.2** By 2006, develop one or more prototypes for a low-power, highly directional hearing aid microphone to help hearing-impaired persons better understand speech in a noisy background. **1.2.3** By 2006, develop methods that can classify at least 75% of proteins from sequenced genomes according to evolutionary origin and biological structure.	**2.2** By 2009, evaluate the efficacy of two novel approaches to prevent weight gain and/or treat obesity in clinical trials in humans. **2.3.2** By 2010, develop one universal antibiotic effective against multiple classes of biological pathogens. **2.3.4** By 2010, develop an HIV/AIDS vaccine. **2.4** By 2009, develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress to reduce related symptom burden and to increase functional status and quality of life.	**3.1** By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease (AD). **3.2.1** By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials. **3.3** By 2013, determine the efficacy of using salivary diagnostics to monitor health and diagnose at least one systemic disease. **3.5** By 2013, identify and characterize at least 2 human candidate genes that have been shown to influence risk for substance use disorders and risk for psychiatric disorders using high-risk family, twin, and special population studies. **3.6** By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.
Medium	**4.2** By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.	**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,	**6.1** By 2012, identify the genes that control the risk of development of age-related macular degeneration (AMD) and glaucoma in humans. **6.3** By 2012, develop a

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
	4.5.1 By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in clinical trials in an effort to identify agents or combinations of agents that are more effective, less toxic, and/or simpler to use than the current recommended HIV treatment regimens. **4.5.4** By 2007, identify 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools. **5.5** By 2008, develop and test two new evidence-based treatment approaches for drug abuse in community settings.	analyze, and utilize chemical libraries, which can be used to discover new medications. Specifically, use these chemical libraries to discover 10 new and unique chemical structures that could serve as the starting point for new drugs. **5.6** By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction. **5.7** By 2010, validate and compare 3 imaging methods that could offer increased sensitivity over computed tomography (CT) as a means of assessing lung cancer response to therapy. **5.8** By 2011, improve device(s) to measure hot flashes and test in clinical studies of hot flash therapies. **5.9** By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations. **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.	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.
Low	**7.2** By 2006, integrate nanotechnology-based components into a system capable of detecting specific biomarkers (molecular signatures) to establish proof of concept for a new approach to the early detection of cancer and, ultimately, cancer preemption. **7.3** By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes. **7.8.1** By 2007, determine the genome sequences of an additional 45 human pathogens and 3 invertebrate vectors of infectious diseases. **7.8.3** By 2006, build a publicly accessible Collection of Reference Sequences (RefSeq Collection) to serve as the basis for medical, functional, and diversity studies. A comprehensive RefSeq Collection will serve as a foundation for genomic research by providing a centralized, integrated, non-redundant set of sequences, including genomic deoxyribonucleic acid (DNA), ribonucleic acid (RNA)	**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	

Risk	1-3 YEARS	4-6 YEARS	7-10 YEARS
	transcript, and proteome (protein product) sequences, integrated with other vital information for all major research organisms.	and Nutrition Examination Survey (NHANES). **8.9.1** By 2010, demonstrate through research a capacity to reduce the total years lost to disability (YLDs) in the United Sates by 10% by (1) developing treatment algorithms to improve the management of treatment-resistant and recurrent depression and (2) elucidating the mechanisms by which depression influences at least two comorbid physical illnesses (e.g., heart disease, cancer, Parkinson's disease, or diabetes). **8.9.2** By 2010, identify culturally appropriate, effective stroke prevention programs for nationwide implementation 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.	

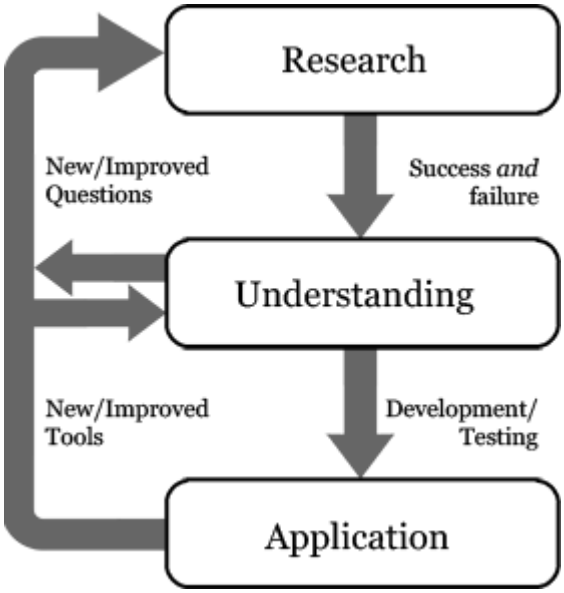
The matrix of goals selected by NIH reflects the challenges of complex biological systems. They range across a continuum of low to medium to high risk, and they have a corresponding timeline for achievement (i.e., 1-3 years, 4-6 years, and 7-10 years, respectively). For example, the NIH portfolio includes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

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

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

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

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



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

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

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

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The target to test antalarmin for relapse prevention in alcoholics is being extended to 2007. For the drug antalarmin, the FDA requires further toxicology studies before approving the Investigational New Drug application. The toxicology studies are being contracted out and will begin shortly. They are expected to be completed by the end of 2006.

Implementation Strategy Advances or Other Highlights

Clinical trials of rimonabant are continuing and on schedule. No problems have been encountered with this project.

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

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

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target has been MET because NIH-supported scientists successfully combined the diaphragm and circuitry into a directional microphone. This directional microphone mimics the auditory system of the parasitic fly Ormia ochracea. The fly's system is an excellent model to imitate because its mechanically coupled ears enable it to detect the direction of sound and because it suggests a way to miniaturize a microphone for use in hearing aids. The scientists used silicon microfabrication technology to make a directional microphone that is small enough to be potentially incorporated into a hearing aid. The directional microphone developed in FY 2005 will ultimately help hearing aid users to better understand speech in a noisy background, such as in a crowded room.

Implementation Strategy Advances or Other Highlights

The primary advances made during FY 2005 include the successful demonstration of an optical sensing scheme that provides an electronic signal that is proportional to the displacement of the directional microphone diaphragm as it responds to sound. This system has been demonstrated using a large-scale bench-top setup. In addition, a miniature version of the optical sensor electronics has been fabricated and demonstrated with a simple, nondirectional microphone diaphragm. The sensor electronics utilize a semiconductor laser and photodetectors that have been integrated onto a 1.5mm by 1.5mm chip. While the current version of the sensor electronics does not yet meet the project power consumption specifications, it demonstrates that significant progress has been made toward miniaturizing the system.

PART

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

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

BACKGROUND

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Production and maintenance of a classification database demand intensive intellectual effort and sophisticated computational and visualization tools. One such tool under development will interactively link displays of evolutionary sequence trees, the taxonomic "tree of life," and ancient recombination history as inferred from protein domain architecture to facilitate assignment of protein domains into useful subgroups. Other computerized procedures will update structure-based alignments and hierarchies of

conserved domains by automatically scanning the PubMed database of biomedical journal literature and identifying new structures, sequences, and citations. In FY 2004 and FY 2005, 1,000 domain families were curated and coverage reached the 75 percent goal at the end of FY 2005.

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

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET in two ways: (1) The "CDTree" software system for molecule evolutionary classification was further developed to implement all original design goals and (2) The Conserved Domain Database curator team was brought to a strength of 16 biologists, with intensive training for newly appointed team members. Together, these efforts enabled the team to produce a total of 2,814 expertly curated protein domain family models. The entries in the CDD now cover an estimated 45% of PubMed sequences and with the first generation alignments, an estimated 75% of PubMed sequences.

Implementation Strategy Advances or Other Highlights

During the course FY 2005 NIH has identified and partially implemented software features that make domain family curation more efficient. One is to streamline the "update" utilities within the "CDTree" package, which the curation team uses to identify and incorporate newly determined sequences and/or structures. Updates can now be done interactively, and optionally focused on portions of the family hierarchy selected by the curator, allowing them to concentrate on new and/or modified subfamilies. Another feature the team has incorporated into the "Cn3D" software is an algorithm for automated refinement of sequence/structure alignments. NIH has found that this procedure improves alignments, in some cases significantly. Now that nearly 3000 domains have been curated, it has also become apparent that earlier classification projects seriously underestimated the number of subfamilies with distinct function. In identifying these subfamilies by molecular evolutionary methods CDD thus achieves a greater "depth" of detailed functional annotation. This is accomplished efficiently only by means of the "CDTree" and "Cn3D" software tools, which largely automate the tasks of ancient subfamily identification and alignment.

Efficiency

NIH curated 2,814 protein domain family models in FY 2005, a 12% increase over the target number of 2,500. This efficiency was largely achieved through enhancements in the "CDTree" software system.

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 65 percent of U.S. adults are overweight or obese; nearly 31 percent of U.S. adults are obese.
- About 16 percent of children and teenagers ages 6 through 19 are overweight, with ominous implications for our Nation's future health.
- Racial and ethnic minority populations are disproportionately affected by obesity, particularly African American, Hispanic American, and American Indian women and children.

Disease Burden

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

In addition to these research efforts, in April 2003 the NIH Director Dr. Elias Zerhouni established the NIH Obesity Research Task Force as a new effort to accelerate progress in obesity research across the NIH. The Task Force is co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases and by the Acting

Director of the National Heart, Lung, and Blood Institute. Currently over twenty different NIH components (Institutes, Centers, and Offices; ICs) are represented on the Task Force. A key element of the NIH Director's charge to the Task Force is the development of a Strategic Plan for NIH Obesity Research. The purpose of the Strategic Plan is to provide a guide for coordinating obesity research activities across the NIH and for enhancing the development new research efforts based on identification of areas of greatest scientific opportunity and challenge. The Strategic Plan was developed with input from external experts through interactions with NIH staff at scientific meetings; through meetings and workshops convened by NIH ICs for the purpose of obtaining research planning advice; through presentations by the co-Chairs of the Task Force to external scientific and health advocacy organizations; through solicitation of comments from scientists and leaders of voluntary and professional health advocacy organizations on a draft of the Strategic Plan; and, subsequently, through posting of a revised draft on the Web for a public comment period. The Strategic Plan for NIH Obesity Research was published in August 2004.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. NIH scientists expanded and randomized a total of 73 children with hyperinsulinemia in a study to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years. Approximately 2,500 letters were mailed to pediatricians, family physicians, and nurse

practitioners in the tri-state area informing them about the study. Accompanying the letters were magnets displaying the contact phone numbers and the basic eligibility criteria.

Implementation Strategy Advances or Other Highlights

In response to the lack of studies examining therapeutic drugs to aid behavioral therapy for weight control in young children, NIH intramural scientists studying growth and obesity are conducting a study to determine whether a promising medication, metformin, may be used for weight reduction in overweight children. The FY2005 Performance Target of enrolling 60 children in the metformin study was efficiently met, actually enrolling a total of 73 children by September 30, 2005.

In an effort to accelerate research in lifestyle-based approaches to obesity prevention, the NIH developed and released an initiative entitled "Site Specific Approaches to Prevention or Management of Pediatric Obesity". In response to the initiative, over one hundred applications were submitted and three were selected as scientifically meritorious and funded.

Efficiency

NIH scientists succeeded in enrolling 73 children, 13 greater than the target number of 60 enrollees, to test the hypothesis that metformin is superior to placebo for the treatment of overweight children ages 6 to 12 years.

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

BACKGROUND

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

Program to develop a small molecule repository and PubChem database, a Molecular Screening Centers Network, and to support the development of screening tools and new assays for high-throughput screening. NIH will continue to support interagency and public-private collaborative research projects to develop new antimicrobial strategies.

Through activities such as the Metagenomic Analyses of the Oral Microbiome Program, NIH plans to support genomics research to identify and characterize bacteria that cannot be grown under laboratory conditions. Such analysis may lead to the identification of new targets for antibiotics against bacterial pathogens whose involvement in infection was previously unknown and may identify strategies for targeting pathogenic microbes while preserving beneficial microbes. NIH also will continue to support research on bacteria found in microbial biofilms (aggregates of microbial cells on solid surfaces), which are 10- to 1000-fold less sensitive to antimicrobials than those that are not growing as biofilms.

In FY 2005, NIH requested a study by the National Academy of Sciences (NAS) to explore potential new directions in the study of antimicrobial therapeutics. As a part of this study, the NAS hosted two workshops in 2005: one on the potential targets within immunomodulatory/host-mediated response pathways that may yield broad spectrum antimicrobial therapies; and one on potential new classes of antimicrobials based on pathogen metabolic pathways. When completed, the findings of this study will provide insight into promising new avenues of research in the field of antimicrobial/antiinfective development.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

NIH MET the FY 2005 target of developing a set of screening tools to be used to evaluate potential compounds or classes of compounds for activity against both bacterial and viral pathogens. Prior to FY 2005, NIH did not have a complete set of screening tools that could be used for this purpose. Through the NIH In Vitro Antiviral Screening Program, NIH had developed a standardized group of assays that could be used to screen compounds for antiviral activity. However, a similar capacity to screen for antibacterial compounds did not exist. A group of in vitro assays to test the minimum inhibitory concentrations (MICs) of compounds for activity against six NIH Category A and B priority bacterial pathogens was developed under NIH contracts in FY 2005. This group of assays, in addition to the assays developed through the NIH In Vitro Antiviral Screening Program, now provides NIH with a set of tools that provide the ready capacity for testing of compounds for activity against both viral and bacterial infectious agents. Together, these antiviral and antibacterial screening activities are referred to as the NIH Pre-Clinical Antimicrobial Screening Programs. Having this broad antimicrobial screening capacity available will accelerate discovery of broad spectrum antimicrobials and provide a higher level of preparedness for public health emergencies which may require rapid, parallel screening of drugs/compounds against multiple infectious agents.

Implementation Strategy Advances or Other Highlights

In FY 2005, NIH continued to support the In Vitro Antiviral Screening Program, which has screened compounds using the tools and resources such as new methodologies, chemical libraries, and software tools.

NIH sponsored a study by the National Academy of Sciences (NAS) to generate ideas for innovative research approaches that would contribute to the development of new antimicrobial therapeutics. The report resulting from this study, 'Treating Infectious Diseases in a Microbial World,' suggests several promising new avenues of research that could revolutionize the field of antimicrobial/ antiinfective development, including exploration of the human natural microbiota and the innate and adaptive immune systems to find ways to modulate them to help fight infection, and exploration of metagenomics for gene products with antimicrobial activity. The report also suggests that development of new fine-tuned, rapid diagnostics, biomarkers of patient immune status, therapeutic vaccines and new vaccine adjuvants could provide important additions to the current arsenal of tools to fight infectious disease. Many of the novel approaches described in this report could be used as adjuncts to currently available antimicrobial therapies.

NIH also requested a study by the NAS to evaluate the potential role of metagenomic research in advancing our understanding of the role of microbes in health and disease. Metagenomics uses a culture independent approach to sequence all of the microbial genes in a niche, and then, using contemporary bioinformatics, evaluate the products of the genes and determine the microorganisms that carry those genes. The approach, if successful, will greatly increase discovery of antibiotic resistance and susceptibility of the totality of microbes on or in the body.

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

BACKGROUND

Prevalence/Incidence

The HIV/AIDS epidemic has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. In 2004, an estimated 40.3 million people worldwide, including 2.3 million children younger than 15 years of age were living with HIV/AIDS. In addition, over 3 million people died from AIDS in 2004, and approximately 5 million people were newly infected with HIV, of which 700,000 were children. The number of people living with HIV/AIDS has seen the steepest increases in East Asia, Eastern Europe and Central Asia. In the United States, at the end of 2003, an estimated 1,039,000 to 1,185,000 people were living with HIV/AIDS. Although in the United States new infections have remained relatively stable at approximately 40,000 per year, AIDS continues to climb among women and racial and ethnic minorities.

Disease Burden

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

Rationale

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

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

In 2003, NIH, began working with the Department of Defense (DoD) and the Royal Thai Government to conduct a Phase III trial of a recombinant canarypox vector vaccine candidate (ALVAC - vCP1521 from Aventis) combined with AIDSVAX B/E recombinant gp120 (from VaxGen) designed for use in Southeast Asia. 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. Significant additional resources will be required to support large-scale manufacture of new candidate vaccines and to conduct large efficacy trials to meet the 2010 goal.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has expanded and will continue to expand breeding and increase output of specific pathogen-free macaques at three or more primate centers for the preclinical testing of vaccine candidates. In addition, NIH will produce and test at least one new virus stock for challenge of vaccinated animals.

In FY 2004 NIH initiated four Phase I trials with the HIV Vaccine Trials Network (HVTN), [HVTN 044, HVTN 049, HVTN 052, HVTN 056] and two with the NIH Vaccine Research Center (VRC) [VRC 006 and VRC 007]. In addition, NIH initiated one Phase I trial in collaboration with the U.S. Military HIV Research Program (USMHRP) and one Phase I through an HIV Design and Development Team award. In FY 2004, NIH also advanced two vaccine candidates into Phase I/II clinical trials, the MRKAd5 gag product (HVTN 050) and the LIPO5 boost of the ALVAC-HIV (vCP1452) (HVTN 042). An estimated six to eight new candidate vaccines are slated to enter Phase I trials in the next two years; they will be produced (according to Good Manufacturing Practices) and tested pre-clinically with NIH funding. NIH will also prepare for and initiate one or two Phase II trials of new HIV vaccine candidates in the next two years, and one of those may be further advanced into a second Phase IIb 'proof of concept' efficacy trial. Such 'proof of concept' trials are designed to determine if the vaccine candidate is effective in either preventing HIV infection or in delaying or diminishing the course of HIV disease in those who do become infected as a result of high risk behavior.

To prepare for future large-scale clinical trials, NIH will compile seroincidence data from two to three sites that focus on populations of minorities in the United States, or on heterosexual transmission in either domestic or international settings, and develop key regional or national laboratories capable of evaluating the safety of candidate vaccines in resource-poor settings. These capacity-building efforts will include providing the necessary training of personnel and developing quality assurance/quality control programs for these activities.

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

PART

This goal was included in the FY 2005 PART of the HIV/AIDS Research Program. NIH continues to make progress toward achieving the HIV/AIDS Research Program goal: to develop an HIV/AIDS vaccine by 2010. The FY 2005 PART targets for achieving this

goal are as follows: 1) Expand breeding of non-human primates: three centers; 2) Test one new virus stock; 3) Test two vaccine candidates in animals; 4) Conduct Phase I human trials: one new vaccine candidate; 5) Compile seroincidence data: three sites; 6) Evaluate vaccine safety: two labs; 7) Initiate four Phases I and II vaccine trials; 8) Produce candidate vaccine for Phase III trials.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. NIH initiated five phase I trials for new products: three trials conducted by the NIH's HIV Vaccine Trials Network (HVTN), one trial conducted through a contract mechanism and one trial as a partnership with the DOD. NIH also initiated six phase I and one phase II trials to further assess existing products. The trials to incorporate new or improved concepts and designs were initiated through HVTN, the Vaccine Research Center (VRC), investigator-initiated grant programs and collaborations with DOD. In addition, NIH expanded its capacity to conduct clinical trials into eight new international settings.

NIH initiated five phase I trials for new products, including:

• a phase I study to evaluate simultaneous administration of two Modified Vaccinia Ankara (MVA)-vectored HIV vaccines as priming doses followed by boosting doses of two fowlpox-vectored HIV vaccines containing inserts identical to those in the MVA vectors (HVTN 055);
• a phase I study of an HIV-1 gag DNA vaccine with or without Interleukin-12 (IL-12)

DNA adjuvant, boosted with homologous plasmids or with HIV Cytotoxic T Lymphocyte (CTL) multi-epitope peptide vaccine RC529-SE, plus granulocyte-macrophage colony stimulating factor (GM-CSF) (HVTN 060);
• a phase I study evaluating HIV-1 gag DNA vaccine alone or with IL-15 DNA, boosted with HIV-1 gag DNA + IL-15 DNA, HIV CTL multi-epitope peptide vaccine or HIV gag DNA + IL-12 DNA (HVNT 063);
• a phase I study to evaluating a multigene, polyvalent HIV-1 DNA plasmid prime and Env protein boost in healthy volunteers was initiated through NIH's HIV Vaccine Design and Development Teams; and
• in collaboration with the USMHRP, NIH initiated a study to evaluate a live viral vector - recombinant MVA-Chiang Mai (Thailand) Double Recombinant (CMDR) vaccine administered intramuscularly (IM) or intradermally (ID) in uninfected adults (RV 158).

NIH initiated six phase I and one phase II trials to further assess existing products, including:

• a phase I dose escalation study to evaluate a multiclade, multivalent recombinant adenoviral vector HIV vaccine (HVTN 054);
• a phase I study evaluating the safety of a multiclade recombinant adenoviral vector HIV-1 vaccine administered to healthy, uninfected participants who received DNA plasmid vaccine or placebo in a previous study (HVTN 057);
• a study to assess the safety, tolerability and immunogenicity of a DNA vaccine prime followed by an adenovirus boost (VRC 008). This study will also examine whether injection of the DNA vaccine using a needle and syringe is similar in safety and immune response to the injection using a needleless device called a Biojector 2000;
• a study (VRC 009) to evaluate a booster dose of a recombinant multiclade HIV-1 adenoviral vector vaccine in healthy volunteers who received 3 injections of a DNA plasmid vaccine in a previous study, and
• a study of a multiclade HIV adenoviral vector as a booster in healthy adults (VRC 010);
• a study to evaluate a multiclade HIV-1 DNA plasmid vaccine in uninfected adult volunteers in Uganda (RV 156) in collaboration with the USMHRP; and
• a phase II study evaluating the safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, followed by a multiclade recombinant adenoviral vector HIV vaccine boost (HVTN 204).

In 2005, the HVTN also enrolled volunteers in recently established sites in Philadelphia, PA; Chicago, IL; and Blantyre, Malawi. New site development is also underway in Kingston, Jamaica; Lince, Peru; and five cities in South Africa: Klerksdorp, Orkney, Stilfontein, Hartesbeesfontein, and Capetown.

Implementation Strategy Advances or Other Highlights
HIV vaccine testing in animal models is an important step in determining whether or not a candidate vaccine will move into clinical trials. There are currently about 20 active studies involving approximately 350 macaques that are being carried out at three Simian Vaccine Evaluation Units (SVEU). Eight protocols were completed in the past year and new viral challenge stocks were tested. These studies will help determine optimal vaccine vectors based on recombinant alphavirus, rabies virus, poxvirus and adenovirus vectors and optimize DNA plasmid vaccines. The SVEUs have also begun assessing whether vaginal

viral loads can be detected in animals chronically infected with Simian Immunodeficiency Virus (SIV) and SHIV, a genetically engineered hybrid virus consisting of HIV and SIV.

NIH has several contract mechanisms that provide the support needed for small-scale research and Good Manufacturing Practice (GMP) production of experimental AIDS vaccines, preclinical testing – including laboratories capable of safety and toxicity testing, and documentation leading to investigational new drug (IND) submission for Phase I clinical testing in humans. Vaccine production projects supported through these contracts in FY 2005, include projects with Chiron (DNA and gp 140 protein), Epimmune (synthetic protein, DNA, and poxvirus), the University of Pennsylvania (DNA), the Institute of Human Virology (protein), Eurovac (DNA and poxvirus), and a consortium including the University of Cape Town and the South African AIDS Vaccine Initiative (SAAVI) (DNA plasmids and poxvirus vector).

A number of important awards were made in FY 2005 that will support various aspects of HIV vaccine research. Fifteen awards were made under the vaccine Innovation Grant Program in areas including; virus and bacterial vector design, T-cell immunology, adjuvant development, and improving envelope-based vaccines to induce broadly reactive neutralizing antibodies. Two contract awards were made under the HIV Vaccine Design and Development Teams that will examine recombinant adeno-associated virus-based vaccines (Children's Research Institute) and alphavirus replicon-based vaccines (Chiron Corporation).

In addition, an award was made during FY 2005 to establish the Center for HIV/AIDS Vaccine Immunology (CHAVI). CHAVI will support intensive and highly collaborative projects addressing key immunological roadblocks to the discovery and development of a safe and effective HIV vaccine as defined by the NIH and the Global HIV Vaccine Enterprise.

A number of vaccine clinical trials are currently in development. Through the HVTN, NIH has approximately six phase I studies in development (HVTN 061, HVTN 064, HVTN 065, HVTN 066, HVTN 067 and HVTN 068). NIH has one phase I/II in development in collaboration with the USMHRP (RV 172); two VRC studies (VRC 011), one of which is a therapeutic vaccine (VRC 101); and one phase I study in collaboration with the International AIDS Vaccine Initiative (IAVI) (IAVI V001).

RV 172 and IAVI V001, as well as HVTN 204 (which has already been initiated) all involve the VRC's muliclade, multigene DNA plasmid vector prime and adenoviral boost, which is the first multigene, multiclade HIV vaccine to reach phase II testing. This marks an important milestone in the search for a single vaccine strategy that targets U.S. subtypes of HIV as well as the majority of clades causing the global epidemic. The major components of all three studies are harmonized.

Efficiency

NIH exceeded the target of initiating four Phase I or Phase II trials. NIH initiated five trials of new products: three trials conducted by the HVTN, one trial conducted through a contract mechanism and one trial as a partnership with the DOD. NIH also was able to initiate seven trials (six Phase I and one Phase II) to assess existing products in larger

numbers, in combinations, in different risk populations, or by different routes of administration. This was possible because of the collaborative Partnerships for AIDS Vaccine Evaluation (PAVE) led by NIH and the streamlined efficiency for protocol development that was undertaken by the HVTN and NIH.

In addition to the international sites that began enrolling vaccine volunteers in late FY 2004, the HVTN enrolled volunteers in one new international site in Blantyre, Malawi. Training, seroincidence studies, and site evaluations have been initiated at 7 additional international trial sites in three countries: Jamaica (1), Peru (1) and South Africa (5). New sites in Peru and South Africa could provide additional enrollment sites within the same countries where HIV vaccine enrollment has been successful. New methodologies for seroincidence are being explored in field sites that may permit determination of seroincidence within a few months rather than a few years. NIH in collaboration with the USMHRP/DOD and the International AIDS Vaccine Initiative (IAVI) has expanded vaccine studies to Uganda (RV 156) and Rwanda (IAVI V001). NIH exceeded the target for conducting clinical trials in three new international settings because of improvements in its operations including streamlined protocol development and by conducting more trials at participating international sites than in previous years.

PART

NIH continues to make progress toward the HIV/AIDS Research Program goal: to develop an HIV/AIDS vaccine by 2010. NIH-sponsored basic research is continuing to provide crucial information necessary for the design and development of new and better vaccine candidates.

The PART annual targets for FY 2005 have been achieved: 1) Breeding of non-human primates (rhesus and pigtailed macaques) has been expanded at three centers to enable future research; 2) Several stocks of virus for animal challenge studies have been produced, and two were assessed in animals during FY 2005; 3) Studies of two new viral vectors as well as other candidate HIV vaccines are being tested in preclinical studies in animals that will continue for 1-2 years; 4) Conducted a phase I study to evaluate the safety of a multiclade recombinant adenoviral vector HIV-1 vaccine administered to healthy, uninfected participants who received DNA plasmid vaccine or placebo in a previous study (HVTN 057); 5) Seroincidence data are being collected at sites in Africa, China and the Caribbean; 6) Two vectored vaccines -- MVA and Fowlpox -- were tested for safety (absence of contaminating viruses) and toxicity (especially at the higher doses) as well as vector insert stability, in 2 different labs plus the lab in which they were manufactured; 7) Three new vaccine candidates were started Phase I trials in early 2005, and two additional new candidates also started Phase I trials by the end of the summer. 8) To save both time and money, NIH has shifted strategy such that HIV vaccine products do not move directly from phase II to very large phase III trials; rather, phase IIb trials are conducted as an interim step to determine if there is substantial efficacy. Thus, this PART goal was met through production of the VRC products for a large Phase IIb efficacy 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 allogenic bone marrow transplantation may develop stomatitis, an inflammation of the lining of the throat and mouth that may lead to ulcerations, mouth and throat pain, and decreased quality of life. Behavioral factors related to symptom burden also affect functional status and quality of life. Examples of behavioral factors include interventions used by patients and families to treat and manage physical and/or other issues resulting from symptoms. The investigation of biological mediating factors, as well as behavioral factors, need to be elucidated to provide the rationale for testing interventions targeted at increasing functional status and quality of life.

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET because an intramural collaboration was established that combines the disciplines of basic research with clinical research in the area of symptom distress/quality of life. The research approach combines state-of-the-art molecular biology and clinical patient experiences to understand the biological basis of fatigue, a factor in quality of life. These research efforts may provide the rationale for future studies of potential interventions.

Implementation Strategy Advances or Other Highlights

In 2005, a collaboration to understand the biological basis of fatigue was established. Also in 2005, clinical trials addressing cancer-related oral complications and oral pain remain open for patient enrollment. Research in these areas may contribute to the identification of interventions that reduce symptom or illness burden.

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

BACKGROUND

Prevalence/Incidence

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

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

Disease Burden

The cost of AD care varies by stage of the disease. In 1996 annual costs of caring for patients with mild, moderate, and severe AD were estimated as $18,408, $30,096, and $36,132, respectively. The national cost of caring for people with AD is now thought to be about $100 billion every year.

Rationale

In 1999, at the direction of Congress, NIH embarked on the Alzheimer's Disease Prevention Initiative. A major focus of this initiative is accelerating the movement of promising new treatments and prevention strategies into clinical trials.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH plans to accelerate discovery of new risk and protective factors and identify promising targets for treating and preventing disease through basic research. Initiatives will speed progress in identifying non-genetic risk and protective factors and genes associated with AD, including new risk factor genes and their interactions with the apolipoprotein E-4 risk factor gene in different populations. Advances in brain imaging will be another key factor in identifying the first brain regions affected prior to clinical diagnosis, when interventions could be most effective.

NIH also plans to speed drug discovery and movement of promising new treatments and prevention strategies into clinical trials. Neurobiologic and epidemiologic research will continue to pinpoint new targets for drug therapy, such as inflammatory processes and toxic oxidative agents known as free radicals. Advances in basic research and drug development are likely to include more effective anti-inflammatory and antioxidant compounds and other types of neuroprotective agents that can more effectively prevent

brain cell death and also substances designed to stop the deposition of amyloid plaques and neurofibrillary tangles in the brain.

Finally, NIH plans to expand strategies for improving patient care and alleviating caregiver burdens. Effective pharmacologic and non-pharmacologic methods to treat and manage cognitive and behavioral symptoms in AD patients could help prevent hospitalizations, decrease unscheduled visits to care providers, delay nursing home admission, delay progression to more intense levels of institutional care, avoid preventable illnesses unrelated to AD, and prevent caregiver burnout.

To date, only one risk factor gene for late onset AD has been identified, despite the intense interest in determining a genetic basis for this disease. The AD genetics initiative was started to develop much-needed resources for geneticists to find the additional key late onset genes; finding and recruiting about 1000 families will be necessary to establish a data base for studies of familial inheritance of AD - just one of the objectives for this resource. Families to be recruited must have at least three members who can donate blood, and need two or more siblings living with AD, which is quite rare and never before attempted for AD research. In addition to blood samples, participants will participate in interviews; agree to a medical record review; be contacted for annual updates; and perhaps, undergo a medical exam, including memory testing. This is an ambitious target that will require much work to achieve by 2006. So far, an unprecedented alliance of AD Centers, researchers, and outreach personnel, aided by the Alzheimer's Association, has collected around 500 of these families, with 500 more to go. The establishment of this database, in conjunction with the need to initiate a complementary case-control study, and to fund geneticists to apply the most up-to-date screening technologies in analyses of these new data resources, are critical components of the effort to elucidate the genetic basis for AD - a likely key factor in successfully finding a clinical intervention to treat or prevent AD.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Initiate a double-blind, placebo-controlled trial of simvastatin (medication used to reduce the amount of cholesterol and certain fatty substances in the blood) to determine whether it can slow the rate of progression of AD.	(FY02) Earlier studies indicate lowering cholesterol levels with statins seems to have a positive impact on brain function and reduces the risk of AD	◆				
FY03	*Actual Performance:* (MET) CLASP study was enacted to further investigate the role that cholesterol has in the pathogenesis of Alzheimer's Disease.					
Identify and implement effective strategies to facilitate drug discovery and development for AD treatment and prevention in collaboration with relevant organizations, as well as through stimulation of relevant research through Program Announcements and/or other mechanisms.	(FY03) Estimated 30 compounds are presently or will soon be tested in human AD clinical trials but additional targets are needed		◆			
FY04	*Actual Performance:* (MET) NIH initiated a preclinical toxicology program and expanded an intravenous testing program to expedite drug discovery, and identified a collaborative opportunity for pre-clinical drug development.					
Launch the Alzheimer's Disease Neuroimaging Initiative to evaluate neuroimaging modalities and techniques and other biomarkers to be used in early diagnosis, follow the progression of mild cognitive impairment (MCI) and AD, and use as potential surrogate markers for drug development and clinical trials.	(FY03) Neuroimaging technologies appear to have considerable potential for early diagnosis of MCI and AD and for measuring disease progression			◆[e]		
FY05	*Actual Performance:* (MET) The NIH launched the Alzheimer's Disease Neuroimaging Initiative in late 2004.					

Identify around 1,000 new late onset AD families to allow geneticists to locate additional late onset risk factor genes for AD that may lead to new targets for drug treatment, and provide a well-characterized population for more efficient clinical trials.	(FY04) The genetics initiative has identified 259 families, too few for researchers to identify the remaining risk factor genes.					◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
Identify and characterize molecular events that may prove to be targets for treating or preventing Alzheimer's disease through initiatives and projects focused on mechanistic and basic studies.	(FY05) New targets need to be identified and known ones characterized to develop therapeutic or preventative interventions.						◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. 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.

The study, which is taking place at approximately 50 sites across the U.S. and Canada, has set up the necessary infrastructure and intends to begin recruitment in the fall of 2005; in all, approximately 800 individuals ages 55 to 90 will participate over the five years of the study.

Implementation Strategy Advances or Other Highlights

The AD Neuroimaging Initiative (ADNI) began enrolling participants in fall 2005. In addition, applications are currently being received and reviewed for program announcement PA-04-158: Ancillary Studies to the AD Neuroimaging Initiative, issued in September, 2004. This PA solicits applications that may propose and measure potential biomarkers, offer new approaches to analyzing the dataset, propose autopsy follow-up studies, or develop parallel neuroimaging studies with a different sample but using a subset of the measures used in the ADNI protocol. In 2006, NIH expects to fund one application, focusing on functional MRI, in response to this PA.

Efficiency

Because of the importance of this effort, the NIH and its partners were able to mobilize and launch the initiative in late 2004 to achieve the FY 2005 annual performance target.

PART

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

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

Whole-pancreas and pancreatic islet transplants offer type 1 diabetics the potential for physiologic control of blood sugar as an alternative to insulin therapy. Whole-pancreas transplantation is a technically difficult procedure, whereas pancreatic islet cell transplantation is a less invasive procedure. 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 prospects for islet transplantation. If confirmed in larger, multi-site studies, these results suggest that approximately 40 to 50 percent of type 1 diabetics can be expected to remain insulin independent two years following islet transplantation. Despite these advances, patients must remain on potent immunosuppressive drugs to prevent immune-mediated rejection of the transplanted islet cells. Immunosuppressive agents may increase the risk of serious infection and other complications, such as 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 islet cells in the absence of the drugs currently used to prevent rejection of the transplanted cell 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.

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

One of the challenges facing islet cell transplantation researchers is the scarcity of islet cells suitable for transplantation. In order to improve procedures for the preparation of islets cells and ensure consistency and quality of across multiple CIT clinical trial sites, current good manufacturing practices (cGMP) will be developed. After cGMP manufacturing processes for preparation of pancreatic islet cells have been employed at

individual CIT sites, the quality of the cells produced at the different sites will be assessed through validation studies. cGMP manufacturing and validation processes for the production of pancreatic islet cells suitable for transplantation developed as part of the CIT may be able to be used for the production of islet cells for use in other clinical protocols.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2004 PERFORMANCE RESULTS

Target

The FY 2005 performance target was MET. In FY 2004, the FDA had placed a clinical hold on the further evaluation of anti-CD3 antibody in clinical trials pending its review of additional safety information on this agent. The NIH submitted a response to the FDA during the first quarter of FY 2005. On April 29, 2005, the FDA released its clinical hold on anti-CD3 antibody. For the reasons elaborated below, NIH clinical trial of anti-CD3 to promote tolerance in patients with transplanted pancreatic islets was cancelled.

The FY 2004 performance target that was extended until FY 2007 was not met in FY 2005. The Phase I trial to evaluate the safety of anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs was cancelled because the amount of anti-CD3 antibody needed for the trial could not be obtained because the pharmaceutical company that owns the agent decided to use it for other clinical trials. Given the limited amount of the anti-CD3 agent that is available, the company owning the agent made a decision to pursue clinical trials for psoriatic arthritis and new-onset type 1 diabetes in preference to islet transplantation. NIH has no control over the decisions of the pharmaceutical company. The company reserves the right to use anti-CD3 antibody in patients who have undergone islet transplantation in the future.

Implementation Strategy Advances or Other Highlights

The FDA clinical hold on the anti-CD3 antibody was lifted on April 29, 2005, but the initiation of the clinical trial was further delayed to evaluate data from clinical trials of the agent in patients with other autoimmune diseases. Then the Phase I trial of the anti-CD3 antibody in patients who had undergone islet cell transplantation was cancelled because the amount of anti-CD3 antibody needed for the trial could not be obtained because the pharmaceutical company that owns the agent decided to use it for other clinical trials. NIH has no control over the decisions of the pharmaceutical company and, thus, had to cancel the NIH clinical trial of anti-CD3 to promote tolerance in patients with transplanted pancreatic islets.

The NIH remains committed to improving the safety and long-term success of methods for transplanting islet cells in people with type 1 diabetes. With the anti-CD3 antibody no longer available for clinical trials involving islet transplantation, the NIH revised this goal and the subsequent annual targets to focus on evaluating islet transplantation in combination with immune modulation strategies. The NIH continues to support research aimed at developing immune modulation strategies that decrease the potentially serious side effects associated with the immunosuppressive regimes currently used.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

The initial goal of demonstrating the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies by 2007 was based, in part, on the anticipated success of the Phase 1 trial of the anti-CD52 antibody in the target population. However, this agent was determined to be an unsafe product in the target population.

The second agent under investigation to be tested in a clinical trial, anti-CD3 antibody, was on clinical hold by the FDA through April 29, 2005. Though the hold was lifted, initiation of the clinical trial was delayed beyond April 29, 2005, so that data from clinical trials of the agent in patients with other autoimmune diseases could be evaluated. Recently, the NIH trial of the anti-CD3 antibody in patients who had undergone islet cell transplantation was cancelled. The company owning the agent made a decision to pursue trials for psoriatic arthritis and new-onset type 1diabetes in preference to islet transplantation. The company reserves the right to use anti-CD3 antibody in patients who have undergone islet transplantation in the future.

The NIH remains committed to improving the safety and long-term success of methods for transplanting islet cells in people with type 1 diabetes. The NIH continues to support research aimed at developing immune modulation strategies that decrease the potentially serious side effects associated with the immunosuppressive regimes currently used. Clinical protocols for trials of immunosuppressive agents that have shown promise in animal studies are under development, and it is anticipated trials of one or more of these agents could begin in several years. Challenges facing islet cell transplantation researchers include the scarcity of islet cells suitable for transplantation and the extraordinary sensitivity of islet cells to acute rejection episodes. The NIH is supporting research aimed at improving the isolation and viability of islet cells to treat type 1 diabetics and provide these cellular products for wider availability which should increase the clinical trials capacity for procedures involving purified islet cells. Current good manufacturing processes (cGMP) will be developed in order to ensure consistent purity and quality of pancreatic islet cells suitable for transplantation with the goal of treating type 1 diabetes.

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

BACKGROUND

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH implemented research projects that integrate technologies to efficiently and simultaneously analyze key components of salivary secretions. Conventional and emerging technologies are used to analyze salivary secretions from the parotid, submandibular, and sublingual glands. Bioinformatics and biocomputational tools catalogue and annotate salivary components, resulting in a fully developed salivary proteome knowledge base. It is anticipated that a multidisciplinary team will ultimately produce a "periodic table" of salivary secretory proteins. Proteomic data will be generated from parotid, submandibular, and sublingual saliva. Saliva samples will be subjected to preliminary size and/or charge fractionation to identify small peptides and larger proteins overa wide concentration range. An antibody library to parotid proteins will be screened and used to produce immuno-affinity resins. Furthermore, NIH plans to develop integrated microsystems to detect disease-associated biomarkers in human saliva.

Taken together, this information will help improve understanding of how salivary components change in the presence of disease or disorder.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET efficiently several months ahead of the targeted date. Integrated microfluidic assay systems have been developed that quantify C-reactive protein in saliva. These systems have been able to detect C-reactive protein at relatively low levels, enabling researchers to compare salivary levels of C-reactive protein in healthy subjects to those in subjects with inflammatory conditions.

Implementation Strategy Advances or Other Highlights

Through the Salivary-Based Diagnostics Technologies program, NIH is building towards a rapid, efficient and cost-effective system to simultaneously analyze multiple substances found in human saliva. Scientists and engineers have developed microchip immunoassays to help detect important analytes such as C-reactive protein, IL-1-beta, TNF-alpha, and IL-8 in human saliva. The development of fully integrated, handheld devices for collecting and analyzing saliva will not only facilitate the detection of known biomarkers, but will also catalyze research efforts to identify new biomarkers for a wider range of oral and systemic diseases and conditions.

Exciting applications for these innovative technologies are being developed. For example, one group of researchers has been using this technology to analyze saliva of kidney

patients before and after they undergo renal dialysis, identifying possible biomarkers for kidney disease while ruling out other candidates. Another set of researchers has concentrated on detecting oral cancer by analyzing salivary composition. They identified salivary IL-8 protein levels as a potential biomarker for oral cancer. In addition, this group has found that certain salivary RNA proteins *in combination* can distinguish cancer patients from control subjects with a high degree of sensitivity and specificity. The researchers are now proceeding to apply this approach to both oral cancer and breast cancer diagnosis and detection. Other research projects are underway to test the use of salivary diagnostics to detect the SARS coronavirus, asthma biomarkers, and other substances.

A complementary effort to the Salivary-Based Diagnostic Program is an effort to identify and catalog the salivary proteome. NIH-funded projects are designed to help identify all protein components in human saliva, as well as their natural variants and complexes. This research will develop a "molecular tool box" for the functional characterization of salivary proteins and establish tools for dissemination of these data to the scientific community. With these baseline data in place, scientists will be able to detect changes in the composition of saliva among people with or at risk for various diseases and conditions. Already, a preliminary catalog of over 300 proteins found in whole saliva, along with their functional categories, has been published. Furthermore, preliminary studies of parotid saliva have identified a number of novel peptides for future analysis.

Efficiency

Electronic microfluidic assay systems to measure C-reactive protein in saliva were developed several months ahead of the targeted date.

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

BACKGROUND

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

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

Prevalence/Incidence

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

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

Co-occurring diagnoses of substance abuse and mental illness are highly prevalent, with some estimates of as many as 7 to 10 million Americans suffering from both. Up to 66% of substance abusers are likely to be diagnosed with a psychiatric disorder during their lifetimes. Persons with diagnoses of severe mental illness are far more likely to have co-occurring substance abuse disorders. 25% of individuals diagnosed with major depression also abuse drugs and/or alcohol. Women with bipolar disorder are seven times more likely to be alcoholics than women without psychiatric diagnoses.

Disease Burden

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

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

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

BACKGROUND

Disease Burden

Although cardiovascular disease (CVD) death rates have declined over the past few decades, CVD (including coronary heart disease (CHD), heart failure, and peripheral artery disease) remains the leading cause of death and disability in the United States. According to the 2002 National Health and Nutrition Examination Survey (NHANES), an estimated 13 million Americans have CHD and 7.1 million have experienced a heart attack. CHD accounted for over 2 million hospitalizations, at a 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. Needed are imaging modalities 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.

Investigators in Germany have used positron emission tomography (PET) to image exogenously administered bone marrow-derived cells. In 3 patients in whom labeled cells were infused into the infarct coronary artery, PET imaging revealed that only 3.4 percent of labeled cells localized to the heart, with the remainder detected in the liver and the

spleen. With intravenous delivery of a similar number of cells in another 3 patients, no cardiac localization of cells could be demonstrated. When CD34+ hematopoietic progenitor cells were administered by intracoronary infusion, 25 percent of labeled cells localized to the heart, especially in the border zones of the infarct. In vivo trafficking of exogenous cell preparations will require longer half-life positron emitters such as 68Ga. A significant technical challenge of PET imaging is incorporating enough radioactive molecules within or on the surface of stem cells to generate sufficient signal for detection above background.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A multimodality imaging effort will be undertaken to develop tools to track cardiovascular stem cells in vivo, and ultimately in patients. The effort will entail:

• Development and testing of MRI agents for ex-vivo labeling and in vivo tracking of cardiovascular stem and progenitor cells. Cell labeling for MRI stem cell tracking has been conducted successfully with various iron preparations. The NIH has already demonstrated in vivo cell tracking of mesenchymal stromal cells (Hill et al. Circulation 2003). NIH investigators also have tracked hematopoeietic stem cells accumulating in injured rat hearts using clinical-grade reagents (EJ Read, JA Frank, submitted 2004). The investigators are preparing an Investigational New Drug application to label and track a variety of cell preparations using MRI. Of the available alternative cellular contrast agents few have so far proven suitably non-toxic. Several prototype agents are under development by the NIH, and several promising commercial agents are being tested. The NIH has also pioneered the use of chemical exchange-dependent probes (CEST) that do not rely on potentially toxic metals. Successful cellular labels would enable serial in vivo surveillance of administered cells.

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

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

• Identification of markers of differentiated cells from originally introduced stem cells. Cell labeling and tracking using optical methods have been hampered by blood

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

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

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Initiate stem cell labeling strategy.	(FY04) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.			◆		
FY05	*Actual Performance:* (MET) NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals.					
Complete optical imaging probe development.	(FY05) Available probes do not permit safe and effective labeling of stem cells for in vivo tracking.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Initiate validation and toxicity studies.	(FY06) Verification is needed to determine whether developed probes are selective for and detectable in stem cells.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. NIH-researchers successfully developed an optical microscope system to monitor single cells in intact animals. Two novel aspects of the new system include: 1) the use of 2-photon excitation microscopy to visualize individual cells inside tissues using infrared light and 2) methods that systemically deliver Syto dye (Molecular Probes Inc.) that stains nuclei to label stem cells and white cells in intact animals *in vivo* with no adverse reaction.

The new system is an essential tool for developing and evaluating potential cell-based therapies in animal models. The system will allow researchers to determine the location of stem cells administered to an animal and also could be used to gain valuable information about the biological state of administered cells. The development of the system in animals is an important step towards the overall goal, the eventual development of a similar system to monitor cells administered to humans for therapeutic purposes (e.g., to treat heart disease).

Implementation Strategy Advances or Other Highlights

Researchers have labeled white cells selectively with nuclear dyes *in vivo* and modeled human colon carcinomas on the leg of a living mouse demonstrating the ability to monitor cell proliferation as well as matrix component deposition during development.

PART

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

SRO-4.2	**By 2005, develop improved animal models that best recapitulate Parkinson's disease (PD) based on emerging scientific findings of genetic or environmental influences or interactions of genes and the environment on the development of PD.**

BACKGROUND

Prevalence/Incidence

PD is a neurodegenerative disease for which there is no known cure.

- Incidence: 50,000 cases per year, increases dramatically after age 50.
- Prevalence: Estimates range from 500,000 to 1 million individuals in the United States.

Disease Burden

PD is a devastating, progressive motor disorder, characterized by rigidity, poor balance, and uncontrollable shaking or tremors; those affected by PD eventually lose their independence. PD is marked by a loss of neurons that produce the neurotransmitter dopamine; these neurons are an essential part of the brain pathways controlling purposeful movement. The total economic cost per year was estimated to be $6 billion in 1992. Most individuals with PD are treated with pharmacologic agents that mimic the actions of the lost dopamine. Although these drugs provide symptomatic relief, they do not cure or slow disease progression, are of limited benefit in later stages of the disease, and can produce undesirable side effects.

Rationale

To facilitate the understanding and treatment of any human disease, it is desirable to create animal models that recapitulate (i.e., reproduce all key features of the disease process, including pathways of disease causation and the impact of the disease on cellular processes, organ function, and, ultimately, behavior). With such models in hand, researchers can track the earliest molecular events in the disease and develop intervention strategies to delay, or even prevent, its progression. In the case of PD, researchers would like to have access to an inexpensive, reproducible animal model that captures both the genetic and environmental roles in causation, reproduces the cellular changes that occur in PD over an appropriate period of time, and leads to behaviors in the animal that approximate the effects of the disease on humans.

Over the years, the research community has developed several animal models of PD that have been instrumental in accelerating the understanding of the disease process. One such model is produced through acute exposure of primates to MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), a chemical substance with structural similarities to some pesticides. Although this model is likely to remain useful for predicting therapeutic efficacy, it is costly and does not reproduce some key features of PD (e.g., the progressive nature of the disease, some cellular features of affected neurons, and the combined effects of the environment and genes on disease causation). By contrast, NHP models have offered important practical benefits for dissecting gene-environment interactions in PD. For example, the creation of mice and fruit flies expressing mutant forms of a gene (alpha-synuclein) implicated in PD have provided an opportunity for studying the effects of environmental agents on key genes and proteins involved in the disease process. Furthermore, the recent discovery that pesticide exposures (e.g., rotenone) can produce

Parkinson-like effects on neurons and behavior in rodents offers another possible strategy for understanding the effects of the environment on this disease.

Together, these models have enabled researchers to learn a great deal about the neural systems that are affected by PD, the molecules within cells that may play a role in the disease process, and the potential for various therapies to treat the disorder. However, each has its merits and limitations, and an optimal model is still not available to the PD research community. For this reason, a collaborative effort will be needed in the future to capitalize on findings related to environmental and genetic influences on PD, develop this knowledge into inexpensive, reproducible animal models of PD that simulate the disease process even more accurately than do the models that are currently available, and improve the ability to test therapies.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

During FY 2003, NIH established a mouse model repository that houses PD genetic models and makes them available to the PD research community. This was intended to facilitate the use of genetic models in various capacities, including the development of gene-environment combined models. In addition, NIH ensured that the mouse repository contained a variety of genetic models (through the animal models supplements initiative for those investigators currently developing models), including transgenics (biotechnology) and KO models for each of the known proteins mutated in PD.

NIH also developed a rotenone mouse model that mimics aspects of human PD. The model was characterized for resulting neuropathological, behavioral, and chemical effects and the protocol was made available to the PD research community. Preliminary studies in normal mice revealed a reduction in dopamine levels after rotenone exposure, and NIH combined it with genes implicated in PD (e.g., alpha-synuclein, parkin) to study gene-environment interactions.

The end result of these strategies is to replicate PD in animal models to better understand the effects of PD in humans. The greater the enhancement PD effects in animal models, the greater opportunity to find a cure for PD.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Establish a mouse model repository at a Morris K. Udall Center of Excellence for Parkinson's Disease Research to house PD genetic models and make them available to the PD research community.	(FY02) No repository with this specific housing and distribution capacity exists for PD research	◆				
FY03	*Actual Performance:* (MET) Mouse model repository to house PD genetic models established.					
Conduct dose response studies of chronic rotenone administration in normal mice and assess resulting changes in striatal dopamine levels and the number of dopamine neurons in substantia nigra. *Previous Target:* Determine if slowing the metabolism of rotenone through cytochrome P-450 inhibition facilitates creation of a mouse model for PD.	(FY03) Cytochrome P-450 accelerates rotenone metabolism in mice so that the PD phenotype cannot be shown		◆			
FY04	*Actual Performance:* (MET) Provided proof of concept in mouse model by administering rotenone and achieving 30-40% depletion of dopamine in striatal terminal fields with clear evidence of degenerating neurons.					

Combine the mouse model with at least one genetic model of PD and assess its interaction with rotenone.		(FY03) A rotenone mouse model is not yet available			◆		
FY05	*Actual Performance:* (MET) Used A53T missense mutation mouse in rotenone model; 100% mortality in test subjects, indicating that this transgenic mouse was probably more susceptible to rotenone than the normal (wildtype) mouse. Goal completed.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. The genetic model used was the A53T missense mutation implicated in human PD. 100% of the A53T transgenic mice died, even though they were given the same doses of the pesticide rotenone as those successfully used in normal (wildtype) mice. Thus, the A53T transgenic mouse was shown to be probably more susceptible than the normal mouse to the effects of rotenone. This finding suggests that lower rotenone doses or different transgenic mouse models will be needed for studies of gene-environment triggers for PD development using this model.

Goal Achievement

The goal to develop a PD animal model that recapitulated PD based on emerging scientific findings of genetic or environmental influences was met in 2005. The pesticide rotenone was used in normal mice to create hallmarks of PD, including dopamine depletion and neuronal degeneration. Showing that rotenone can be used in mice to duplicate events that are common in PD will open new paths for discovery of how environmental agents can interact with underlying genetic susceptibility to initiate molecular pathways that lead to PD symptoms. Such insights can ultimately help scientists create early biomarkers of PD development, as well as new therapeutic and intervention strategies.

Implementation Strategy Advances or Other Highlights

A number of lines of investigation have been ongoing, all focused on developing improved animal models for PD.

A rotenone model that built on earlier success in rats was successfully duplicated in mice. Using normal (wildtype) mice, rotenone administration yielded a 30%-40% depletion of dopamine in striatal terminal fields with clear evidence of degenerating neurons, thereby duplicating many of the hallmarks of PD.

In addition to the rotenone model, a number of ongoing studies have used insight into genetic components of PD development to engineer new animal models for study of this disease. For example, mice lacking the parkin gene exhibit normal brain structure and numbers of dopamine neurons, but display subtle abnormalities in dopamine system function and behaviors that rely on these neurons. More recent research from this laboratory suggests that these mutations also can impair the function of mitochondria and cause oxidative damage, even in the absence of cell death. Interestingly, a different NIH-supported laboratory has found that a different deletion in the parkin gene can impair neuronal survival. These effects, however, are not observed in the substantia nigra – the area of the brain most frequently involved in sporadic late-onset PD – but rather in the locus coeruleus, a part of the brain that is involved in arousal, fear, and stress responses. In addition to these effects, at least one behavior that is mediated by the locus coeruleus – the startle response evoked by a noise stimulus – is also impaired. Together, these critical

animal models of PD are providing important insights into the complex role that the parkin gene may play in the development of the disease in humans.

Researchers have also known for several years that mutations in the alpha-synuclein gene contribute to PD in some families that have inherited the disorder. Alpha-synuclein protein is also found in Lewy bodies, protein accumulations inside the cell that are a hallmark of both inherited and sporadic forms of PD. Thus, an understanding of synuclein's function will be important to our understanding of the disease process. Although research has suggested a role for alpha-synuclein in synaptic function, its similarity to another protein, beta-synuclein, has been a potentially confounding factor in some of these studies. To address this problem, NIH-funded researchers engineered mice with deletions of the alpha-synuclein gene, the beta-synuclein gene, or both, to evaluate the impact of each specific gene on neuronal function. By assessing synaptic function at multiple levels, the investigators demonstrated that basic functions such as the release of neurotransmitters and the plasticity of synaptic responses, as well as the development of normal synapse structure, do not require synuclein expression. However, if both forms of synuclein are eliminated, dopamine levels in the nigrostriatal system (the neural circuit implicated in PD) are significantly reduced. This study expands the body of knowledge about the function of these complex proteins and the basic biology of PD.

Four lines of transgenic mice were made that express mutant A53T human alpha-synuclein from a bacterial artificial chromosome and transmit the mutant gene in their germlines. Colonies of two of these lines have been established and bred to alpha-synuclein-ablated mice to establish permanent lines that are homozygous for the mutant transgene and homozygous for the deleted mouse gene. These lines are now being crossed to create mice that have four copies of the mutant human gene and no copies of the endogenous mouse gene. These mice are being monitored for development of neurological symptoms and pathology.

In addition to manipulating genes to generate useful animal models, researchers continue to use environmental exposures to produce critically-needed models. For example, NIH-funded investigators have recently demonstrated that exposure of rats to toxicants that inhibit normal protein degradation systems in the cell can produce a slowly progressive parkinsonian syndrome, characterized by slowness of movement, rigidity, and problems with posture; destruction of neurons in the substantia nigra and several other brain regions affected in PD; and the presence of cellular structures resembling Lewy bodies in affected neurons. These data not only provide evidence that effects on this system by environmental exposures can contribute to the development of PD, but they also make a novel animal model – and one that recapitulates several critical features of PD – available for further investigation.

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

BACKGROUND

Prevalence/Incidence

AIDS has killed more than 22 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide. At the end of 2004, an estimated 40.3 million people worldwide, including 2.3 million children younger than 15 years of age were living with HIV/AIDS. In addition, over 3 million people died from AIDS in 2004, and approximately 5 million people were newly infected with HIV, of which 700,000 were children. In the United States, at the end of 2003, an estimated 1,039,000 to 1,185,000 people were living with HIV/AIDS. Although in the United States new infections have remained relatively stable at approximately 40,000 per year, AIDS cases continue to climb among women and racial and ethnic minorities.

Disease Burden

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

Rationale

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

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

Building on the successful demonstration in 1996 that highly active antiretroviral therapy (HAART), including a protease inhibitor (PI) and two other antiretroviral (ARV) drugs,

results in significantly decreased viral loads and increased CD4 levels, NIH-supported studies have continued to define treatment regimens that slow disease progression. These powerful drug combinations have resulted in a decline in the incidence of new AIDS cases and HIV-related death rates. Since 1996, several new classes of ARVs, including fusion inhibitors, PIs, and nucleotide analogs, have been developed and shown to be safe and efficacious. Although these multiple drug combinations can successfully reduce viral load and restore immune responses in many HIV-infected individuals, metabolic and morphologic complications associated with these treatment regimens present significant morbidity and mortality, thus warranting additional investigation.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

In 2004, NIH initiated 11 adult clinical trials of anti-HIV therapies and two adult clinical trials for the treatment of HIV/tuberculosis co-infection. In addition, two perinatal transmission trials were initiated, as well as seven clinical trials for children and adolescents (four of anti-HIV therapies and three to evaluate treatment regimens for complications of HIV).

In 2005, NIH initiated new clinical trials of anti-HIV therapies (including studies of therapeutic vaccines) and/or anti-HIV multidrug regimens to identify treatment regimens with increased efficacy, fewer toxicities and side effects, improved bioavailability, minimal development of drug resistance, and easier compliance. In the coming years, NIH also plans to develop and/or test one new approach that may inhibit MTCT and will implement studies to examine the impact of preventive MTCT regimens, including studies of nevirapine resistance on future treatment options. NIH will also participate in the development and/or testing of three or four agents for the prevention or treatment of HIV-associated manifestations, such as co-infections with hepatitis C virus or hepatitis B virus, opportunistic infections (including tuberculosis), cancers, neurological disorders, or organ-specific complications.

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

PART

This goal was included in the FY 2005 PART of the HIV/AIDS Research Program. NIH continues to make progress toward achieving the HIV/AIDS Research Program goal: By 2007, evaluate the efficacy of three new treatment strategies for HIV infection in phase

II/III clinical trials. The FY 2005 PART targets for achieving this goal are as follows: 1) develop three anti-HIV compounds; 2) initiate four drug clinical trials; 3) develop/test two agents to prevent/treat drug complications; and 4) develop/test one new approach to inhibit mother-to-child transmission.

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

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 performance target was MET. In FY 2005, NIH initiated one clinical trial of a new anti-HIV drug and four trials of anti-HIV drug regimens through the NIH-sponsored Adult AIDS Clinical Trials Group (AACTG) and the Comprehensive International Program of Research on AIDS (CIPRA).

NIH initiated one clinical trial of a new anti-HIV drug through the AACTG:
• a phase I/II trial to determine the safety of AMD11070, an orally administered CXCR4 entry inhibitor.

NIH initiated four clinical trials of anti-HIV multi-drug regimens through the AACTG and CIPRA:
• the first NIH-supported large phase III international HIV treatment trial, which began enrolling participants in the United States and several resource-limited settings including

sites in Sub-Saharan Africa, India, Brazil, Thailand, Haiti, and Peru. The trial compares a standard twice-daily antiretroviral (ART) regimen (efavirenz, zidovudine and lamivudine) with two different ART regimens that can be administered once daily as initial therapy for HIV-infected individuals (ACTG A5175). This trial is being conducted in conjunction with a trial in the NIH-sponsored HIV Prevention Trials Network (HPTN 052) that is comparing the effectiveness of two treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples;
• a phase III trial comparing the efficacy, safety, and tolerability of four anti-HIV multi-drug regimens;
• a clinical trial in South Africa designed to determine whether an ART therapy regimen administered and monitored by primary health care nurses is comparable to treatment monitored by a physician and whether directly observed therapy administered by trained community members is comparable to clinic-based treatment support (CIPRA); and
• a pediatric phase III/IV trial comparing time to failure of first-line ART or time to death among HIV-infected infants in South Africa who are randomized to three treatment regimens: immediate short course, long-course ART, and deferral of treatment until pre-defined disease progression parameters are met (CIPRA).

Implementation Strategy Advances or Other Highlights
NIH supports the HIV/Opportunistic infections (OI) Therapeutics Database of 125,000 compounds and testing data for potential inhibitors of: HIV, HIV-associated OIs, and several other viruses of medical importance. It also sponsors the Cell/HIV Protein Interaction Database, which catalogues cellular proteins known to interact with HIV proteins during viral gene expression and replication. This database, with nearly 1,200 unique protein interactions of the HIV proteins with human cell proteins, can be used to elucidate molecular mechanisms in HIV infection and virus-host interactions relevant to discovery of anti-retroviral drugs and development of vaccine candidates.

The two regulatory proteins of HIV, Rev and Tat, and their mechanism of action with viral RNA, represent targets of high priority for the development of new therapeutic drugs to treat HIV infection and AIDS. During the past year, 719 compounds (from governmental and private sector sources) were screened for activity against Rev and its interaction with Rev Response Element (RRE), a component of RNA that binds to Rev and is essential for RNA transport, or Tat and its interaction with TAR, a component of RNA, which along with Tat is essential for HIV transcription. Thirty-three compounds exhibited the ability to inhibit Tat/TAR interactions; 12 were capable of blocking Rev/RRE interactions. These lead compounds are undergoing additional testing.

Scientists completed and/or newly initiated several studies to better define how antiretroviral combination regimens should be used and to determine the impact of treatment during initial stages of HIV infection on disease progression. The results of these studies will be useful to clinicians in prescribing initial drug regimens for HIV-infected patients.

In an effort to develop improved strategies to prevent and to treat mother-to-child transmission of HIV/AIDS, researchers are evaluating three regimens to prevent mother to child HIV transmission in infants born to mothers who did not receive any antiretroviral prophylaxis. During the first six weeks of life, infants may receive: 1) zidovudine, 2)

zidovudine plus three doses of nevirapine in the first week of life, or 3) zidovudine plus two weeks of lamivudine and nelfinavir. In another study, scientists are comparing the safety and efficacy of a standard treatment (zidovudine, lamivudine and lopinavir/ritonavir) to a non-standard one (zidovudine, lamivudine, and abacavir) to improve antiretroviral therapies for pregnant HIV-infected women who do not require treatment for their own health. Studies are also underway investigating the effects of single dose Nevirapine (SD NVP) on future treatment options for women, and examining strategies to minimize viral resistance after SD NVP are being tested in two different studies, one primarily in Africa, India and Haiti and another in Thailand. In FY 2005, NIH also completed two trials and initiated approximately 10 new international trials focusing on the treatment of HIV co-infections. A number of clinical trials are also ongoing in the U.S. to evaluate treatment of complications of HIV.

To enable approval of new anti-HIV drugs for infants and children, scientists are also conducting several phase I and I/II studies in the U. S. and internationally, evaluating: 1) lopinavir/ritonovir plus two reverse transcriptase inhibitors in very young infants; 2) atazanavir, alone or in combination with ritonavir, plus two nucleoside analogue reverse transcriptase inhibitors; and 3) tipranavir, plus two reverse transcriptase inhibitors. In collaboration with the Pediatric European Network for Treatment of AIDS, scientists are also conducting an ongoing international pediatric strategy study to evaluate the optimal initial antiretroviral therapy and optimal virologic time to switch therapy in children.

Despite dramatic progress in controlling HIV in the body, most antiretroviral drugs do not cross the blood-brain barrier and the virus often causes serious neurological problems. By studying a closely related virus, simian immunodeficiency virus (SIV), in non-human primates, scientists have now shown that the antibiotic minocycline can protect the brain. The drug not only reduced inflammation and protected simian brain cells, but also appeared to reduce replication of the virus in the brain. Human clinical trials will be necessary to determine whether this drug is as effective in protecting people with HIV infection.

PART

The PART FY 2005 targets have been achieved: 1) Three lead anti-HIV compounds are progressing through the drug discovery and drug development pipeline; 2) Four clinical protocols are being developed and enrollment will be initiated for the conduct of phase I, II, and/or III clinical trials of drug combinations against HIV and its associated co-infections, opportunistic infections, and malignancies; 3) Two potential agents and lead compounds against drug-associated complications are undergoing drug development, pre-clinical testing, and/or evaluation in clinical trials; and 4) Studies are underway in domestic and international sites to develop and evaluate a safe, effective, affordable, and sustainable intervention to block MTCT of HIV, including transmission associated with breastfeeding.

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

BACKGROUND

Disease Burden

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

with a total of more than 80,000 compounds—for activity at D1 dopamine receptors to develop a selective D1-dopamine receptor agonist as a potential treatment for cocaine addiction.

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

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

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Expand the National Cooperative Drug Discovery Group Program model to target mental disorders and nicotine addiction to advance the development/testing of fundamentally new medications/treatments for mental disorders and nicotine addiction.	(FY02) None of the NCDDG Programs focus on mood disorders and nicotine addiction	◆				
FY03	*Actual Performance:* (MET) Three grants modeled on the National Cooperative Drug Discovery Group (NCDDG) Program were awarded for development/testing of new medications/treatments for mental disorders and nicotine addiction. Prior to these awards, the NCDDG did not address these conditions.					
Identify potential research tools and drug leads for neurological disorders by developing/utilizing high-throughput screening programs, including assay development.	(FY03) 1,040 FDA-approved drugs and >23,000 potential anti-epileptic compounds screened		◆			
FY04	*Actual Performance:* (MET) 76 promising compounds identified in various assays; 2 potential epileptic therapies advanced to clinical testing. Proof-of-concept tests initiated for alcohol abuse and addiction screening.					
Create a publicly available collection of 750 bioactive compounds, with defined activity in the nervous system, from industry, academia, and government sources, to be used in screens for potential drugs, research tools, and diagnostic agents.	(FY03) Known bioactive compounds require further evaluation of activity and improved availability			◆		

FY05	*Actual Performance:* (MET) Compounds selected based on evaluation of properties; collection assembled for public use.							
Test the ability of at least one promising compound to extend survival and reverse molecular effects of SMA in a mouse model of the disorder.	(FY04) SMA program established; 3 promising compounds identified in screens; SMA mouse models available					◇		
FY06	*Actual Performance:* Performance results will be reported in February 2007.							
Complete goal of identifying 20 small molecules that are active in models of nervous system function or disease and show promise as drugs, diagnostic agents, or research tools.	FY06 results						◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.							

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. NIH has created a collection of small molecules that is sufficient to yield multiple hits in most screens, yet small enough to be utilized without robotic equipment, making the collection broadly and immediately useful to investigators in both academia and industry. NIH selected the compounds for the collection via a thorough, multi-stage process that involved substantial input from extramural scientific experts. NIH began by hosting a workshop to identify criteria for compound selection. The workshop participants agreed to base compound selection on bioactivity, stability, and purity. Chemists contracted by NIH then assembled a list of approximately 2,000 compounds that met these criteria. At the time, with the information available, the scientists involved in the project determined that this collection of 2,000 compounds was too large for rapid, non-automated screening, but that a handpicked subset of approximately 750 would be a manageable and productive size. Consequently, NIH held a second workshop to narrow the list of 2000 compounds to within this range. Participants recommended focusing on compounds that have a history of clinical use or testing and that are not available in other public collections. Researchers who screen this collection would avoid redundancy with other collections, and should they find a promising drug lead, the existence of clinical data would help accelerate the process toward FDA approval. As of November 2005, 578 compounds met these more stringent requirements and were immediately available to NIH. This collection of compounds was smaller than the 750 originally estimated, but NIH and its scientific advisors concluded that the benefits of adopting the selection criteria from the second workshop more than compensated for the smaller collection size, and that the 578 compounds were sufficient for the type of screening projects originally envisioned. NIH is making the compound collection available to the public through a contract that allows cost recovery. This collection of bioactive compounds will be used in screens for potential drugs, research tools, and diagnostic agents, enabling progress toward the overall goal.

Implementation Strategy Advances or Other Highlights

NIH-funded researchers made substantial progress in FY 2005 in identifying and developing drug leads and imaging agents for neurological and psychological conditions. For example, a public-private partnership established through the NIH Anticonvulsant Screening Program enabled the completion of preclinical studies for the successful filing of two Investigational New Drug Applications (INDs). These novel small molecules are being clinically tested for epilepsy, anxiety, and pain indications. Laboratories in the Neurodegeneration Drug Screening Consortium published papers describing 78 drug leads

for ALS, seven for Huntington's disease, and one for neurodegenerative disorders. Other researchers identified seven compounds with analgesic properties, two novel compounds with neuroprotective effects, and three compounds with promise in treating drug addiction. NIH grants and contracts for the NIMH Psychoactive Drug Screening Program and Treatment Units for Research on Neurocognition and Schizophrenia led to the identification of several new molecules that interact with neurotransmitter systems and are now in various stages of preclinical and clinical development. New radioligands have been identified for brain imaging, including compounds that bind nicotinic and opioid receptors and the central nervous system serotonin transporters (SERTs).

NIH awarded new contracts to accelerate the development of drugs and imaging agents over the next few years. The SMA Project awarded five subcontracts in FY 2005 to facilitate drug development for spinal muscular atrophy (SMA). Two subcontracts support the development of SMA cell models for drug screening. The others are for an information technology system, a facility for medicinal chemistry, and drug screening efforts. NIH awarded a new contract to SRI International in September 2004 entitled 'Investigational New Drug Toxicology for Drugs to Treat Alzheimer's Disease and Other Aging-Related Diseases.' Under this contract, approximately 14 studies have been initiated during the past year on two drug candidates and a compound for imaging a protein associated with Alzheimer's disease (amyloid) via PET.

NIH released two program announcements (PAs) aimed at the discovery, development, and preclinical testing of novel compounds for the prevention and treatment of Alzheimer's disease symptoms. The ultimate goal of these PAs is submission of INDs to the Food and Drug Administration for the initiation of new clinical trials. The PAs will run for three years, with several application receipt dates per year.

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

BACKGROUND

Disease Burden

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

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A five-year study, known as the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythymatosus) trial, will test 280 children diagnosed with systemic lupus erythematosus (SLE). 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). It will enroll a total of 280 children with recent-onset lupus who will be treated with the medication atorvastatin for 36 months, establishing the largest cohort of pediatric lupus patients ever prospectively studied in the United States.

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.

The study staff has developed approaches to improving carotid intima medial thickening (IMT) certification rate, IRB approval rate, contract execution and regulatory documents. To maintain enthusiasm in enrolling sites and in sites not yet activated, the study staff hold regular conference calls and training sessions as well as promote sharing of positive experiences between sites. To assure that enrollment of 75% is complete by 2006, the investigators plan to activate sites as quickly as possible and replace non-performing sites quickly.

Baseline data analysis on enrolled patients will be completed in FY 2006, including any adverse events. Data on monitoring study progress and adverse events are routinely provided from the clinical sites to NIH.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Complete the training of personnel involved in conducting the trial, including sonographers and those operating the Interactive Voice Response System.	(FY02) Standard operating procedures are being completed but training not yet done	◆				
FY03	*Actual Performance:* (MET) Training of all appointed sonographers has been completed.					
Launch patient enrollment in at least 10 of the 20 planned sites.	(FY03) Protocol for patient enrollment established		◆			
FY04	*Actual Performance:* (MET) There are currently 16 sites actively recruiting patients into the study.					

Conduct ancillary studies, leveraging the investment of the trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus.	(FY03) One ancillary study approved to assess the effect of statins on blood cells	◆
FY05	*Actual Performance:* (MET) The ancillary studies are underway. One example is a study that explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus in pediatric patients.	
Complete baseline data analysis on the enrolled patients, including any adverse events.	(FY04) 14% of patients are enrolled and data analysis of enrolled patients is complete, including any adverse events	◇
FY06	*Actual Performance:* Performance results will be reported in February 2007.	
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.	Number of Clinical Sites: 20	◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.	

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. The ancillary studies are underway to leverage the investment of the APPLE trial in areas related to the determination of the efficacy of statins in preventing progression of atherosclerosis in children with lupus. For example, one ancillary study explores the relationship between nitric oxide and the effects of statins in atherosclerosis and lupus. Specifically, researchers are investigating plasma nitric oxide (NO) metabolite levels and expression of nitric oxide 2 and 3 (NOS2 and NOS3) in endothelial cells. Nitric oxide is an important molecule that mediates many vascular and inflammatory processes that participate in tissue damage in lupus. Institutional Review Board (IRB) approval for the ancillary studies has been obtained or is in progress in 12 of the 15 participating sites. Submission is pending in the three remaining sites. Sample collection is underway at six sites.

Implementation Strategy Advances or Other Highlights

The clinical trial APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus), a multicenter, randomized, double-blinded, placebo-controlled, interventional study to evaluate the safety and efficacy of a lipid-lowering agent in reducing the progression of carotid IMT in early childhood SLE, continues to enroll patients. As of FY 2005, 363 eligible children with lupus have been screened, and 109 of them have been enrolled in the clinical trial. 18 of the 23 approved clinical sites are actively enrolling patients. Five sites have not begun enrollment for reasons usually related to contractual agreements between the leading institution and the performing sites. Other reasons include personnel turnover and special clearance requirements for international recruitment sites.

Sonographers have been certified in 22 sites. Personnel turnover and hiring delays are the reasons cited for delays in certifying sonographers. To maintain technical consistency, the certification of newly recruited sonographers and re-certification of sonographers on site are ongoing.

Retention rates have been excellent, with only three percent of patients permanently discontinued from the study. Baseline characteristics of the study population have been analyzed, and results shared with the Study Data and Safety Monitoring Board (DSMB). Distribution between treatment groups and the randomization plan are on target. Safety

monitoring has continued as planned. Monthly reports have been produced on time and shared with the DSMB and NIH staff. An expanded plan for assignation of serious adverse events was developed by the principal investigator at the request of NIH and approved by the DSMB.

Training of investigators and technicians has resulted in improved approaches to patient recruitment and retention that are likely to influence the performance of future trials in children with lupus. Families consider lack of time and distance to clinical sites as the major impediments to enrolling in the study. In addition, about 28 percent of eligible patients did not consent to participate because they believe they are already taking too many medications. These observations indicate that the "logistics" related to study design (i.e., number of visits) and the underlying disease requiring aggressive therapy are important factors that affect recruitment success rates.

Recent studies have provided new data on the rate of progression of arterial medial thickening in adults with lupus. In addition, new research suggests that lipid-lowering agents not only slow, but may also reverse some of the damage to the arterial wall caused by fat deposition. These advances lay the groundwork for achievement of future targets under this goal.

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

BACKGROUND

Rationale

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

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A total of four Centers of Excellence in Chemical Methodologies and Library Development have been established and five new multi-institutional "Groups" and seven planning grants were funded to develop natural products drug discovery programs under the International Cooperative Biodiversity Groups Program. In FY 2004 and beyond, these centers and "Groups," as well as new initiatives to be supported through the NIH Molecular Libraries and Molecular Imaging Roadmap, will focus on (1) developing innovative methods of synthesis and library creation; (2) increasing the sharing of

knowledge among researchers, (3) increasing access to research results by exploring and developing systematic means to inventory newly created chemical libraries and methods of synthesis, (4) biologically screening the libraries and inventorying the outcomes of these screening procedures as new libraries are created, and (5) coordinating and setting priorities for these initiatives through the use of scientific advisory groups. The FY 2007 target will contribute to the achievement of the overall goal by guiding the design of new chemical libraries toward compounds with the best drug properties.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Fund two additional Centers of Excellence for Chemical Methods and Library Development to develop chemical libraries and high-throughput methods for screening potential therapeutic compounds.	(FY02) Prior to FY 2003, only two centers existed.	◆				
FY03	*Actual Performance:* (MET) Two additional Centers of Excellence for Chemical Methods and Library Development were established at Harvard Medical School and the University of Kansas.					
Investigate at least six innovative methods to synthesize chemical libraries and employ successful methods to create new libraries through the funded Centers. Ensure that inventories of libraries and successful methods are established so that the results of this work can be readily accessible to the scientific community for drug development.	(FY03) High throughput methods for making chemical libraries for drug development are limited.		◆			
FY04	*Actual Performance:* (MET) Established CMLD centers investigated at least ten (10) innovative methods to synthesize new chemical libraries while making results of these new libraries and successful methods available to the scientific community.					
Facilitate the identification of promising therapeutic compounds by funding the biological screening of chemical compounds contained in the libraries and provide an inventory of the results.	(FY03) CMLD centers are currently being established; screening of their libraries has not yet begun.			◆		
FY05	*Actual Performance:* (MET) Support for CMLD centers provides facilities to validate new methodologies used to synthesize chemical libraries. These new methods are being made available to the scientific community.					
Begin development of new methodologies for production, isolation, and identification of new, bioactive compounds from nature (natural products).	(FY 03) Due to the expense and the time required to isolate, purify, and identify new compounds, few pharmaceutical companies include natural products in their drug discovery programs.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Begin development of predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) behavior of bioactive compounds.	(FY05) Current toxicity prediction models may fail to detect human safety problems with many new chemical agents.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target to continue development of innovative methods of synthesis and library creation through the Centers for Chemical Methods and Library Development (CMLD) was MET. Each CMLD center features a team of faculty-level project leaders working synergistically on several method-related projects. Each center also includes a library synthesis core facility (i.e., personnel plus equipment), the purpose of which is to validate new methodologies and to carry out the synthesis of chemical libraries using these new methodologies as well as other, existing methodologies, as necessary. These new methods are being made available to the scientific community through publications, and information on compound libraries generated by the CMLD centers will be accessible

through PubChem, which will provide an inventory of results, and new screening centers being established through the NIH Molecular Libraries Roadmap Initiative.

Implementation Strategy Advances or Other Highlights

In FY 2005, NIH made several advances that are related to this goal. NIH continues to support a Resource for Solid State NMR (Nuclear Magnetic Resonance) of Proteins at the University of California, San Diego (UCSD), where researchers have developed a large magnet for a very high field spectrometer for solid-state NMR studies of proteins. This technology may prove useful in high-throughput screening of chemical libraries. Researchers are using this technology to determine the structure of G-protein coupled receptors, the major class of drug receptors, which may aid in the development of new therapeutic agents. Researchers also are using this technology to analyze the structure of membrane proteins. Membrane proteins are a major target of therapeutic agents, and increased understanding of their structure may further the development of new therapeutic agents.

Two new International Cooperative Biodiversity Groups were begun in 2005, bringing to seven the number of groups creating both physical and virtual natural product chemical libraries of plants, marine invertebrates, marine and terrestrial microorganisms, and endophytic fungi. Isolated chemical compounds and extracts from these libraries are being screened in a wide range of bioassays representing multiple therapeutic areas, including new assays introduced through the two new projects. Novel bioactive compounds have been isolated.

Finally, NIH has established the Roadmap Molecular Libraries Screening Centers Network. This collaborative research network will use high-tech screening methods to identify small molecules that can be used as research tools. Certain small organic chemical compounds can be valuable tools for understanding the many important cellular events involved in health and disease, which is key to identifying possible new targets for diagnosis, treatment, and prevention. To date, most useful small molecules have been found serendipitously. The molecular libraries screening program is an effort by NIH to take an efficient, high-throughput approach toward the discovery of many more useful compounds.

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. An estimated 68.7 million Americans age 12 or older used an illicit drug or a tobacco product in 2002. Recent epidemiologic studies have shown that between 30 and 60 percent of drug abusers have concurrent mental health disorders, in addition to comorbid alcohol abuse. Despite the extensive prevalence of drug abuse and addiction, the lack of effective treatment for certain types of addictions or population groups, and the lack of utilization of those treatments known to be effective, continue to be substantial barriers to reducing the prevalence and impact of this major health problem.

Disease Burden

The total costs of illicit drug abuse and nicotine addiction to our Nation are almost $300 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

Planned Implementation Strategies

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 approximately 1000 patients will be completed for participation in BSFT, Seeking Safety, or MET treatment protocols.

In order for NIH to be successful in achieving this goal, a series of ambitious steps have been planned. These steps include 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.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. As of October 2005, a total of 184 treatment providers have been trained, 94 more than the original target of 90. All 184 treatment providers are expected to participate in the trials. There are three trials: Brief Strategic Family Therapy (BSFT), Seeking safety, and Motivational Enhancement Treatment (MET). In FY 2005, treatment providers were actively trained only for the BSFT trial, and training was provided at five sites. There are 20 sites that have participated in the three trials to date. No more training is required.

Implementation Strategy Advances or Other Highlights

Patients are enrolled in the three behavioral treatment interventions adapted for community-based settings. BSFT, Seeking Safety, and MET are being delivered to diverse communities that are 22%, 34% and 41% African American, respectively, and 7%, 7%, and 14% Hispanic, respectively.

Efficiency

To achieve this goal, 184 treatment providers, 94 more than planned, have been trained. The CTN concentrates on effectiveness studies that use standardized treatment interventions. In addition to the availability of standard methods, courses, or guidelines, the training of treatment providers is an integral part of the CTN activities. Training has had to be an ongoing priority to ensure the continuity of treatment in the delivery of care. Extra treatment providers must be trained for two important reasons: (1) to accommodate the requirements of shift work/service provision, and (2) in anticipation of the different turnover rates of providers at the sites.

To achieve continuity of treatment, a central training committee and coordinating centers work closely with the investigators to ensure adequate training of treatment providers at each site. It is standard procedures that each node has an identified person to oversee training and a training tracking database keeps investigators informed of the needs within their site. Expert trainers are provided either by contract or from expertise within the members of the CTN to attend to these needs.

The CTN training has been achieved efficiently. More treatment providers have been trained than was planned, and the continuity of treatment in the trials has been ensured. Furthermore, in accommodating the turnover rate of trained providers, the skills from the training are being translated farther than the CTN sites, since the trained therapists will influence practice and treatment delivery as they move out of these sites and on to non-CTN sites.

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

BACKGROUND

Tobacco use in the United States is a major cause of death and disability. Approximately 440,000 deaths in the U.S. each year are attributed to cigarette smoking. The high failure rate reported for smoking cessation efforts (75-90%) challenges health care professionals to explore innovative approaches to treating the highly addictive behavior of tobacco use. The agent largely responsible for maintaining tobacco addiction is nicotine. In addition to animal studies that have shown the addictive properties of nicotine, studies in humans show that smokers adjust their smoking behavior to maintain a relatively stable concentration of nicotine and that the reinforcing effects of nicotine are blocked by pretreatment with the nicotinic receptor antagonist, mecamylamine. Nicotine addiction perpetuates itself by enhancing the release of multiple neurotransmitters to produce stimulation, pleasure, and reward. Tolerance to elevated nicotine levels develops over time, as does the dependence upon nicotine to maintain brain function. Withdrawal symptoms after abstinence result from a return to subnormal levels, of some of these neurotransmitters. Withdrawal symptoms, such as depressed mood, anxiety, insomnia, irritability, difficulty concentrating, increased appetite, and decreased heart rate, usually peak at one week after abstinence and taper off over time.

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

Prevalence/Incidence

Forty years after the Surgeon General's first report on smoking and health, tobacco use continues to pose an enormous public health threat to the United States and the world. In 2003, the median prevalence rate of current cigarette smoking by adults among the different states comprising the United States was 22.1%. This prevalence rate is still nearly double the nation's year 2010 healthy people goal of achieving a 12 percent prevalence rate. The prevalence rates among some adult minority population groups is nearly four times the desired rate, and prevalence rates for youth are also very high.

Disease Burden

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

Rationale

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

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Identify 1-2 promising compounds as candidate medications for tobacco addiction.	(FY05) Current medications inadequate to address tobacco addiction.			◆		
FY05	*Actual Performance:* (MET) Four candidate medications, instead of two, have been identified for tobacco addiction, and research is continuing on these candidates.					
Begin at least one clinical trial of a candidate medication for tobacco addiction.	(FY05) NicVAX shows promise in pre-clinical or early clinical trials.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Develop and test 1-2 potential new compounds for tobacco addiction in animal models.	To be determined by results in FY06.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET efficiently. Four, instead of two, candidate medications have been identified for tobacco addiction: selegiline, nicotine vaccine, and two compounds that enhance GABA, CGP44532, and tiagabine.

Tobacco addiction is a preventable cause of disease and death, and the identification and development of candidate medications for smoking cessation is critical for improving public health. The four candidate medications that have been identified all have the potential to aid in smoking cessation through their ability to counteract the effects of cigarette smoking on the brain. For example, selegiline acts by inhibiting an enzyme which is thought to be involved in the development of withdrawal. The GABA agonists reduce the effects of nicotine on the pleasure pathway in the brain. The nicotine vaccine would prevent nicotine from reaching the brain, thereby preventing its effects on the brain and behavior.

Implementation Strategy Advances or Other Highlights

Another neurotransmitter system was identified for its potential relevance to medications development for tobacco addiction. $GABA_B$ potentiating compounds decreased self-administration of nicotine and other drugs in rats and decreased the reinstatement of cue-induced nicotine-seeking.

Efficiency

Four candidate medications have been identified for tobacco addiction instead of two. In addition to promising research on a nicotine vaccine and the medication selegiline, new results from additional NIH-funded research on the effects of a GABA agonist on nicotine withdrawal in humans suggests that GABA agonists may also be promising medications for smoking cessation. As a result, two additional compounds have been included as candidate medications towards this goal. Pre-clinical trials have demonstrated the efficacy of all four medications in animal models, and research is progressing in clinical trials.

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

BACKGROUND

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

Rationale

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

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

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

treated with the anti-vascular endothelial growth factor (VEGF) drug bevacizumab (Avastin).

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Clinical Trials

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

Test-Retest Reproducibility

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

Electronic Infrastructure

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

Consensus Standards

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

Therefore, the implementation strategy consists of several parts. In FY 2005 a clinical trial protocol was conducted to include serial FDG-PET scans in Stage III and IV lung cancer patients before and after therapy. Therapy will be standard, not experimental, therapy. Scans will be done on state-of-the-art combined PET-CT scanners. The trial will be conducted during FY 2006 and FY 2007 by the NIH-funded imaging cooperative group known as ACRIN (www.ACRIN.org). Half of the patients will receive duplicate

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

Similar trials using FLT-PET and DCE-MRI may be launched in FY 2006 or FY 2007.

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

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Convene workshops of relevant experts on PET and MRI scanning to develop consensus standards and quantitative tools for image assessment.	(FY05) Workshop planned.			◆		
FY05	*Actual Performance:* (MET) FDG-PET and DCE-MRI workshops have been held. Consensus guidelines are on the Cancer Imaging Program web site: imaging.cancer.gov.					
Initiate lung cancer therapy trial with serial functional imaging scans and perform preliminary analysis of test-retest repeatability data from 1st year of trial.	(FY05) Test-retest (repeatability) data not currently obtained in a standardized manner.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Complete accrual in lung cancer therapy trial and perform final analysis of test-retest reproducibility of functional imaging scans.	(FY05) Trial not complete.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target has been MET because both the FDG-PET and DCE-MRI workshops have been held. The FDG-PET workshop was held January 10-11, 2005, and the report from that workshop is in its final editing stage. The DCE-MRI workshop was held November 22-23, 2005. A report from that workshop was published in Clinical Cancer Research, and the consensus guidelines are on the Cancer Imaging Program web site: imaging.cancer.gov. The FDG-PET workshop was held January 10-11, 2005, and the report from that workshop is in its final editing stages. Examples of the guidelines include:

- Study design should incorporate quality assurance of the MR system, sequences,

set-up procedures and radiological processes (e.g., T1 accuracy, system stability, B1 homogeneity).
- Pharmacodynamic assessment should use T1 weighted studies of low molecular weight gadolinium chelates.
- When available, preclinical tumor data should be used to determine timing of DCE-MRI measurements for drugs with novel mechanisms of action.
- Adjust orientation so that motion is in-plane when motion effects cannot be avoided (e.g., liver, lungs).

Implementation Strategy Advances or Other Highlights

A protocol team has been established within ACRIN to develop the protocol for the FDG-PET lung trial. The current draft protocol is being reviewed by FDA staff members and representatives from the pharmaceutical industry.

A proposal to study volumetric algorithms for lung cancer response is circulating for comment within pharmaceutical companies and academic sites. In September 2005, a public web site called I3 Imaging Archive, which provides a central repository for images for development and evaluation of algorithms such as 3-D volumetric assessment, was made available. A large number of serial CT scans from patients with lung cancer are available at that web site.

A Memorandum of Understanding (MOU) with the American College of Radiology (ACR) has been signed to create an activity to centralize and disseminate consensus guidelines for clinical trials. The steering committee held its first meeting in September 2005, and created a public web site, upict.acr.org. The acronym UPICT stands for Uniform Protocols for Imaging in Clinical Trials. The recommendations from the Clinical Trials Working Group state that all NIH-funded protocols should use standard imaging protocols if they exist in UPICT, unless there is good justification not to.

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

BACKGROUND

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

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

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Initiate at least 3 research projects to improve objective measures of hot flash frequency.	(FY04) Currently available monitors are not suitable for multiple day ambulatory studies.			◆		
FY05	*Actual Performance:* (MET) NIH initiated seven research projects.					
Develop and validate improved devices to measure hot flash frequency.	(FY05) Improved devices not yet available.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Continue validation of at least 2 devices to measure hot flash frequency.	(FY06) Prototype device from FY05 target should be available for additional validation testing.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. NIH initiated seven new research projects to improve the measurement of hot flashes in ambulatory settings, exceeding its FY 2005 target. This new series of research projects aims to develop lightweight, unobtrusive, and easy to use devices for measuring hot flashes, some weighing as little as 15-20 grams (less than three quarters). Other prototypes being tested can be used up to four weeks between battery changes.

Efficiency

Because of the number of strong applications submitted and the availability of funds in the Small Business Innovation Research (SBIR) program, NIH was able to initiate seven research projects to improve the objective measurement of hot flash frequency, four more than initially planned.

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

BACKGROUND

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

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

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

Prevalence/Incidence

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

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

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

Rationale

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

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

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

HapMap to identify and validate genes that influence the development and progression of prostate cancer and to assess their contribution to racial and ethnic disparities for this malignancy.

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

likely to contain them. Currently, FBPP data are available only to outside investigators and collaborators when authorized by the FBPP. In its next phase, pooled data generated by the FBPP will be available to other researchers, and data training workshops will be held to facilitate research in this area. The goal of the FBPP is to enable improvements in hypertension prevention and treatment.

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Collect a cumulative total of 5.8 million genotypes from the FUSION study.	(FY04) 3 million genotypes collected in the FUSION study.			◆[e]		
FY05	*Actual Performance:* (MET) The FUSION study collected 3.0 million genotypes, making a cumulative total of 6.0 million genotypes collected for this study of genetic variants that predispose to common type 2 diabetes. The cumulative total exceeded the projected target by 200,000 genotypes.					
Release Phase 1 core pooled data with documentation to the public, create a web utility for sharing Family Blood Pressure Program data and hold a training workshop for the scientific community.	(FY05) No FBPP data publicly available to the scientific community.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Perform initial whole genome scan for prostate cancer susceptibility genes in the C-GEMS study.	(FY06) Scientific infrastructure established and RFP for initial scan released.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET efficiently. The FUSION study collected 3.0 million genotypes, leading to a cumulative total of 6.0 million genotypes that have been collected for this study of genetic variants that predispose to common type 2 diabetes (T2D). The cumulative total exceeded the projected target of 5.8 million genotypes by 200,000.

Implementation Strategy Advances or Other Highlights

During FY 2005, the FUSION study collected 3.0 million genotypes. These additional genotypes increased the total to 6.0 million genotypes that have been collected for this study of genetic variants that predispose to common type 2 diabetes (T2D). This significant increase in data was largely a result of a project in which a large region of chromosome 14 was fine-mapped for T2D-associated genetic variations. Variations in T2D candidate genes published in the literature or from the FUSION genomic regions of

interest were also tested for association with T2D. The majority of this genotyping was performed at the Center for Inherited Disease Research (CIDR) at NIH using high throughput genotyping, a technology which rapidly detects genetic variation with high cost efficiency.

Efficiency

With continually increasing information in public genomic database resources such as dbSNP, HapMap database has (1) increased the number of identified variants in the genome, (2) provided information regarding the correlation among variants, and (3) provided information as to the potential functional affects of such variants. FUSION utilized this wealth of information to efficiently select variants for genotyping that are optimized for coverage of the genome and have increased chances of being the causative variants of this disease. Advances in both genotyping technology and data management, as well as reduction in cost, were also major factors in FUSION's ability to collect such a large volume of data in a very short time frame.

PART

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

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET through the collection of blood samples from over 4,000 well-characterized patients with either AMD or glaucoma from NIH-supported studies such as the Age-Related Eye Diseases Study (AREDS), the Ocular Hypertension Treatment Study (OHTS), the Collaborative Initial Glaucoma Treatment Study (CIGTS), the Beaver Dam Eye Study, and others. Linkage analysis, identification of candidate genes and DNA sequencing as well as other biotechnologies were used to successfully achieve this target. The NIH has also increased the scope and availability of genomic resources to researchers through the NEIBank.

Additionally, the NIH announced the creation of the National Eye Disease Genotyping Network (EyeGENE) that will assist in developing public and professional awareness of genotype/phenotype resources that are available to people with various ocular genetic diseases, their clinicians, and scientists studying these diseases. The network will enroll patients interested in participating in future therapeutic clinical trials to treat or prevent genetic eye disease.

Implementation Strategy Advances or Other Highlights

Four different NIH supported laboratories identified a common variation in a gene called complement factor H (CFH) that accounts for as much as 50 percent of AMD cases, thereby partially achieving this long term goal. The CFH protein regulates an inflammatory response—the alternative complement cascade—that is typically triggered by infectious microbes. From a research perspective, discovery of the CFH gene's role in AMD is the first time scientists have uncovered the genetic complexity of a late onset

disease. Much of this work relied on the use of data from the emerging International HapMap Project. This project seeks to catalog the genetic variation that exists in the large blocks of DNA that are inherited without undergoing recombination. It is thought that about 95% of human DNA is inherited in these larger haplotype blocks, making it much faster and easier to perform genome wide scans to look for the causes of genetically complex diseases. Discovery of a common polymorphism in AMD is the first validation of this research tool. From a disease perspective, inflammation is thought to play a role in many common diseases such as Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, stroke, and atherosclerosis. Although the cells, tissues, and molecular events in these diseases are diverse, they may share common disease mechanisms that present an opportunity to cross pollinate findings from diverse research areas. In the short term, it will be possible to develop an animal model for AMD and evaluate therapies that control or minimize complement activation.

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 2004, the prevalence of diabetes in the United States was approximately 18.2 million people, or 6.3 percent of the population, with approximately 90-95 percent of this number having type 2 diabetes.
- CVD accounts for two-thirds of deaths among people with diabetes.
- Chronic kidney disease is estimated to affect as many as 10 to 20 million Americans and can lead to kidney failure. While this estimate is used by advocacy groups, there is substantial uncertainty in the numbers. Unpublished internal NIH analyses suggest lower estimates for chronic kidney disease.
- The number of patients with kidney failure or end-stage renal disease (ESRD) has doubled over the past decade and now stands at nearly 400,000.
- Heart disease and stroke are the leading causes of death in patients with ESRD.

Disease Burden

The Nation faces national epidemics of both type 2 diabetes and ESRD. In 2002, the economic cost of diabetes in the United States was estimated at $132 billion. Once considered a disease of adults, type 2 diabetes now increasingly strikes during childhood. Rates of type 2 diabetes are approximately twice as high among African Americans and Hispanic Americans as among Caucasian Americans and are even higher among American Indians. Among adults with diabetes, heart disease death rates are two to four times higher than in the general population. Diabetes also negates the protection gender affords non-diabetic women. Even among individuals with impaired glucose tolerance, in which glucose levels are higher than normal but do not yet indicate diabetes, CVD death rates are elevated 1.4 fold. Chronic kidney disease is also a significant health burden. In its most severe forms, it leads to ESRD, where either dialysis or kidney transplantation is required to maintain life. About half of new cases of ESRD have kidney disease as a consequence of diabetes. The number of patients with ESRD has doubled over the past decade, with the increasing disease burden most pronounced among minority populations, especially African Americans and American Indians. The markedly reduced life expectancy of patients with ESRD is due largely to death from heart disease and stroke; rates of CVD are tenfold to a hundredfold greater than in the general population. Even among chronic kidney disease patients with a mild to moderate reduction in kidney function, CVD rates are increased twofold to fourfold. The cost of caring for the ESRD population was $19.4 billion dollars in 2000 and consumed about 6 percent of the Medicare budget.

Rationale

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

Goal SRO-6.2 also addresses a critical knowledge gap. While some clues and some promising therapies have emerged from previous epidemiologic and clinical trials, many unanswered questions remain. For example:

- Recent clinical trials established the benefit of the management of both blood pressure and low-density lipoprotein-cholesterol (LDL) in reducing CVD risk in type 2 diabetes and of glucose control in reducing CVD risk in type 1 diabetes, but a number of potential strategies to reduce CVD risk require further study.
- Although even moderate weight loss can dramatically reduce the development of type 2 diabetes among those at high risk, a benefit of intentional weight loss in preventing cardiovascular complications in people with diabetes has not yet been established.
- Even though improved blood glucose control dramatically reduces the eye, kidney, and nerve complications of diabetes, and has recently been shown to reduce CVD in type 1 diabetes, its benefits in reducing CVD in type 2 diabetes are not fully established, and it is not known whether insulin-providing or insulin-sensitizing strategies for glucose control is more effective in reducing CVD mortality.
- Lowering of LDL cholesterol has been shown to prevent CVD in general, but type 2 diabetes is associated with a distinct lipid profile, with low high-density lipoprotein (HDL) cholesterol and increased triglycerides. Research is needed to establish optimal management of lipids and blood pressure to reduce CVD in type 2 diabetes.
- Homocysteine, an amino acid produced in the body, is a known risk factor for CVD. Folate and B-vitamin supplementation can normalize homocysteine levels in patients with mild chronic kidney disease, their effect on CVD risk remains to be determined.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

overweight or obese at study entry (BMI of 25 or over) are enrolled.

Note: Although the Look AHEAD clinical trial will not be completed until 2013, it will generate intermediate outcomes that will contribute to realizing GPRA Goal SRO-6.2 by 2011. For example, the Goal SRO-6.2 target for FY 2006 is to provide outcome data on the success of the one-year intensive weight loss phase and the effect of the weight loss intervention on important clinical measures such as diabetes control, lipids, blood pressure, and fitness. Significant cost savings will accrue from not having to conduct similar studies in a separate trial.

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

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

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

FREEDOM [Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease] Trial. This trial will compare, in 2,400 diabetic patients, a multivessel stenting strategy, using drug-eluting stents, to coronary artery bypass graft (CABG) surgery. The primary outcome is the difference in mortality rates between the stent group and CABG group over a 5-year period.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Assess the effect of intensive versus conventional glycemic control on intima media thickening of the carotid artery, a marker for progression of atherosclerosis, in participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.	(FY02) No effect of intensive vs. conventional blood glucose control was seen in earlier carotid ultrasound measurements	◆				

FY03	*Actual Performance:* (MET) Effects of intensive versus conventional glycemic control were assessed in EDIC study participants. Finding suggests that aggressive management of blood glucose levels can produce short- and long-term benefits.	
	Complete recruitment for the Action for Health in Diabetes (Look AHEAD) study (5,000 patients), in order to compare the effects on cardiovascular events of an intensive lifestyle intervention designed to achieve and sustain weight loss versus support and education in obese individuals with type 2 diabetes.	(FY03) Look AHEAD had recruited about half (2,500) of its patients
FY04	*Actual Performance:* (MET) Look AHEAD exceeded its target goal of 5000 obese patients who have type 2 diabetes, and enrolled 5,145 participants by May 2004.	
	Complete recruitment for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (10,000 patients), which is comparing effects on CVD of intensive versus conventional interventions of lowering blood glucose, blood pressure; and treating blood lipids in diabetic patients at high risk for CVD.	(FY03) ACCORD had recruited 1,184 participants in a Vanguard phase
FY05	*Actual Performance:* (MET) The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005.	
	Look AHEAD aims to report outcome data on the success of the one-year intensive weight loss intervention and its impact on CVD risk factors such as diabetes control, lipids, blood pressure, and fitness.	(FY05) Information is not available regarding the impact of a one-year intensive weight loss intervention on these parameters in a similar diabetic population
FY06	*Actual Performance:* Performance results will be reported in February 2007.	
	To complete at least 90% of the total enrollment for the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial which aims to determine whether reduction of total homocysteine by means of a multivitamin in clinically stable kidney transplant recipients results in significant reduction in atherosclerotic CVD.	(FY04) As of August 2004, a total of 2,000 study participants have been randomized into the trial.
FY07	*Actual Performance:* Performance results will be reported in February 2008.	

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. The NIH enrolled 10,000 patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial by September 30, 2005. As of October 29, 2005 an additional 251 participants had been enrolled bringing the total enrollment to 10,251. In addition, ACCORD achieved 37.7 percent minority representation, exceeding its target of recruiting at least 33 percent minorities. The study population is 40.6 percent female, close to its 50 percent female goal.

The ACCORD trial is the largest long-term randomized trial ever conducted in a type II diabetes population. ACCORD is being conducted at 77 clinical sites across the U.S. and Canada. Recruitment targets were met despite the fact that ACCORD participants needed to be eligible for two of the interventions (blood glucose as well as either blood pressure or lipid) and that the interventions and follow-up requirements can very demanding for the participants.

Implementation Strategy Advances or Other Highlights

The participants in the ACCORD trial are being randomized to receive either intensive blood glucose treatment or standard blood glucose treatment. A total of 4,733 participants have been randomized to be treated to a systolic blood pressure goal of <120 mmHg versus a blood pressure goal of <140 mmHg; 5,518 have been randomized to be treated with a fibrate plus a statin versus a statin alone for their blood lipids. All participants are being followed to determine effects of the treatments on major cardiovascular events,

defined as nonfatal heart attack, nonfatal stroke, or cardiovascular death. The study is performing well in achieving the treatment targets.

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 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.

BACKGROUND

Disease Burden

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

Rationale

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

environmental disease. Designed initially as an interpretive tool for toxicogenomics, the CEBS knowledge base will ultimately become a knowledge base to support both discovery- and hypothesis-driven research.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

NIH, international counterpart databases (e.g., European Bioinformatics Institute Tox-ArrayExpress), industry, and academia will collaborate 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.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Launch a pilot prototype database project to test the design and implementation of the knowledge base components and system architecture.	(FY02) Intramural databases and commercial software to build ProtoCEBS available	◆				
FY03	*Actual Performance:* (MET) ProtoCEBS launched, tested, and implemented.					
Create the capability to import, export, and link molecular expression data by extending the Chemical Effects in Biological Systems (CEBS) database object model to include toxicology/pathology fields, and by creating a data portal that will load toxicology data.	(FY03) CEBS object model to capture molecular expression data (only) designed but not tested		◆			
FY04	*Actual Performance:* (MET) CEBS now has a data portal that loads toxicology data. CEBS can import, export, and link molecular expression data to toxicology/pathology fields.					
Create and provide public access to a global molecular expression and toxicology/pathology database of both chemicals found in the environment and drugs that have an effect on biological systems (CEBS), featuring simple query download capability.	(FY03) CEBS version 1.0 launched in August 2003 contains only microarray data.			◆		
FY05	*Actual Performance:* (MET) CEBS versions 1.5 and 1.6 have been made available to the public. These programs provide simple query download capability of global molecular expression and toxicology/pathology data on a select number of studies of chemicals found in the environment and drugs that have an effect on biological systems.					
Enhance the CEBS to allow the capture and integration of transcriptomics, proteomics, and toxicologic data for the same compound.	(FY04) The CEBS is limited to individual data sets and cannot integrate data from multiple data sets for a single compound				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					

Enhance electronic sharing of 'omics and biology endpoint data	Initial integration of microarray and toxicologic/histopathologic data achieved	◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.	

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. As of June 2005, version 1.5 of CEBS has been available to the public on the CEBS website (http://cebs.niehs.nih.gov). This program provides 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. On August 30, 2005, version 1.6 was released which implemented the display of multiple stressors and associated experiment factors (e.g., time, dose).

Implementation Strategy Advances or Other Highlights

The CEBS System Biology object model (CEBS SysBio-OM) was completed to enable capture of multi-domain –omics datasets (e.g., transcriptomics, proteomics, and metabonomics). In addition, a CEBS ToxArm was designed and implemented to enable capture of information on the toxicogenomics study design and toxicology/pathology outcome datasets.

Version 2.0 of CEBS is now being developed. This version of CEBS will capture much more detail of individual studies (e.g., type of diet, room temperatures, light/dark cycle), and will contain results of many more studies. Currently, staff is defining the content and prototyping the functionality of each page needed for this more robust toxicogenomics database.

PART

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

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

Rationale

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

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

Glycans are molecules that may play a role in host defense, including defense against viral airway infection, one of the most common triggers for AE. An individual's "secretor" status is defined by enzymatic activity involved in glycan biosynthesis (glycosyltransferases) and glycan degradation (glycosidases). The secretor status and frequency of viral airway infection in asthmatic patients hospitalized for management of acute asthma symptoms will be compared to asthmatic individuals without a history of exacerbation requiring hospitalization. The role of glycans and glycosidases during virus-induced AE will also be studied (FY 2006 performance measure).

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 (FY 2007 performance measure). During the course of the studies, investigators will meet to share experiences, successes, and concerns, as well as to assess the state of the field.

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Initiate study of molecular, cellular, and genetic causes in AE.	(FY05) Little is known about the factors that predispose asthmatics for exacerbation.			◆		
FY05	*Actual Performance:* (MET) Developed and funded a program consisting of twelve studies which will examine the molecular, cellular, and genetic causes of AE.					
Initiate study to compare glycosidase activity in hospitalized asthmatics and asthmatics with no AE history.	(FY05) Little is known about the role glycosidase activity may play in modification of airway glycans and the promotion of virus-induced AE.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Analyze data from studies of molecular, cellular, and genetic causes in AE.	(FY05) Little information is available on how environmental factors affect the lung and subsequently result in AE.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY05 target was MET by developing and funding, during the Spring and Summer of FY05, a program consisting of twelve studies to examine the molecular, cellular, and genetic causes of AE. The NIH initiative, entitled "Asthma Exacerbations: Biology and Disease Progression", solicited clinical and basic research projects to help elucidate the biologic mechanisms of AE biology and resolution and their impact on lung physiology and disease state. Twelve meritorious applications were funded in response to the initiative. The studies will address the mechanisms by which a number of biologic effector molecules interface with environmental triggers (e.g., pollutants, allergens, viruses), the immune system and the lung to promote AE and their impact on lung physiology. Additional studies will also examine the role of the pulmonary structure and individual genetic predisposition in AE. The proposed research will provide a comprehensive program, by bringing together several different scientific disciplines, which will address the biology of AE and the impact on disease state. This knowledge will provide the basis for development of interventions that will target ongoing, downstream processes and result in altered immune response and airways physiology and function.

Implementation Strategy Advances or Other Highlights

To date, individual studies have been funded from one to four months. Recruitment for at least one of the clinical studies has already been initiated and data collection has begun.

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

BACKGROUND

Prevalence/Incidence

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

Disease Burden

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

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

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

sciences for the translation of nanotechnology into clinical applications.

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target has been MET because nanosensors and nanoparticles have been integrated into a platform technology for development in applied research settings. Examples of this achievement include: (1) nanoscale dendrimers, (2) nanowires and functionalized carbon nanotubes, and (3) targeted quantum dots.

Implementation Strategy Advances or Other Highlights

Nanoscale dendrimers, a type of spherical polymer, have shown promise as multifunctional delivery agents for anticancer drugs and imaging agents. Investigators have developed silver-containing dendrimers that can function as non-toxic intracellular molecular beacons that should be capable of labeling individual biomolecules within a cell.

Nanowires and carbon nanotubes each show promise as key components in future biosensors. Combining the two nanoscale sensors into one device may prove to have even greater potential for manufacturing the next generation of biomarker detectors. Researchers have first developed a novel chemical method for attaching antibodies directly

to indium oxide nanowires. The investigators then combined the antibody-labeled nanowires with antibody-labeled carbon nanotubes to create a device for detecting PSA at levels suitable for clinical detection of this prostate cancer biomarker. This combination device was capable of detecting 5 nanograms of PSA per milliliter of solution, well within the clinically useful range of sensitivity.

NIH-supported researchers have developed a water soluble formulation of fluorescent quantum dots labeled with a monoclonal antibody that binds to epidermal growth factor receptor (EGFR). Since EGFR is found in excess of normal amounts on the cell surface of several types of cancer, it is a likely candidate as an early predictive marker for cervical cancer. Using the labeled quantum dots, which fluoresce strongly when irradiated with white light, the investigators demonstrated that they were able to distinguish between cultured cells that overproduce EGFR and those that do not. Based on these results, the researchers are planning to determine if the quantum dots can be used to image EGFR-positive cells in an animal model of cervical cancer.

Additional research has demonstrated that fluorescent quantum dots can be customized to concurrently image and differentiate tumor vessels from the perivascular cells and the surrounding matrix. Quantum dots were also used to measure the ability of different sized particles to access the tumor. Researchers also successfully monitored the recruitment of quantum dot-labeled bone marrow-derived precursor cells to the tumor vasculature. This work shows the versatility of quantum dots for studying tumor pathophysiology and creating avenues for treatment.

NIH-supported research led to the achievement of the FY 2005 target by integrating nanoparticles and nanosensors into a platform technology for development in an applied research setting. A number of these platform technologies have also made substantial advances toward achieving the FY 2006 target of integrating nanotechnology-based components into a system capable of detecting biomarkers in vitro.

PART

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

SRO-7.3	**By 2005, create the next-generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.**

BACKGROUND

Prevalence/Incidence

Virtually all diseases have a genetic component. While the DNA sequences of any two people are 99.9 percent identical, there are at least 10 million DNA sites where people commonly differ. Some of these variations will affect an individual's risk for disease or response to drugs.

Disease Burden

A major goal of genetic research is to identify gene variants that contribute to disease. Finding these variants allows an understanding of the disease process, thus enabling development of methods for disease prevention and treatment. For single-gene disorders, diseases like Huntington disease or cystic fibrosis with a relatively straightforward genetic basis, current methods have been highly successful in locating the genes involved. Most people, however, do not have single-gene disorders but develop common diseases such as diabetes, cancer, hypertension, heart disease, and psychiatric disorders, which occur because of interactions of multiple genetic and environmental factors. Strategies that work well for single-gene disorders lack the power to map such "polygenic" disorders; thus, relatively little is known about the genetic basis of these common diseases or the factors that determine individual risk of disease, clinical course, or response to treatment.

Rationale

Sites in the genome where individuals differ in their DNA spelling by a single letter are called single nucleotide polymorphisms (SNPs). Recent work has shown that about 10 million SNPs are common in human populations. SNPs are not inherited independently; rather, sets of adjacent SNPs are inherited in blocks. By understanding the way in which genetic variations are correlated in these DNA "neighborhoods" or "haplotypes," considerable savings in time, effort, and cost can be achieved in uncovering the hereditary factors in disease. Although a region of DNA may contain many SNPs, it takes only a few SNPs to uniquely identify or "tag" each of the haplotypes in the region. This presents the possibility of a major shortcut in identifying hereditary factors in disease.

Most common haplotypes occur in all human populations, although their frequencies may vary considerably. Initial studies also indicate that the boundaries between the blocks are remarkably similar among populations in Europe, Asia, and Africa. These data indicate that a human haplotype map (HapMap) built with samples from these three geographic areas would apply to most populations in the world, although additional testing of this conclusion is needed.

NIH has taken a leadership role in the development of the HapMap, a catalog of the haplotype blocks and the SNPs that tag them. The HapMap is a tool that can be used by researchers studying many diseases to find the gene variants that contribute to those diseases. HapMap will be a description of the patterns of human genetic variation. It will

be a tool that researchers will use to find genes and genetic variations that affect health and disease. The HapMap will reduce the number of SNPs required to examine the entire genome for association with a phenotype from the 10 million SNPs that exist to roughly 200,00-500,000 tag SNPs. This will make genome scan approaches to finding regions with gene variants that affect disease risk much more efficient and comprehensive, since efforts will not be wasted typing more SNPs than necessary, and all regions of the genome can be included. In addition to its use in studying genetic associations with disease, the HapMap should be a valuable resource for studying the genetic factors contributing to individual variation in response to environmental factors, in susceptibility to infection, and in effectiveness of, and adverse responses to, drugs and vaccines. This new tool will thus allow researchers to study how disease processes work, which will lead to interventions to prevent, delay, or cure diseases.

Despite the progress this map will enable, it will be difficult to quantify fully the impact of the HapMap for some 5-10 years beyond its completion. During that time, it will be possible, however, to quantify how much the HapMap data are used, and to monitor the diseases and other phenotypes that will be studied using the HapMap.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To conduct the HapMap project, NIH organized an international consortium of researchers in Canada, China, Japan, Nigeria, the United Kingdom, and the United States, including eight genotyping research groups, five data analysis groups, a data coordination center, and four sample collection groups. The consortium had originally planned to identify an additional 3 million new SNPs needed to fill in areas where the current density of SNPs in public databases is not sufficient, but due to advances in technology the project has already identified a total of 6 million new SNPs. The consortium collected samples from four populations (CEPH [U.S. residents with ancestry from Western and Northern Europe], Yoruba in Nigeria, Chinese, and Japanese). The consortium also developed scientific strategies to choose which SNPs to study and how best to assess the quality of the data and derive haplotypes from the SNP data.

The genotyping research groups had originally planned to genotype about 1.6 million SNPs to discover the pattern of variation among the samples, but due again to improved technology, the team has been able to study many more SNPs. As a result of advances in genotyping technology, in April 2004 NIH released a Request for Applications (RFA) soliciting applications for a cooperative agreement to augment the International HapMap Project by supporting the genotyping of 4.6 million SNPs across the genome in 270 samples from these four populations, at high quality and at a cost of about 1 cent per genotype. This cost is substantially lower than when HapMap was begun in 2002. The data from this effort contributed greatly to the development of the HapMap. These genotype data were analyzed to derive haplotypes, develop the HapMap, and identify a "gold standard" set of SNPs that contain most of the information on the patterns of genetic variation, thereby making the HapMap maximally useful and efficient for later studies relating genetic variation to health and disease. Review of available SNPs has already demonstrated that the haplotypes in the Yoruba samples are shorter and therefore will require a denser SNP map.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
For existing blood samples from U.S. residents of Western and northern European ancestry, obtain additional consent from the donors for this new use and begin genotyping 300,000 single nucleotide polymorphisms (SNPs, sites in the human genome where individuals differ by a single letter) in those samples.	(FY02) 90 existing samples, none of which included the necessary consent for genotyping	◆e				
FY03	*Actual Performance:* (MET) All needed consents obtained and genotyping performed on 132,000 SNPs.					
Collect samples from populations in Japan, China, and Nigeria; complete collection of additional 3 million SNPs and release in public databases.	(FY03) 2.4 million SNPs in database		◆e			
FY04	*Actual Performance:* (MET) Sample collection has been completed, and greater than 3 million SNPs have been released in the public database.					
Develop a first-pass draft HapMap containing 600,000 SNPs.	(FY03) 2.4 million SNPs in database but none of the samples genotyped to produce any part of the HapMap			◆e		
FY05	*Actual Performance:* (MET) Completed first-pass draft HapMap with 1.007 million SNPs, an increase of more than 400,000 SNPs over the projected total of 600,000. Goal completed.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. A first-pass draft of the HapMap containing 1.007 million SNPs, an increase of more than 400,000 over the projected total of 600,000, was completed.

Goal Achievement

The goal to create the next-generation map of the human genome, a haplotype map or 'HapMap,' by identifying the patterns of genetic variation across all human chromosomes was completed in 2005. The 2004 samples were used to complete the first-pass draft of the HapMap. Eight centers genotyped a total of 1.007 million SNPs in all the samples. The patterns of human genetic variation were obtained from these data. The methods used to choose the tag SNPs that describe these patterns are available from the HapMap web site. These tag SNPs will be useful in later studies of many diseases. For instance, the HapMap can be used by researchers who are trying to identify genetic variants associated with a medical condition and would want to compare the SNPs in individuals afflicted with the disease and those who are not. If a particular SNP is more common among individuals with the disease, that SNP could be used as a marker to locate and identify the gene associated with the condition. Instead of testing all SNPs in each individual, the HapMap enables researchers to take advantage of how SNPs are organized and focus their efforts on a relatively small number of tag SNPs to find candidate genes associated with the disease.

Implementation Strategy Advances or Other Highlights

In FY 2005, Phase 1 of the International HapMap Project was successfully completed. In addition, genotyping has been attempted on an additional 4.6 million SNPs. The data have been released on the HapMap web site. A paper describing the results of this landmark study was published in the October 27, 2005 issue of the journal Nature.

Efficiency

A first-pass draft HapMap was completed with 1.007 million SNPs, an increase of more than 400,000 SNPs over the projected total of 600,000 at the project's inception. All SNPs

are of high quality. As a result of advances in genotyping technology, NIH has been able to increase genotyping efficiency. High quality genotyping was performed at a cost of about 1 cent per genotype, substantially lower than when HapMap was begun in 2002.

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

BACKGROUND

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Complete the genomic sequences for at least five bacteria and two protozoa that cause infectious disease.	(FY02) Genome sequences for 32 bacterial pathogens, 1 protozoan parasite, and 1 insect completed.	◆[e]				
FY03	*Actual Performance:* (MET): Genomic sequences were identified for 8 bacterial pathogens and 3 protozoans.					
Complete the genomic sequences of at least five bacterial pathogens, two protozoa, and three fungal pathogens that cause infectious disease.	(FY03) Genome sequences for 40 bacterial pathogens, 4 protozoan parasites, and 1 insect completed		◆[e]			
FY04	*Actual Performance:* (MET) Genomic sequences were identified for 18 bacteria, 4 protozoan parasites, and 3 fungi.					
Complete the genomic sequences of at least five bacterial pathogens, four protozoa, two fungal pathogens that cause infectious disease.	(FY04) Genome sequences for 58 bacterial pathogens, 8 protozoan parasites, 3 fungi and 1 insect completed			◆[e]		
FY05	*Actual Performance:* (MET) Genomic sequencing projects for 30 bacteria, 1 protozoan, 1 insect and 3 fungi were completed.					

Complete the genome sequence of at least six bacterial pathogens, two protozoan parasites, and one invertebrate vector of infectious diseases.	(FY05) Genome sequences for 63 bacterial pathogens, 12 protozoan parasites, 5 fungi, and 1 invertebrate vectors of infectious diseases completed				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Complete goal of determining the genome sequences of 45 human pathogens and 3 invertebrate vectors	FY06 results.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded. Genome sequencing projects of 30 bacterial pathogens, one protozoan parasite, three fungal pathogens and one insect disease vector were completed by NIH. Completion of some projects earlier than anticipated is largely due to advances in molecular biology that have led to remarkably fast and accurate methods for sequencing genomes. Briefly, 30 (rather than five) bacterial pathogen sequencing projects were completed in FY 2005, including Burkholderia mallei (5 strains), Burkholderia pseudomallei, (6 strains), Burkholderia thailandensis, Ehrlichia spp., Escherichia coli (8 strains), Shigella boydii, Vibrio cholerae (6 strains) and Yersinia pestis (2 strains). DNA sequencing projects for one protozoan parasite (Giardia lamblia), one insect vector (Aedes aegypti) and three fungi (Aspergillus terreus and Histoplasma capsulatum (2 strains) also were completed. Although the FY 2005 target for sequencing of protozoa was four new genome projects completed, three of those four were completed ahead of schedule in previous years, with one being completed in FY 2005. The targeted projects scheduled for completion between FY 2003-FY 2005 included a total of 8 protozoa genomes; whereas, the actual performance was 9 protozoa genome projects completed. As of FY 2005, NIH has supported a total of 105 pathogen and invertebrate vectors of infectious diseases genome sequencing projects: 88 bacteria, 6 fungi, 9 parasitic protozoans, and 2 invertebrate vectors of infectious diseases.

Implementation Strategy Advances or Other Highlights

In FY 2005, NIH supported 40 large scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites and invertebrate vectors including: Hepatitis C, Coronaviruses, Bacillus anthracis, Bacillus cereus, Bartonella baciformis, Burkholderia cenopcepacia, Burkholderia dolosa, Camplyobacter, Coxiella burnetii, Escherichia coli, Listeria, Pseudomonas aeruginosa, Shigella, Vibrio paramaeolyticus, three strains of Aspergillus, additional strains of Entamoeba, Plasmodium falciparium, Toxoplasma gondii, one strain of Ricinus communis as well as additional sequencing of Plasmodium vivax and Trichomonas vaginalis.

Efficiency

Technological developments have resulted in a great increase in efficiency and drastic decrease in the cost to sequence DNA . The sequencing process has become faster and more accurate. The Institute for Genomic Research (TIGR), an international microbial sequencing center, reported that the price to sequence a piece of DNA approximately 650 nucleotides in length decreased from $7.70 in 1996 to $0.98 in 2004. In 2005, the cost of sequencing continued to decrease due to improvements in technology.

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

BACKGROUND

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

and richly annotated view of sequence and gene data.

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

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. The expansion and curation of the RefSeq collection is supported by numerous collaborations, the Genome Project database, and targeted outreach activities.

NIH has developed a strategy and implemented the management, database, and software

infrastructure to manage a larger number of collaborations to support the RefSeq collection. Collaborations were established at multiple levels including working with genome sequencing centers that submit assembled annotated genome sequence data to research groups that contribute information about specific subsets of data such as gene-families or features of proteins, or even single genes.

Collaborations are supported by two complementary approaches that include database support for tracking and managing large-scale data as well as a curation team that engages in outreach, education, and data curation for targeted organisms.

The Genome Project Database, released in January 2005, is used to track the status of whole genome sequencing projects as they proceed from a funded proposal to submitted sequence data in GenBank and in the RefSeq collection. In 2005 the International Nucleotide Sequence Database collaboration (INSD) between GenBank, EMBL, and DDBJ agreed that future submissions of whole genome assemblies will require a registered ID in the NIH Genome Project database. The NIH is working on a web service to support assignment of project IDs for EMBL and DDBJ submissions in addition to the support already implemented for GenBank submission. The project ID number is included when sequence data representing a whole genome, whether complete or incomplete, is submitted to the INSD; the Genome Project ID is used to track the association between the submitted sequence data, the project description, and the resulting records generated for the RefSeq collection. The Genome Project ID is only used for submissions of large-scale sequence data generated by sequencing projects aiming to provide a sampling (whether complete or incomplete) of the entire genome for an organism; submissions of genomic sequence data that represent a small portion of the complete genome are not in scope. The availability of this type of tracking is significant as it helps ensure that expansions and updates to the RefSeq collection continue to be comprehensive and timely.

As of November, 2005 the Genome Project database included over 2,700 genome sequencing projects of which over 2,100 have available sequence data. The majority of these projects were defined by NIH staff and processing of data already included in the RefSeq collection. To date, 127 Genome Projects have been defined by collaborators who use the public project submission web site (http://www.ncbi.nlm.nih.gov/genomes/mpfsubmission.cgi).

A complementary approach, the Genome Champion project, was initiated to expand and support collaborations based on establishing a team of expert scientists who serve multiple roles including:

- provide training and education to the scientific communities using the RefSeq collection and other NIH resources
- active outreach to research groups inviting them to submit sequence, map, and other descriptive information and to make it publicly available in a highly integrated set of resources that includes RefSeq, Gene, Genome Project, and the NIH Map Viewer.
- facilitate submission of data by research communities to available NIH databases
- provide “Genome Guide” web pages that serve as a central portal to inform scientific communities about available information, and to facilitate access to this information
- provide a known point-of-contact for research communities
- provide quality assurance testing of submitted data as it becomes available in NIH public

resources
• provide curation support for the inter-related projects RefSeq, Gene, and Genome Project

The Genome champion project has been well-received and welcomed by the sequencing and research communities. This project has resulted in active communication with research communities representing over thirty different organisms; members of these research communities have supplied additional information to expand and/or update records in the RefSeq collection as well as contributing other related information such as descriptive names or mapping data. Both sequencing centers and research communities are requesting a Genome Champion to support their needs including participation in several regular conference calls for sequencing projects that are currently at various stages of completion.

Implementation Strategy Advances or Other Highlights
To expand support for generating the class of RefSeq that represents whole genome sequence data more robustly, databases, software, and a series of processing steps were designed and implemented. The Genome Project database content is updated regularly by both automatic processing that relies on the INSD-approved use of the Genome Project ID, and by ongoing manual curation by NIH scientists to add descriptive information about the projects and organisms that are included in the database.

The complementary Genome Champion project is supported by expansions to the existing RefTrack database to track collaborations in more detail, and by establishment of guidelines and protocols for the project activities. Established collaborations include the Consensus CDS (CCDS) collaboration between the NIH, European Bioinformatics Institute (EBI), Wellcome Trust Sanger Institute (WTSI), and the University of California at Santa Cruz (UCSC). The CCDS collaboration evaluates annotation of the human genome that is provided by the NIH, EBI, and WTSI to identify those that are identical and those that have quality concerns. An active collaboration reviews the annotation of the human genome to make improvements by updating or adding data. This activity results in updates and additions to the RefSeq collection. The Genome Champion Conserved CDS (CCDS) project required development of a tracking database, expanded quality assurance tests, a public web site, and an internal web site that supports ongoing curation by the members of this collaboration. The CCDS collaboration will be expanded to include evaluation of the mouse genome.

The table below shows the growth of RefSeq, Entrez Gene, and the collaborations.

RefSeq Growth:

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

Entrez Gene Growth:

Time Frame	Number of Species	Number of Records

As of October 2003	Resource not available	Resource not available
As of December 2003	1,982	708,846
As of October 2004	2,491	1,071,343
As of September 2005	2,913	1,492,065

Collaborations Growth:

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

Efficiency

The RefSeq project has met the FY 2005 annual target over 8 months early through the deployment of a database and web site that both tracks the submission of genome sequencing projects and supports the generation of RefSeq records from those submissions. The utility of this approach is validated by the recent International Nucleotide Sequence Database collaborative agreement to require that sequencing centers include a NIH Genome Project identifier in all whole genome sequence submissions.

The Genome Project web site provides direct access to the genome sequence portion of RefSeq collection as well as indirect access to transcripts and proteins annotated on the genomic RefSeq records. The availability of the Genome Project ID in submissions to the INSD supports timely generation of RefSeq records. The representation of the genomic portion of the RefSeq collection in the Genome Project database facilitates access of these RefSeq records and associated curated descriptive information available on the sequence records and in Entrez Gene. This enables thousands of US scientists to use their valuable research time more efficiently.

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 then replaced with new bone. The regulation of the balance between bone resorption and new bone formation, which can be affected by nutritional, endocrine, and pharmacological factors, is critical to maintaining bone mass and preventing fracture. An excess of resorption over formation underlies many bone diseases, such as postmenopausal osteoporosis. Osteoblasts are the cells that form new bone during bone turnover. In addition, some osteoblasts remain embedded in the bone, becoming osteocytes. Recent work has shown that osteocyte survival is an important requirement for skeletal health. Bone is composed of mineral crystals embedded in a matrix made up of many different proteins. There is evidence that interactions between matrix proteins and proteins found at the cell surfaces of osteoblasts and osteocytes produce signals that are important for the regulation of bone turnover and the survival of osteocytes. However, the molecular details of cell-matrix interactions have been explored in only a few instances. If known, the mechanisms of these interactions could yield targets for new drugs that might act to stimulate bone formation or block bone resorption. Understanding how the number and activity of osteoblasts are controlled could lead to new therapies for restoring lost bone, either with drugs or by tissue-engineering approaches.

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

To date, nine relatively abundant proteins have been identified in bone matrix, in addition to collagen, the principal structural component of bone. Two of the non-collagen

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

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

NIH will also employ genetic engineering technology to generate new mouse strains: (1) mice that allow for visualization of matrix proteins in tissue samples and (2) mice in which the matrix proteins are produced in certain cells, at specific stages of development. Using new mouse strains will help determine the effects of matrix protein-osteoblast interactions at different stages of osteoblast development. This strategy adds to the information gained by the first strategy, placing the initial observations in the context of time and place. Knowing where and when the matrix proteins are produced in a normal mouse gives a rough idea of which cells must be targeted in designing a therapy and at what stage in cell development the effect is most critical. Producing the proteins at specific times and places by genetic technology establishes these parameters more precisely. Although mice wholly deficient in fibronectin are not viable, it may still be possible to selectively engineer osteoblasts to be deficient in this protein. If this ambitious target is successful, then it will be possible to dissect fibronectin's role in bone formation. Such information will have a direct relationship to successfully achieving the goal.

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was extended. Analysis of cells recovered from bone marrow suggests that stromal cells are the principal source of thrombospondin-2 (TSP2). Furthermore, these cells increase production of TSP2 when treated with a protein that stimulates bone formation. However, the relationship between TSP2 levels and bone health is clearly complex: mice that lack TSP2 actually have more bone than normal, and are protected against the bone loss that occurs when estrogen levels are low (see below). It is likely that the time and place of TSP2 production are critical to its effect.

Generation of mice in which the genetic elements controlling TSP2 production are also used to control production of a fluorescent "reporter" protein would allow for more precise studies of TSP2 production. The standard way to create such a mouse is to isolate the region of mouse DNA that normally controls TSP2 production (called the "promoter"), link it to the gene for the fluorescent protein, and introduce the combined DNA into a mouse. For most genes, the promoter region is immediately adjacent to the gene it regulates, and is of a size that is relatively easy to manipulate. The investigators conducting this project began with such a fragment of DNA, normally found adjacent to the TSP2 gene. However, before introducing the combined DNA into a mouse, it was critical to test whether the putative promoter region controls the fluorescent reporter gene correctly. Investigators tested this by introducing the DNA into cultured cells, where previous work has revealed variation in TSP2 production in response to specific chemical

signals. This experiment showed that the isolated DNA fragment was not sufficient to reproduce normal control of TSP2 production in cultured cells. Thus, use of this DNA fragment to create a mouse would probably not yield useful information. This result is not unprecedented. A number of promoters have been found at considerable distances from their target genes. Identifying and isolating such distant regions can be challenging. Techniques have been devised to search more comprehensively for the TSP2 promoter, and performance will be reported again in 2007.

This delay is not expected to have a significant effect on progress toward the FY 2006 and FY 2007 targets, which reflect studies of different proteins, and are not dependent on the results of the TSP2 project. Similarly, although creation of the TSP2 reporter mouse is a particularly effective way to study its production in the intact animal, there are alternative approaches to getting this information. Thus, even if this target is eventually not met, the overall goal is still achievable.

Implementation Strategy Advances or Other Highlights

Significant progress has been made on other aspects of this goal. Studies of female mice lacking TSP2 show that they are protected against bone loss after removal of the ovaries, a model of post-menopausal osteoporosis in humans. This result reflects effects on both bone formation and bone breakdown, indicating that TSP2 is an important factor in the control of these key processes.

In other work, studies of fibronectin (the focus of the FY 2006 target) and biglycan have yielded a significant new insight into how these bone matrix components may influence bone cells. Both fibronectin and biglycan have been shown to mediate the incorporation into bone matrix of a third protein called transforming growth factor beta (TGF-beta). TGF-beta is well known to have important effects on many kinds of cells. Thus, one important role of fibronectin and biglycan may be to influence the exposure of bone cells to TGF-beta, in addition to any direct interactions between these molecules and bone cells. This insight has implications for how bone cell-matrix interactions might eventually be exploited in developing therapies for bone loss. It will also inform the interpretation of experiments to be performed in pursuit of future targets under this goal.

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

BACKGROUND

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

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

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

Rationale

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

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

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

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

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

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

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET by 1) completing the IDeA/BRIN evaluation design to determine a list of target indicators and 2) assessing the results of the COBRE evaluation design study. The IDeA/INBRE evaluation design was completed in September 2005. The final report included a confirmed list of target indicators to measure INBRE impact. Target indicators are separated into short-term and long-term goals. Examples of short-term indicators include: improved research facilities and support services, including bioinformatics; successful recruitment of junior and senior investigators from different disciplines; increased collaboration among researchers and institutions; more students majoring in science and health-related fields; more students and faculty participating in research activities; more science faculty and permanent research positions; more scientific publications and presentations; more applications for NIH research grants; and more undergraduate students pursuing science and health-related careers. Long-term indicators include: development of a statewide multidisciplinary research network; more science courses and programs offered; more undergraduate and graduate degrees awarded in science and health-related fields; increased success competing for NIH research grants; increased state and institutional commitment to research; and increase in the proportion of total NIH funding received by the state. The success of this program, as demonstrated by

the indicators, will serve as a building block toward increasing the research potential of the Nation.

NIH assessed the design of the COBRE evaluation and decided to eliminate the long-term goals of the evaluation as the program is too young to produce valid long-range outcomes within the time frame of the evaluation. The evaluation will focus on intermediate outcomes.

Implementation Strategy Advances or Other Highlights

To assist in measuring the impact of IDeA/INBRE on enhancing the pipeline for outstanding students and bolstering the quality of science faculty at baccalaureate and other participating institutions and the development of competitive investigators and their capacities to compete for NIH research funding, two contracts have been put in place. One contract deals with design and maintenance of a data collection and management system; the second focuses on conducting an initial INBRE evaluation design, which will identify the data needed to conduct the IDeA/INBRE full-scale evaluation. Using the database, NIH will be able to confirm that validity of potential target indictors needed to determine the impact on research competitiveness and research capacity. The INBRE evaluation design was completed in FY 2005 and will be followed by an evaluation of the short term goals that is anticipated to be completed in FY 2009.

NIH started the necessary paperwork to request funding for the evaluation and the solicitation and awarding of a contract for the COBRE evaluation. It is expected that an award will be made in FY 2006.

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

BACKGROUND

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

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

Rationale

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

A new enabling technology, computerized adaptive (or dynamic) health assessments, can yield a more efficient and easier-to-use set of validated clinical research tools. Two critical concepts form the basis of this new technology. The first is that by collecting a large set of questionnaire items in subjects with the widest possible range of severity of disease and levels of health, one can construct reliable models (i.e., item response theory models) that predict the probability of specific responses by patients based on their answers to initial questions. The second concept uses software programs to control the specific set of

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A multi-disciplinary network of cooperative agreements (PROMIS) has been funded to develop an item bank, test item response theory models of item performance, and develop a computerized adaptive testing system to measure a select number of health-related quality of life (HRQOL) domains and non-disease specific symptoms in patient with chronic illnesses. In FY 2006, the network will characterize the ability of commonly used instruments to capture these domains. The strengths, deficiencies, gaps, and redundancies in the most common instruments for these domains will be described. Network experts will guide 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 will be initiated in a wide range of patients suffering chronic diseases and conditions.

In order to achieve this goal, NIH proposes an ambitious roadmap that includes the plans to systematically perform a comprehensive analysis of domains of health-related quality of life in chronic disease. Subsequently, NIH will develop and administer instrument(s) to a chronic disease patient sample.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. The investigators thoroughly researched existing questionnaires measuring the specific domains selected for development by the Steering Committee: Pain, Fatigue, Physical Functioning, Emotional Distress, and Social Role Participation. One investigator was designated to lead the work on a particular domain, and coordinated identification of existing items and questionnaires for that domain, resulting in identification of thousands of items for potential inclusion in the item pool to be tested in subsequent phases of the project. The Statistical Coordinating Center (SCC) provided a template that was used by each domain group for standardized presentation of the items, which were then sent to the SCC for inclusion in a master data set. A procedure was developed for evaluating items and deciding whether to eliminate them from the item pool to be tested or retain them for further evaluation. For each domain group, items were winnowed or 'binned' (grouped into subcategories) in a systematic manner. Information regarding the original format and provenance of all items is retained.

Several important decisions have been made regarding the nature of items and questionnaires to be included in the final item banks. Widely used 'legacy' questionnaires for each domain and for general self-reported health status will be used, intact, along with the other items in the bank to allow for cross-calibration between the PROMIS domain measures and the instruments with which clinical researchers are most familiar. T-scores (a standardized scoring system) will be used to report scores on all domains. A reference period of 7 days for questions has been selected, and item analysis and qualitative item review protocols have been developed. The response scale to be adopted is under consideration, and design and methods for conducting focus groups and cognitive interviewing to refine the item pool further are under development.

Implementation Strategy Advances or Other Highlights

The PROMIS network was funded as 7 cooperative agreements (one Statistical Coordinating Center and 6 Primary Research Sites), and is governed by a Steering Committee (SC). The SC meets monthly, either in person or by teleconference. During FY 2005, the SC developed and adopted a Governance Document, decided on domains to be measured and approaches to be taken in developing item pools, formed subcommittees to work on outreach/end-user needs, publications and intellectual property, and formed working groups for specific issues such as pediatric measurement, development of a domain framework, development of item pools for specific domains, and qualitative item review. In addition, the investigators discussed ensuring items would be useful for individuals with low literacy or disabilities. A special software interface is being designed to accommodate individuals needing assistive technologies to access and respond to testing, and additional funds have been secured to allow for Spanish translation. Investigators are actively educating various clinical research communities about the PROMIS and have begun drafting manuscripts for a possible supplemental issue of the journal *Medical Care*. In addition, the PROMIS has started a website to provide the public with information about its activities.

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

BACKGROUND

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

Disease Burden

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

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

NHANES has an internal process for deciding which components are included during each survey cycle. It is conceivable that inclusion of a vision component will be requested in 2009-2011 to provide baseline data for Healthy People 2020. Alternatively,

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Extend NHANES and survey approximately 7,000 people.	(FY06) Very little reliable data on the prevalence of visual impairment in the U.S.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

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

BACKGROUND

Disease Burden

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

Rationale

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

Although effective depression treatments are currently available, only an estimated 20 percent of patients obtain adequate treatment. Rates of underutilization are higher for persons of color, elderly persons, youth, and young and middle-age males. Although

several models of care have proven effective in delivering adequate depression treatment, the uptake and maintenance of these patterns of delivery of care remain poor.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH investigated basic mechanisms underlying depression that may serve as important targets for intervention, such as the role of vascular changes in aging towards development of depression. Research has improved upon the definition and assessment of depression treatment outcomes and identified predictors of treatment response at various points throughout the course of illness. NIH plans to test interventions that produce longer recovery periods for those most at risk for relapse in community populations, such as the elderly. Research will identify factors that have an impact on effective and sustainable dissemination and implementation of scientific findings at multiple environmental levels. Finally, NIH anticipates identifying the mechanisms and processes by which depression has a relatively large influence on the course or outcome of a comorbid disorder associated with disability or premature mortality.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET due to significant progress in identifying potential individual characteristics associated with differing responses to depression treatments in efficacy and effectiveness studies. Characteristics that mediate or moderate treatment response have been identified across many levels of analysis, from genetic variation to psychosocial factors. For example, variation among individuals in the genes that encode

the serotonin transporter or the serotonin 2A receptor is associated with differential response to antidepressant medication treatment.

In FY 2005, the largest practical study ever undertaken to examine different treatment strategies for treatment-resistant depression was concluded. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial examined treatment outcome as a function of a number of demographic and clinical factors that characterized individual subjects. Findings indicate that participants treated in either psychiatric or primary care ("real world") settings who were female, married/cohabitating, or with fewer general medical disorders were more likely to successfully respond to treatment with citalopram, a selective serotonin reuptake inhibitor. Further studies will be needed to assess and validate the clinical implications of these findings. Nevertheless, these and other findings are likely to lead not only to better understanding of patient characteristics and underlying physiological mechanisms driving patients' response to depression treatments, but also to improved treatment algorithms, such that treatment for depression may be optimized for each individual patient.

Implementation Strategy Advances or Other Highlights

NIH is investigating the relationship between depression and several neurological conditions, including Parkinson's Disease (PD), epilepsy, traumatic brain injury, and pain. The NIH Work Group on Depression and Parkinson's Disease recently published a journal article recommending new diagnostic criteria for depression in PD patients, based on an NIH-sponsored workshop. Earlier criteria were difficult to use and excluded perhaps half of PD patients with comorbid clinically significant depression. The new diagnostic criteria may help facilitate the testing and application of new interventions for depression in PD patients.

In addition, NIH is sponsoring a Request for Applications (RFA) to solicit research proposals that examine comorbid mental and neurological disorders. In this RFA, applications that focus on Parkinson's disease and comorbid mental illness are specifically identified as high priority.

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

BACKGROUND

Disease Burden

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

Rationale

There is a wide range of hypothesized causes of the excess stroke mortality in the southeastern United States and among African Americans. The prevalence of stroke risk factors and the potential impact of reducing those factors vary among racial/ethnic groups, with potentially greater impact associated with reduction or elimination for minorities. Patterns of accessing the existing health care system for acute stroke also vary among racial/ethnic groups; for example, minorities are less likely to use the emergency medical system when experiencing a stroke. The reasons for these racial/ethnic variations in stroke-related risk factors and utilization of health care are not fully understood. Prevention programs are a preferred strategy for reducing or eliminating racial/ethnic disparities in stroke and include both primary and secondary approaches.

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has established a program to create Nursing Partnership Centers to reduce health disparities. These centers established collaborations between research-intensive schools of nursing and minority-serving university schools of nursing to address health disparities, including stroke. The Centers focus on influential factors that reduce health disparities, such as ways to promote healthy behaviors, reduce risks that contribute to chronic diseases, and develop ethnically and culturally sensitive health care interventions. Qualifying minority-serving institutions, either in the United States or in territories under U.S. jurisdiction, are those in which students of minority groups who are

underrepresented in nursing research (e.g., African American, Hispanic American, Native American, Alaska Native, Native Hawaiian, Pacific Islander, Asian American, and Philippine nurses) constitute a significant proportion of the enrollment and have a track record of commitment to the special encouragement of minority faculty, students, and investigators.

Building on several years of experience with an acute stroke research and care center in the Washington, D.C., metropolitan area, another hospital, which serves predominantly nonwhite, Hispanic, and Latino populations, was recruited to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and the effectiveness of treatments and quality of care within the specific racial/ethnic communities served by the hospital. The study also will address how to tailor stroke prevention and intervention programs to those populations.

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

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

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Establish a 5-year program to create about 12 to 14 Partnership Centers to Reduce Health Disparities that will focus on influential factors that reduce health disparities.	(FY02) Piloted programs to build nursing center research capacity focused on health disparities	◆e				
FY03	*Actual Performance:* (MET) Seventeen Nursing Partnership Centers established to reduce health disparities, including stroke, which link research-experienced nursing schools with minority-serving nursing schools across the nation.					
Establish a minority-focused, acute stroke research and care center to conduct a study of the epidemiology of stroke, barriers to acute stroke care, and quality of care within the specific racial/ethnic communities being served by the care center.	(FY03) Acute stroke center exists but is not focused on stroke disparities or in a minority community		◆			
FY04	*Actual Performance:* (MET) Acute stroke care center serving a minority community in the Washington DC metropolitan area has been established.					
Establish the infrastructure for a Stroke Prevention and	(FY03) Minority institution research			◆		

Intervention Research Program (SPIRP) at a minority institution.	/training programs exist but not on stroke prevention/intervention						
FY05	*Actual Performance:* (MET) Established research infrastructure and advisory committees, and hired director for SPIRP.						
Establish the infrastructure for a pilot Alaska Native Stroke registry that will facilitate identifying risk factors and strategies to improve stroke prevention and quality of stroke care provided to Alaska Natives.	(FY04) Several registries for Alaska Natives exist, including for cancer and diabetes, but none for stroke				◇		
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
Initiate at least two collaborative, community-based prevention projects at the Stroke Prevention and Intervention Research Program (SPIRP).	Cooperative agreement awarded establishing SPIRP infrastructure, but stroke prevention projects have not yet begun					◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET through the establishment of infrastructure for a Stroke Prevention/Intervention Research Program (SPIRP) at a minority institution, Morehouse School of Medicine (MSM), a historically black institution committed to the primary healthcare needs of the underserved. The long-term objective of the program is to conduct population-based studies of risk factors, prevention, incidence, prevalence, natural history, treatment, and rehabilitation of cerebrovascular disease in targeted African American communities. The SPIRP has also created both internal and external advisory committees and hired a leading stroke expert as the SPIRP Director. The Internal Advisory Committee includes members of the MSM's Cardiovascular Research Institute, Clinical Research Center, Department of Community Health and Preventive Medicine, Neuroscience Institute, and Office of Research Development and supervises the interactions among the SPIRP and its stakeholders within the MSM research community. With this infrastructure in place, the SPIRP will soon begin pilot research studies and planning efforts for collaborative, community-based prevention projects that make up the FY 2007 target.

Implementation Strategy Advances or Other Highlights

NIH continues to support the Nursing Partnership Centers. In FY 2005, NIH awarded thirteen (13) new pilot projects within minority-serving institutions through the Nursing Partnership Centers on Health Disparities initiative. The Nursing Partnership Centers link research-experienced nursing institutions with minority-serving nursing institutions across the country.

In support of the FY 2006 target, NIH has funded an application from the Alaska Native Medical Center to establish an Alaska Native Stroke Registry. Building on the Center's existing experience with chronic disease registries, the investigators will develop and implement a pilot stoke registry to monitor stroke incidence, prevalence, mortality, and risk factor data on Alaska Natives.

Another notable achievement relevant to the overall goal is the establishment of six prevention and education outreach projects, called Enhanced Dissemination and Utilization Centers (EDUCs), to improve cardiovascular health in high-risk communities (defined as communities with coronary heart disease and/or stroke death rates that rank in the top 15% nationwide). The EDUCs, now in their third and final year, were established to address growing health disparities in cardiovascular disease and involve strong

community-based organizations as well as health systems. Results from the EDUCs will be available in FY 2006.

In September 2004, five research grants were funded in response to the RFA (Request for Applications) "Interventions to Improve Hypertension Control in African Americans." The objective of the program is to evaluate clinically feasible interventions to effect changes in medical care delivery leading to an increase in the proportion of treated hypertensive African American patients whose blood pressure is controlled to levels specified by Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) guidelines. The ultimate goal is to prevent complications of hypertension, and thus increase quality and years of healthy life in African Americans ─ a group with the highest prevalence and earliest onset of hypertension, and disparately high premature cardiovascular mortality and morbidity. All projects are currently in a planning phase. Annual meetings and monthly conference calls serve as forums to share experiences, exchange ideas, and develop common measures when appropriate. The investigators had their first meeting on June 6-7, 2005.

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

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

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

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

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

Rationale

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

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

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

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

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

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

effort is also expected to serve as a model for new NIH neuroinformatics initiatives that can link to the anatomic MRI database.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Prepare and disseminate the first of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children to the research community.	(FY04) First of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.			◆		
FY05	*Actual Performance:* (MET) Enrolled 504 children, and prepared and disseminated the first stage of scans, demographic, medical, cognitive, and behavioral data collected from 430 children, age 4.5 to 18, to the research community.					
Complete the second of three stages of neuroimaging scans and data collection of approximately 500 children across the United States.	(FY05) The first of three stages of scans, demographic, medical, cognitive, and behavioral data were collected from 500 children and disseminated to research community.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Complete preliminary analyses of changes of brain growth in children over time and share findings with research community.	(FY06) First and second of three stages of scans, demographic, medical, cognitive, and behavioral data collected from approximately 500 children.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET. A total of 504 children have been enrolled in the study. Scans, demographic, medical, cognitive, and behavioral data have been collected from 430 children, age 4.5 to 18, and were disseminated to the research community. After completing several iterations of quality control, the data are now available to project scientists via a user-friendly Web-based interface. Plus, the first peer-reviewed scientific report, "The NIH MRI Study of Normal Brain Development," describing the project methodology and preliminary results of the first wave of data was accepted for publication in Neuroimage. Recruitment, scans, and data collection are also ongoing for the 74 children younger than age 4.5 because brain growth and development are more rapid compared to the older age group. The data from these younger children will be available after high-quality scans from 100 children are collected.

Implementation Strategy Advances or Other Highlights

Of the children in the younger age group (up to 4.5 years old), 57 percent completed at least three assessments and scans and 30 percent completed four or more assessments and scans. In addition, the next or second stage of data collection for the older age group (4.5 to 18 years old) is nearly complete. Approximately 87 percent of these children have completed the second wave of scans and data collection. The overall project attrition rate is only four percent, which is outstanding and maintains the number of families needed in the study to represent the full spectrum of ethnic, minority, and socio-economic statuses in the United States.

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 the public health and advancing the research enterprise.

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

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

BACKGROUND

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

Rationale

Since the launch of the campaign in 1994, 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.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Various strategies have been developed to satisfy the overall goal of SIDS reduction in African American communities. First, regional summits were held across the country to train and educate local community members and leaders about SIDS and to raise awareness about approaches to reducing SIDS risk. Representatives of organizations attended to ensure that appropriate guidance was delivered. 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. Second, the NIH conducted informal interviews to determine subsequent outreach strategies that developed as a result of their participation. Third, NIH identified eight national organizations that can help promote the Back to Sleep campaign messages to local communities. Fourth, NIH will work with nursing organizations to promote Back to Sleep campaign messages to their members who have access to patients who may directly benefit from the information.

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

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET and exceeded in that 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. In our ongoing collaboration with national nursing organizations, the NIH partnered with national organizations to develop a training and continuing education (CE) module in SIDS risk reduction. The members of the national nursing organizations who complete the CE will receive Continuing Education Units from the Maryland Board of Nursing. The leadership of these national organizations helped to develop, review, and revise this module. The NIH held a teleconference with the national nursing organizations in October 2004 to review the module and discuss dissemination plans. The participating organizations were as follows: 1) the Academy of Neonatal Nursing, 2) American College of Nurse Midwives, 3) Association of SIDS and Infant Mortality Programs, 4) Association of Women's Health, Obstetric and Neonatal Nurses, 5) March of Dimes, 6) National Alaska Native American Indian Nurses Association, 7) National Association of Pediatric Nurse Practitioners, and 8) First Candle/SIDS Alliance.

Implementation Strategy Advances or Other Highlights

The NIH developed radio Public Service Announcements (PSA) in collaboration with three national organizations: the Alpha Kappa Alpha Sorority (AKA), the Women in the NAACP (WIN), and the National Coalition of 100 Black Women (NCBW). During Winter 2004-2005, the NIH held several meetings with senior executives of Radio One, Inc. a large minority-owned media company comprised of 69 radio stations located in 22 urban markets in the United States. Radio One, Inc. agreed to broadcast the NIH PSAs throughout the Winter months on the 69 radio stations. In March 2005, the NIH supported the Association of SIDS and Infant Mortality Programs annual conference by providing ten speakers for general sessions, workshops, and in-depth pre-conference trainings. Attendees included public health nurses, social workers, state and local public health department staff, tribal community staff, Healthy Start representatives, health professionals who work with fetal and infant mortality (FIMR) and child death review (CDR) programs, directors and coordinators of SIDS/Infant Death bereavement programs and Title V directors throughout the United States. The NIH was a sponsor for the annual First Candle/SIDS Alliance conference held in September 2005 that brought together professionals and volunteers to discuss ways of addressing issues such as SIDS, stillbirth and other prenatal losses. The sponsorship supports world renowned researchers to speak on issues related to infant mortality and supports scholarships to junior researchers in hopes of encouraging them to enter the field of SIDS and/or stillbirth research.

Efficiency

The NIH surpassed its target of involving a minimum of six national organizations in SIDS training and educational activities by working with eight organizations to review a training and continuing education module in SIDS risk-reduction and developing dissemination plans as well as collaborating with three additional organizations to develop Public Service Announcements.

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

BACKGROUND

Rationale

Stroke places a major health burden on U.S. society in death, disability, and economic costs. About 700,000 new strokes (first and recurrent) are reported every year in the United States. Stroke is the third leading cause of death and is a leading cause of serious, long-term disability among adults. Stroke costs the United States $51.2 billion per year in direct and indirect costs. To bring important health messages to the public and in response to the mandate by Congress in the FY 2001 House and Senate Appropriations Committee reports, the NIH created the multifaceted communication effort "Know Stroke. Know the Signs. Act in Time." The campaign aims to increase awareness of the symptoms of stroke and the need for urgent action. Next year, NIH will focus its campaign resources in at least five communities where the impact of stroke is particularly great.

In addition, NIH will begin an outreach program targeted specifically to African Americans because the need for stroke information is especially important among this population. African Americans suffer strokes at a disproportionate rate and are more likely to die from them than other racial groups.

Stroke is a medical emergency. Rapid identification of a stroke is essential to treatment and positive outcomes. When given within 3 hours of the onset of symptoms, a clot-busting drug called tissue-type plasminogen activator (t-PA) can reduce and even reverse the impact of a stroke by dissolving the blood clot that causes damage to the brain. A NIH study found that patients who received t-PA were at least 30 percent more likely to recover with little or no disability after 3 months. Without t-PA, stroke patients often suffer disabilities that require extensive rehabilitation. The window of opportunity to start treating stroke patients is 3 hours from the onset of symptoms, but to be evaluated, patients should arrive at the hospital within 60 minutes.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The "*Know Stroke*" campaign is a multiphase effort. In the first phase, NIH developed materials in collaboration with key stakeholders in the stroke community, and focused efforts on reaching health care providers. In the second phase, NIH developed and executed transit public service advertising in communities across the country where stroke has a particularly negative impact.

In FY 2004, NIH continued to cultivate its partnership with ASA to extend the "*Know Stroke*" campaign. NIH organized a strategy session with ASA Operation Stroke program directors from 20 communities across the country. Using the "*Know Stroke*" materials and information, ASA program directors worked within their communities to educate providers and the public about the importance of rapid treatment for stroke. Five of these

communities received special focus in FY 2004.

During FY 2004, 3,000 "*Know Stroke*" community education kits were distributed within local communities with at least 15 percent African American population, and 100,000 "*Know Stroke*" brochures were distributed (of which 25,000 were distributed to African American audiences). In addition, NIH initiated strategic activities to reach African Americans.

Using a phased approach, NIH participated in and disseminated materials at large cultural events within the African American community in Washington, D.C. NIH then built partnerships through ASA and African American organizations in targeted areas with large African American populations to disseminate materials and messages and extend the reach of the "*Know Stroke*" campaign into communities most affected by stroke. During FY 2005, NIH distributed an additional 5,000 kits (of which 1,000 were through African American partners).

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Work with partners in five communities with at least 15 percent African American audiences to extend the Know Stroke campaign messages by attending community fairs and collaborating with local leaders and health educators to disseminate 3,000 Know Stroke community education kits and 100,000 Know Stroke brochures (25,000 will be distributed to African American audiences).		(FY03) National partnerships developed; no current comprehensive local partnerships		◆			
FY04	*Actual Performance:* (MET) Completed outreach programs in 5 U.S. cities. Distributed 109,619 brochures, including 27,236 to African American audiences. Distributed 3,000 kits through national marketing campaign to city and county health officials.						
Extend the outreach program to an additional five communities nationwide, arming community leaders with tools and information to distribute an additional 5,000 Know Stroke community education kits (1,000 will be through African American partners).		(FY03) Five Partnerships developed in FY 2004.			◆		
FY05	*Actual Performance:* (MET) Planned outreach programs in 5 U.S. cities. An additional 5,686 Know Stroke community education kits are being distributed (approximately 1,000 through African American partners). Distribution efforts are under budget by $142,000 and 686 kits over the projected target.						
Complete goal of increasing awareness among the general public about the symptoms of stroke and the need to seek treatment rapidly by partnering with providers and volunteers in at least 5 communities and extending the impact of the campaign, "*Know Stroke. Know the Signs. Act in Time."*		FY05 results				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target was MET efficiently. NIH extended its stroke outreach programs into five additional U.S. cities, conducting programs in three cities and planning programs in two cities for early 2006. By educating active community leaders about stroke and arming them with *Know Stroke* materials, 1,286 kits were disseminated to community members. Additionally, 4,400 *Know Stroke* community education kits are being distributed through a partnership agreement with the General Federation of Women's Clubs (GFWC). In total, 5,686 community education kits, an increase of 686 over the original target of 5,000 kits, are being distributed through targeted educational programs. Included in this total are approximately 1,000 kits distributed through African American partners as part of the

Know Stroke community outreach.

Distribution activities were completed for approximately $235,000. This figure is $142,000 under the $377,000 originally budgeted.

Implementation Strategy Advances or Other Highlights
In FY 2005, NIH continued its partnerships with the CDC, the American Stroke Association (ASA), and the National Stroke Association (NSA) to extend the *Know Stroke* campaign. In cooperation with these partners and community organizations, NIH planned outreach activities in five cities (Boston, St. Louis, Cleveland, Atlanta, and Jacksonville, Florida). These cities were selected because they had an increased incidence of stroke and an established stroke treatment infrastructure.

Working with the ASA, NSA, and CDC state heart disease and stroke prevention programs in each city, NIH identified 10-12 individuals who were active in the senior citizen, African American, and Hispanic communities. These people, NIH/CDC "Stroke Champions," were trained about stroke and how to discuss the *Know Stroke* campaign messages and distribute materials within their communities. The Stroke Champions conduct outreach activities at community events in each city. The ASA and NSA provided valuable logistical support in each city through their local chapters.

Additionally, NIH developed a partnership with the General Federation of Women's Clubs (GFWC), a national organization with 160,000 members, whose average age is 55-65. The risk of having a stroke more than doubles each decade after age 55, making GFWC members a target audience for *Know Stroke* education materials.

Through these and other outreach activities, NIH is distributing 5,686 *Know Stroke* community education kits.

Efficiency
FY 2005 activities were completed for an estimated $235,000, which is less than the $377,000 originally budgeted for these activities. Moreover, the total number of community education kits being distributed is 686 over the projected target of 5,000. These efficiencies are being achieved through a partnership with GFWC, which allows NIH to distribute a larger number of kits than originally estimated (4,400 in one mailing) at a lower cost than originally budgeted. Partnerships were also formed with community organizations in each of the cities selected for the stroke outreach program, allowing NIH to distribute kits through these local partners at a lower cost than initially planned.

CTR-3	By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.

BACKGROUND

NIH has a longstanding tradition of promoting science with the ultimate goal of improving the public health on a global scale. One manner in which this is accomplished is by ensuring the availability of new therapeutic drugs, vaccines, devices, and other products that improve human health by linking technologies resulting from NIH and FDA intramural research with the private and public sectors through Public Health Sector (PHS) technology transfer activities. In this regard, NIH, on behalf of HHS, is one of the most active agencies in the Federal Government, participating in infrastructure and policy-building workshops hosted in the U.S. and overseas. OTT's participation in symposiums and workshops usually includes meetings and discussions with foreign delegations interested in replicating or adapting the successful partnerships among government, industry, and academia occurring within the United States.

To more fully utilize these partnerships to meet the NIH mission, there is a need to enhance the capacity of key personnel in developing countries to adapt and build the infrastructure for transferring laboratory discoveries to the bedside. Capacity building, within countries, is best achieved with active participation by local experts. Sometimes, however, local expertise first must be developed. This can be achieved by establishing a program for providing technical assistance and specific information to scientific and administrative personnel in developing countries on technology transfer activities and operations. This program can be carried out first with countries identified through previous collaborations as having the foundation (e.g., R&D experience, cadre of scientists, and government interest in science, technology and commercialization) necessary to establish technology transfer offices.

Rationale

The mission of the NIH, an Agency of the Department of Health and Human Services (HHS), is to support "science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability." Thus, promotion of science at NIH has the goal of not only improving the health of the American public but also ultimately enhancing human health on a global scale.

The OTT supports this goal by ensuring through its technology transfer activities that PHS health-technologies become available to the public in the U.S. an abroad. Moreover NIH institutes and centers are increasing their efforts worldwide by supporting centers of excellence in developing countries. The proposed international capacity building program will join in the NIH effort to be sure that countries receiving NIH funds have the ability to appropriately handle patents and licenses arising from NIH funding. It is a requirement that NIH grantees comply with Bayh–Dole provisions and thus need training on handling such matters appropriately consistent with the terms of their grants, the law, and U.S. policy interest. This is also in the U.S. public interest and, ultimately, results in improvement in public health.

As noted in the NIH Roadmap, “public-private partnerships have become a model for advancing science and communicating results of medical advances to improve the quality of life for all people.” In its routine functions relating to intellectual property, patents and licensing, and through its daily interactions with NIH scientists, universities and industries, OTT has been at the forefront of this endeavor. Thus, undoubtedly, OTT can provide leadership through this technical assistance program in building bridges worldwide “among researchers in academia, government and the private sector” to move research results and to make technologies accessible to the public in form of products.

HHS is committed to “finding and sharing solutions to shared health problems with our global partners”. This goal of strengthening the capacity of developing countries to identify technologies and pursuing their development into products fits within the spirit of the HHS Office of Global Health Affairs, which is charged with the mission of “promoting the health of the world's population by advancing the Department of Health and Human Services' global strategies and partnerships” including those global efforts targeted to reduce the burden of diseases such as HIV/AIDS, tuberculosis, and malaria.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Establishing an in depth and long-term technology transfer assistance (TA) program to provide guidance and information related to technology transfer to scientific and administrative personnel in the appropriate institutions within developing countries will require extensive preparation. NIH plans to establish a working group in the Office of Technology Transfer (OTT) that will formulate recommendations. The recommendations will serve as the basis for a proposal for a needs assessment study that can be supported through the NIH One Percent Evaluation Set-Aside Program. This formal need assessment will systematically detail the nature and extent of issues that the technical assistance program should address and determine appropriate program goals and outcomes.

The strategy for program design (including selection of training personnel) is dependent on the outcome of the needs assessment which was conducted in FY 2004. NIH will identify appropriate institutions in developing countries that are in need of targeted technical assistance to address national and regional public health needs, and will administer appropriate capacity-building activities.

Securing potential partners is critical for full implementation of the technical assistance program. Thus, during FY06, potential partners from international organizations, private foundations, other federal agencies and professional societies will be identified. Identifying and acquiring these partners will require intensive dialogue and negotiations with numerous organizations and agencies, and relating the aim of the technical assistance program to their respective objectives, goals, missions, and strategic plans. Additionally, must commit to providing guidance and support throughout the development and implementation of the technical assistance program. As partners sign on to the goal, the program is likely to sustain itself and expand.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Develop a needs assessment study for a technical assistance program in technology transfer for developing countries to systematically detail the nature and extent of issues that the TA program should address.	(FY03) No known needs assessment studies exist for developing technology TA program.		◆			
FY04	*Actual Performance:* (MET) Developed a 'needs' assessment study for a technical assistance program.					
(Target 2) Based on results of the needs assessment, recruit and select personnel to design and implement the technical assistance program.	(FY03) No personnel.			◆		
FY05	*Actual Performance:* (MET) Personnel joined OTT to design and implement the TA program based on the results of the needs assessment study.					
(Target 3) Identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside.	(FY03) Limited access to targeted training in developing countries.			◆[e]		
FY05	*Actual Performance:* (MET) OTT identified and targeted appropriate institutions in seven developing countries for participation in either an educational and technical assistance internship program (China, South Africa, India, and Brazil) or an on-site training seminar (Ghana, Zambia and Korea).					
(Target 4) Complete goal of through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products. *Previous Target:* Secure potential supporting partner(s) to support the onset of the technical assistance program	FY05 results				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The target to develop a needs assessment study for the technical assistance (TA) program, was MET in FY 2005. The Office of Technology Transfer (OTT) formulated and executed a method for meeting this goal, comprising: (1) compiling a list of institutions (by region) in developing countries that could become potential partners with OTT/NIH; (2) developing an inventory of international organizations, US government agencies, and other entities that could serve as stakeholders with OTT in any partnerships with such institutions; (3) networking with representatives from institutions in developing countries to identify specific needs and capabilities related to, or supporting, technology transfer and development activities; and (4) continuously updating the compilation of institutions in developing countries and potential stakeholders based on the foregoing. As such, OTT's activities identified institutions in developing countries with specific needs and capabilities that serve to forge a foundation for effective global technology transfer programs.

Target 2

The target to recruit personnel to design and implement the international technology transfer program based on the results of the needs assessment study, was MET in FY 2005. An intern from the United Kingdom completed a three month internship, and an American Association for the Advancement of Science (AAAS) fellow joined OTT to assist its Senior Advisor for International Technology Transfer (SAITT) in designing and implementing the technology transfer program. The AAAS fellow and the SAITT (collectively, "the TT personnel") have continuously revised and updated a database of companies and institutions in developing (and transitional) economy countries that could become possible NIH partners. Additionally, the TT personnel and other members of OTT

have collaborated with other technology transfer organizations to develop and present training programs to representatives from developing countries. Finally, the TT personnel have worked to design internship programs for representatives from institutions in developing countries that are tailored to the unique goals and needs of each partner institution. The TT personnel have crafted an internship program that, inter alia, includes one or more of the following: (1) training in intellectual property management, licensing practices, and marketing and commercialization strategies; (2) course work in technology transfer; and (3) presentations and networking at conferences.

Target 3

The target to identify and target appropriate institutions in at least three developing countries in order to educate members on adapting and building infrastructure for transferring laboratory discoveries to the bedside, was MET and exceeded in FY 2005. OTT identified and targeted representatives from institutions in seven developing countries for educational programs that included on-site internship programs and training sessions. Institutions in four of the countries (China, South Africa, India and Brazil) were targeted for participation in an on-site internship and educational program. Representatives from China and South Africa began or completed internships in FY 2005, while representatives from India and Brazil are expected to begin internships in FY 2006. Similarly, OTT conducted on-site training sessions for representatives from Ghana, Zambia and Korea.

Implementation Strategy Advances or Other Highlights

The initial approach to meeting Target 1 was reformulated by OTT after OTT researched and identified institutions in developing (and transitional) economy countries that could become possible partners with OTT/NIH and, correspondingly, identified an inventory of international organizations, US government agencies, and other entities that could serve as stakeholders with OTT in forming partnerships with institutions in developing countries. Through an extensive networking approach, OTT met with representatives from institutions in developing countries and stakeholders at a number of conferences. As such, OTT continuously updated the compilation of institutions and stakeholders to include more specific information about partner institutions and stakeholders. OTT has developed an established and effective process that identifies institutions in developing countries with specific technology transfer and assessment needs and capabilities.

In FY 2005, academic and governmental institutions in at least three developing countries were identified and targeted in order to educate their members on building a technology transfer infrastructure. OTT developed a multi-faceted approach that provides both training and internships to institutional representatives from developing countries. OTT conducted training seminars for professionals from at least three developing countries, Ghana, Zambia and Korea. These training sessions provided visitors extensive information and support on technology transfer related issues, including intellectual property and commercialization avenues. Correspondingly, in FY 2006, representatives from OTT are scheduled to participate in public/private partnership workshops in India that will focus on intellectual property management and technology innovation. In addition, OTT has actively engaged in securing partners with international organizations to sponsor three month educational and internship programs on-site at OTT. The internships are tailored to meet the specific goals of the interns by addressing not only their experiential and educational backgrounds but also the interests and needs of the institutions they represent. At present, the following OTT on-site internships have been completed, or are anticipated

to begin in FY 2006: (1) a representative from the Chinese Academy of Sciences completed an internship in FY 2005, returning to China to establish the Office of Technology Transfer within the Chinese Academy of Sciences; (2) a representative from The Council for Scientific Industrial Research (CIGR) of South Africa, the largest research and development Institution in Africa, interned during Fall 2005; (3) representatives from India are expected to begin internships in FY 2006; and (4) a representative from a university-industry consortium in Brazil is expected to begin an internship in FY 2006.

Efficiency

Target 3 was met efficiently in FY 2005 for at least the following reasons. First, appropriate institutions from seven developing countries were identified and targeted for educational programs related to adapting and building infrastructures for transferring laboratory discoveries from the bench to the bedside. More specifically, institutions in four countries (China, South Africa, India and Brazil) were identified and targeted for participation in on-site internship and educational programs. Representatives from China and South Africa completed internships at OTT by November 2005. Similarly, OTT conducted on-site training sessions for representatives from Ghana, Zambia and Korea. Second, the internships for the representatives from institutions in China and South Africa were supported by funding from their institutions or other organizations.

CTR-4	**By 2008, increase the percentage of Small Business Innovation Research (SBIR) program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.**

BACKGROUND

Established under the Small Business Innovation Development Act of 1982 (Public Law 97-219), the Small Business Innovation Research (SBIR) program was initiated to stimulate technological innovation, use domestic small businesses to meet Federal research/research and development (R/R&D) needs, foster and encourage participation by socially and economically disadvantaged persons and women-owned small businesses in technological innovation, and increase private sector commercialization of innovations derived from Federal R/R&D.

The SBIR program is a highly competitive, three-phase award system. In Phase I, the objective is to establish the technical merit and feasibility of the proposed R/R&D efforts and determine the quality of performance of the small business awardee organization prior to providing Federal support. In Phase II, the objective is to continue the R/R&D efforts. In Phase III, the objective is for the small business to pursue, with non-SBIR funds, the commercialization objectives resulting from the research conducted in Phases I and II. Early-stage financing of innovation through public-private sector partnerships, such as those in the SBIR program, plays an instrumental role in supporting the development of new technologies and is an effective means for accelerating the progress of the technology from the laboratory to the market. The small business research community often lacks the expertise, contacts, and funds necessary to support the commercialization of products/processes/services that are developed with NIH SBIR funds.

Rationale

To facilitate the translation of SBIR innovations into commercially viable products that will have societal benefit, NIH will develop a program of technical assistance services. These services will assist SBIR awardees in their transition from the "test tube to the medicine cabinet" and will serve as a means for leveraging NIH resources (SBIR funds) to foster new public-private sector partnerships. Because areas of need are varied and numerous, NIH envisions providing a "menu" of services from which SBIR awardees can choose to address their individual needs. Through the development of technical assistance programs, NIH will be able to catalyze the matching of SBIR recipients with the resources/partners needed for them to bring their concepts to commercialization.

By consolidating the funds available through individual awards, NIH can create a program to assist SBIR awardees as they address the technical challenges that arise during the conduct of SBIR projects. NIH has already conducted two pilot assistance programs and has completed one year of a trans-NIH fully implemented program. These programs offered Phase II awardees business planning assistance and opportunities to "marry" their technologies with potential targeted strategic alliances and investors, and Phase I awardees to learn of possible additional applications of their technologies thereby possibly opening up additional markets.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Several technical assistance programs aimed toward commercializing SBIR-developed products will be developed over a three-year period to meet the SBIR GPRA goal. The intent is to develop a menu of assistance programs from which SBIR awardees may choose to enroll that will help them fill a void in their ability to commercialize their federally-funded technologies. To achieve this end, modules expected to assist in the commercialization of SBIR products will be piloted. Effective pilots will be transitioned into programs. At that time, critical elements for monitoring performance will be identified. These critical elements will be monitored over time to report on performance and to make adjustments as needed to enhance the services.

NIH will first pilot programs that expand the availability of business planning and strategizing assistance to small businesses. These pilots will target specific commercialization issues such as business planning, technology valuations and niche assessments, manufacturing issues, regulatory hurdles (for biologics, therapeutics, new drugs, and devices) and licensing. Programs that are successful in their pilot phases will be introduced to the greater pool of SBIR awardees the following year. For example, NIH used the results of the completed FY03 Pilot Commercialization Assistance Program (CAP) to develop a trans-NIH CAP Program in FY04. The program included one-on-one business counseling; development of a business/strategic plan; and identification of key customers, investors, and business partners. Fifty SBIR awardees participated in the business planning portion of the pilot. Of these participants, 35 presented their business opportunities at an investment event with the intention of attracting and/or obtaining investment funding and/or strategic alliances. These companies will be tracked for a period of 18 months to determine if they did in fact make an investment or partnering deal.

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

Using this model of pilot testing programs one year and implementing trans-NIH programs the next, by the end of FY 08, it is anticipated that a minimum of three programs will then be items on the Technical Assistance Program menu. If each is successful in becoming a menu item, the final menu could consist of CAP, Technology Niche Assessment, and Manufacturing Assistance Program. Implementation of these programs will be done through solicited contracts with business consulting firms specifically trained to provide such services.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Pilot test specific technical assistance program(s) to further development of SBIR projects toward commercialization (FY 04) CAP (FY 05) Niche Assessment (FY 06) Manufacturing or FDA Regulatory Assistance	No current programs.		◆	◆[e]	◇	◇
FY04	*Actual Performance:* (MET) Completed Pilot CAP with 50 participants. Selected vendor for pilot Niche Assessment Program.					
FY05	*Actual Performance:* (MET) Completed pilot Niche Assessment Program with 100 participants.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) Implement effective piloted programs to create a menu of technical assistance programs	Pilot Assistance Programs (i.e., CAP, Niche, etc.).		◆[e]	◆[e]	◇	◇
FY04	*Actual Performance:* (MET) Initiated trans-NIH CAP with 130 participants.					
FY05	*Actual Performance:* (MET) 114 participants completed a trans-NIH CAP program and 68 of those presented their business opportunities at an investment forum.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 3) Report critical elements to assess advances of each technical assistance program	Pilot programs converted to program implementation.		◆	◆[e]	◇	◇
FY04	*Actual Performance:* (MET) Pilot CAP-- 50 participants of which 35 presented business opportunity at investment event. At 6 month mark, 33% had increased sales or were in negotiation.					
FY05	*Actual Performance:* (MET) Pilot CAP -- 40% of forum presenters received additional private investments or sales. Cumulative private sector funding/sales received was $37,764,520 with most received by five firms.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The target in FY 05 for piloting a Niche Assessment Program was MET. Under a contract with Foresight Science and Technology, Inc., TNA™'s (Technology Niche Analyses) for 100 NIH FY 2004 Phase I awardees were completed.

Target 2

The target goal for FY 05 of implementing a trans-NIH CAP program was also MET. One-hundred fourteen NIH SBIR Phase II awardees completed the program and 68 of those presented their business opportunities at an investment forum.

Target 3

The target for FY 05 for reporting critical elements was MET. Information concerning the progress of those who participated in the NIH pilot CAP has been received indicating companies have made some progress with their commercialization efforts.

Implementation Strategy Advances or Other Highlights

Pilot Niche Assessment Program -- One-hundred NIH FY 2004 Phase I awardees provided technical information to the contractor, Foresight Science and Technology, Inc., about their ideas and the markets they were expecting to enter. Foresight performed due diligence and prepared reports specific to each company's technology indicating the needs and concerns of the end-users, the competitive advantages of their technologies, additional possible markets, and a market-entry strategy. Possible partners and/or investors were

identified for consideration. All 100 participants received their reports in FY 2005. Eighty-six percent of those who provided feedback felt they have a more realistic understanding of their target markets and 14% felt the program did not impact their understanding of additional markets. 100% said they would recommend the program to others.

CAP -- Larta Institute, the contractor assisting with implementing the NIH CAP, provided individualized business counseling to the 114 participants of the program and assisted each with their commercialization strategy. Each company prepared either a business/strategic plan, licensing package, or a regulatory plan depending on their specific needs. Each also prepared business presentation materials consisting of an executive summary and PowerPoint presentations for audiences specifically unique to their needs. Sixty-eight of the 114 presented their business opportunities at the program's culminating investment event. Commercialization baselines are currently being collected for each participant so progress may be tracked at 6-month intervals for the next 18 months.

Pilot CAP -- Participants were followed at six-month intervals for a period of 18 months following completion of the pilot. After 18 months, there was evidence that participants increased their business knowledge and were able to identify and negotiate deals and partnerships to help commercialize their SBIR-developed products. Forty percent of those who presented at the investment forum received additional private sector investment and/or sales related to their technology. Cumulative private sector funding/sales received was $37,764,520 with most of the money received by five firms.

Efficiency

Pilot Niche Assessment Program -- Final cost of $400,000 right on target with projection and completed one month earlier than planned.

CAP -- As reported in FY 04, final cost of CAP was below budget resulting in a budget savings of $650,000.

CTR-5	**By FY 2013, improve marketing and management of NIH intellectual property assets by building text mining capability.**

BACKGROUND

The mission of the NIH is to support "science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability." Thus, promotion of science at NIH has the goals of pursuing knowledge as well as transferring that knowledge and related technology to the private sector for further development. The attainment of those goals, ultimately, can lead to significant improvements in human health and the quality of life and ensure a continued high return on the public investment in research.

Technology transfer is a vehicle through which the fruits of NIH intramural research are transferred to industry to be developed ultimately into preventive, diagnostic, and therapeutic products to advance public health. For the United States to remain a world leader in technological and scientific innovation, both the public and private sectors must work together to foster rapid development and commercialization of useful products to benefit public health, stimulate the economy, and enhance our international competitiveness, while at the same time protecting the taxpayers' investment and safeguarding the principles of scientific integrity and academic freedom.

Evaluating, protecting, monitoring, and managing the NIH invention portfolio is accomplished largely through overseeing patent prosecution, negotiating and monitoring licensing agreements, and providing oversight and central policy review. The marketing and management of the vast and varied portfolio of intramural inventions is a critical aspect in translating scientific discoveries into products that can benefit public health.

NIH will establish a Knowledge Management (KM) system, composed of software, hardware and databases, to enable professional staff to keep pace with, explore, gain knowledge, and bring meaning and relevancy to large sets of scientific, technical, and legal documents using one single KM interface to access real-time information relevant to the NIH intramural inventions. NIH will focus immediate efforts to leverage text mining software to perform needed high-powered analyses. Text mining technology relies on finding patterns, not single facts, and is analogous to data mining. The difference is that it mines unstructured text, where data mining extracts patterns from numeral records stored as structured data in relational databases.

Rationale

Approximately 90 percent of the scientific community's explicit information currently is found in text documents that describe the existing state of knowledge, technology, and scientific innovation, and the potential partners for further development and commercialization of NIH's intramural invention portfolio. Without an integrated way to process or "mine" all this information, the ability of NIH to utilize information currently available to assist in licensing efforts is severely compromised.

Establishing a real-time KM system will improve marketing and management of NIH intellectual property assets. Using text mining tools to create a single KM interface to access real-time information relevant to NIH's intellectual property assets and related information will increase the efficiency and effectiveness of technology transfer operations.

The long-term benefits to NIH of adopting such technology include: (1) improved management of NIH technology portfolio; (2) expanded outreach efforts for licensing of NIH technologies, including foreign entities; (3) increased partnering through identification of Cooperative Research and Development Agreements (CRADA) and academic or for-profit collaborators; (4) identification of materials and research tools worldwide for use by the NIH research community; (5) enhanced fiscal management related to patenting; and (6) improved reporting capabilities and ability to provide better responses to questions from the Congress and the public.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Establishing an in-depth and long-term technology transfer marketing and management program for intramural intellectual property will require extensive coordination. It is critical to identify and target those individuals and businesses most likely to be interested in licensing available technology. In order to accomplish this, NIH plans to focus on leveraging a text mining software engine (NIH currently owns a 10-year internal use license for this software technology) to perform needed high-powered analyses.

Initially, the project will concentrate on text mining the following data sources: PubMed, science news wires, TechTracS, and CRISP. Using a Knowledge Management system, NIH can more quickly and easily identify potential licensees and, for each available technology, electronically transmit an abstract describing the technology and instructions for licensing. Additionally, such targeted marketing allows NIH to determine quickly whether further research and development are needed before a technology is ripe for licensing.

Text mining of additional data sources will be accomplished in FY 2006, including the NIH Intramural Scientist Database, the Food and Drug Administration Orange Book (patents covering approved drugs), Clinicaltrials.gov, Biotechnology Industry Organization and Pharmaceutical Research and Manufacturers Association members' websites, and business press release databases.

In FY 2007, NIH intends to establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually. Some technologies have limited applicability and licensing ability as a single technology. By identifying complementary technologies held by other entities and marketing them as a single package, there is a greater likelihood that the combined technologies will be attractive to a licensee and that they could be developed into a product that benefits the public health.

The Knowledge Management system will also allow NIH to quickly and easily identify those technologies that are too early stage for licensing and, thus, require further research and development before they are marketable. Decisions can be made at an earlier stage regarding whether to abandon the patents or whether NIH should pursue additional collaborations to advance the technology to the point of marketability. Additionally, the system would enable NIH to identify and contact potential CRADA partners for these critical collaborations.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Identify and text mine at least four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	(FY04) NIH does not have a text mining marketing and management system for distribution of technologies available for licensing.			◆[e]		
FY05	*Actual Performance:* (MET) Identified and text mined five relevant data sources: TechTracS, CRISP, PubMed, Science News Wire, and the USPTO's patent database (2001-present).					
Identify and text mine an additional four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.	To be determined by results of FY05 target.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Establish an automated computer system to allow for synergistic marketing to potential licensees of groups of technologies held by NIH and non-NIH entities that will identify and market technologies with minimal value if marketed individually.	To be determined by results of FY06 target.					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The target, identifying and text mining at least four relevant data sources for automated distribution of focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing, was MET and exceeded in FY 2005. Under a contract with Discovery Logic, Inc., five relevant data sources were identified and text mined (TechTracS, CRISP, PubMed, Science News Wire, and the U.S. Patent and Trademark Office's (USPTO) patent database (2001-present)). The resulting software tool, presently registered as GovPatents.com, is now in use within the Office of Technology Transfer (OTT). The tool provides focused information to potential licensees to identify prospective licensees and technologies requiring further research and development before they are ripe for licensing.

More specifically, in FY 2005, OTT entered into a contract with Discovery Logic, Inc. to text mine data sources, leveraging a pre-existing NIH internal use license for its text-mining software engine. The following relevant sources were identified and text mined: (1) TechTracS (the database for OTT's intramural technology portfolio); (2) CRISP (a biomedical database system containing information on research projects and programs supported by the Department of Health and Human Services); (3) PubMed (a service of the National Library of Medicine that includes over 15 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s); and (4) Science News Wire. Additionally, a fifth source, the USPTO's patent database, from 2001-present, was

text mined. The resulting software tool, currently registered at GovPatents.com, now in use within OTT, represents a unique tool for performing high powered analyses related to targeted marketing of NIH's technologies and identifying technologies ripe for research and development activities.

Efficiency

The use of a pre-existing NIH internal license for a text mining software engine increased the efficiency of the text mining process and contributed to the text mining being extended to a fifth source (the USPTO's patent database (2001-present)).

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.

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.

Initiatives To Increase Diversity. NIH-supported research training and career development programs help ensure that a diverse pool of highly trained scientists are available in adequate numbers to address the Nation's biomedical, behavioral, and clinical research needs. In order to achieve this objective, every NIH supported institutional predoctoral and postdoctoral training grant must have a minority recruitment plan in place prior to award. In addition, enhanced opportunities designed to increase the diversity of the pool of research scientists beyond the standard institutional training grant practice include Minority Access to Research Careers (MARC), Career Opportunities in Research Education and Training (COR), and Research Supplements to Promote Diversity in Health-Related Research.

Initiatives To Augment the Supply of Clinical Investigators. The expansion and support of the clinical research workforce is a priority of the national clinical research effort. NIH uses several complementary approaches to stimulate the supply of clinical investigators.

Multidisciplinary Teams. Health science increasingly draws on a broad range of fields, including those not traditionally associated with biomedical sciences. In addition to physician-scientists, NIH will be developing creative approaches to address the supply of health science investigators in fields such as engineering, imaging, physics, nursing, mathematics, statistics, computer science, behavior, pharmacology, and epidemiology.

Community and International Partnerships. Health research increasingly requires partnerships between investigators and indigenous personnel. Many important health questions are best addressed by going to unique populations, here in the United States and abroad, that due to geography, population structure, or disease burden, provide unique opportunities to understand disease pathogenesis, anticipate disease trends, or develop interventions.

Mechanisms of Support. Extramurally, NIH offers a flexible and varied series of high-quality training opportunities that are 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://grants.nih.gov/training/extramural.htm. Intramurally, many training and career development opportunities also are available in NIH laboratories. The Web site at the following link provides information on the different intramural training positions: http://www.training.nih.gov/.

Loan Repayment. NIH Loan Repayment Programs are a vital component of the Nation's efforts to attract health professionals to careers in clinical, pediatric, health disparity, or contraceptive and infertility research.

Research Resources. The availability and accessibility of essential research tools, cutting-edge technologies, adequate facilities, animal models, reagents, and other repositories are fundamental to the productivity of the research enterprise. This is because research resources often set the boundaries as to which questions can and cannot be investigated. Within research resources, new information technologies (IT) to share, transfer, and mine vast amounts of complex data electronically are revolutionizing the conduct of science and the management, administration, and support of the research enterprise.

NIH has an active history of using IT to contribute to the success of its mission as well as to the efficiencies of all aspects of its administrative and scientific functions. For example, in February 2000 NIH launched ClinicalTrials.gov, a Web-based database that provides patients, family members, health care professionals, and members of the public with easy access to information on government- and industry-sponsored clinical trials. NIH also developed an IntraMall, a Web-based system for easily locating, ordering, and recording purchases of scientific supplies, computer equipment, and office supplies. IntraMall is the Federal Government's largest online purchasing system.

The promise of IT continues to be realized. Currently, NIH is involved in three major IT

initiatives, known collectively as enterprise systems.[2] 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 DHHS 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 DHHS, that is, a vision to help DHHS evolve from a collection of distinct and separate agencies into "One Department." To achieve his goal of managing DHHS IT on an enterprise basis, the Secretary directed the development and execution of the Draft DHHS 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 DHHS IT resources and will drive progress for public health and human services. All the NIH enterprise systems dovetail with the draft DHHS Enterprise IT Strategic Plan.

[2] Enterprise systems are broadly based IT systems that are expected to be used widely across NIH and interface with other major IT systems. At NIH, responsibility for the enterprise systems involves a partnership between the functional area manager/program official, who serves as the business owner of the system, and the chief information officer.

CBRR-1	**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. (ongoing)**

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. At the same time, NIH believes strongly that training and supporting a research community that reflects the Nation's diversity is a top priority. Accordingly, NIH has designed a number of training programs to provide support to a diverse population of graduate and postdoctoral students and to recruit them into research at all career levels. NIH also has developed programs designed to enhance the retention of women in biomedical research careers and support for individuals with disabilities. Continual monitoring of the demographics of the participants in NIH programs is an important aspect of fostering a diverse cadre of researchers able to conduct basic and applied scientific research.

This monitoring enables NIH to implement corrective actions. For instance, if application rates for a particular program fall below historical rates, NIH determines the reason and responds accordingly. Possible actions include developing and issuing new or updated funding initiatives to ensure that the needs of the scientific research community are served, increasing applicants' probability of success (the success rate), increasing benefits for awardees, or improving outreach. Success rates affect the attractiveness of an award since applicants who think they are unlikely to receive an award may opt for other sources of support. It is, therefore, important for NIH to maintain stability in the overall success rate so that applicants know what to expect.

Success of NIH training programs can be measured, in part, by the number of trainees that apply for and receive subsequent NIH support; subsequent support is an indicator of retention success in the research arena.

Rationale

The NIH is dedicated to improving the health of Americans by supporting biomedical research that will help prevent, detect, treat and reduce the burdens of disease and disability. In order to achieve these goals, it is essential to ensure a diverse available pool of highly trained scientists in adequate numbers and in appropriate research areas to address the nation's biomedical, behavioral and clinical research needs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A number of activities are conducted to support the achievement of this goal. These include: issuing new and updated research training, fellowship, career development and student loan initiative announcements to ensure that the needs of the scientific research community are served; engaging the National Research Council of the National Academies to perform periodically evaluative studies of the National Research Service

Award program; informing the scientific research community of new, updated and ongoing training and career development opportunities through presentations at national, regional, and local meetings; and communicating with other Federal agencies that support similar training and career development goals.

NIH seeks to increase research workforce diversity by providing enhanced training or career development opportunities for individuals from disadvantaged or underrepresented groups. Each of these opportunities is in addition to the required minority recruitment plans for all NIH supported institutional predoctoral and postdoctoral training grants, and presents a balanced and effective means to reflect achievements designed to increase research workforce diversity. The assumption is that awards made or positions supported increases the diversity of the pool of researchers because they support individuals from disadvantaged or underrepresented groups. Therefore, the baseline is zero and the number of enhanced opportunities is the number of additional positions supported each year.

Target 4 was achieved in 2005 and is anticipated to be realized in 2006; it will expire in 2007. These programs were initiated in 1999, and they have since become integral components of NIH training opportunities offered to investigators pursuing patient-oriented research careers.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation.		(FY04) NRSA Group: 20.5% Comparison Group A: 7.0% Comparison Group B: 2.9%		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) Award rate to comparison groups exceeded by 12%						
FY05	*Actual Performance:* (MET) Award rate to comparison groups exceeded by at least 14%						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 2) Ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of termination.		(FY04) NRSA Group: 34.7% Comparison Group: 20.8%		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) Award rate to comparison groups exceeded by 14%						
FY05	*Actual Performance:* (MET) Award rate to comparison groups exceeded by at least 13%						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 3) Ensure that there is multidisciplinary /interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Field of Training, or Discipline/Specialty Field codes or departments.		(FY04) 556 multidisciplinary or interdisciplinary grants		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) The reported rate of multidisciplinary grants was 44%						
FY05	*Actual Performance:* (MET) The reported rate of multidisciplinary grants was 27%						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 4) Achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research.		(FY03-FY06) Awards granted K23 120 K24 50 K30 50		◆	◆[e]	◇	
FY04	*Actual Performance:* (MET) All annual targets achieved (K23=222, K24=50, K30=59)						
FY05	*Actual Performance:* (MET) All annual targets achieved (K23=223, K24=76, K30=51)						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						

(Target 5) Provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity. *Previous Target:* Increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups.	(FY04) 0 additional positions supported			◆	◆	◇	◇
FY04	*Actual Performance:* (MET) The percentage of under-represented minorities rose by 2.4% in FY 2004.						
FY05	*Actual Performance:* (MET) Provided enhanced opportunities to recruit and retain underrepresented groups to biomedical research						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 6) Recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs.	(FY04) LRP applications received: 2,498 LRP contracts awarded: 1,407			◆	◆	◇	◇
FY04	*Actual Performance:* (MET) Applicants 2,498, Awards 1,407 (56% of applicants received an award)						
FY05	*Actual Performance:* (MET) Applicants 3,290, Awards 1,600 (49% of applicants received an award)						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1. The FY05 target to ensure that the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by 10% within 10 years of graduation was MET.

Using data spanning 1984 through 1994, the proportion of pre-doctoral trainees and fellows applying for and receiving subsequent NIH support exceeds relevant comparison groups by greater than 14%.

	PERCENT SUBMITTING APPLICATIONS	PERCENT RECEIVING AWARDS
NRSA Study Group	34.3%	21.5%
Group A	13.6%	7.0%
Group B	6.6%	2.9%

Target 2. The FY05 target to ensure that the proportion of postdoctoral trainees and fellows applying for and receiving subsequent NIH support research grants exceeds relevant comparison groups by 10% within 10 years of termination was MET.

The application and award rates for NRSA recipients exceeded those of their comparison group. Of the 10,392 individuals who received NIH NRSA-Kirschstein postdoctoral fellowship support during 1984 through 1994, 5,285 (50.9%) applied for research project grant support and 3,498 (33.7%) received a grant.

Of the 10,712 unsuccessful applicants for NIH NRSA-Kirschstein postdoctoral fellowship support, 3,679 (34.3%) applied for research project grant support and 2,137 (20.0%) received a grant.

Group	Applied for a grant	Received grant
NRSA	50.9%	33.7%
Other	34.3%	20.0%

Target 3. The FY05 target to ensure that there is multidisciplinary/interdisciplinary training on at least 10% of all training grants as evidenced by program or trainees reporting different Fields of Training, or Discipline/Specialty Field codes or departments was MET.

The NIH collects information on the Field of Training (FOT) at the time of each trainee's appointment and the NIH can track these opportunities to particular training grants. The research training grants that include training positions reporting more than one FOT are considered interdisciplinary for this target. As indicated in the baseline year (2004), the NIH found 556 institutional training grants that were considered multidisciplinary using this criterion. In FY 2005, the number had increased to 623 training grants, or approximately 27% of all training grants reported.

Target 4. The FY05 target to achieve 100% of the asymptotic targets for the number of K23, K24, and K30 awards developed in response to the recommendations of the NIH Director's Panel on Clinical Research was MET and exceeded.

In FY 2005, the NIH made 223 competing K23 awards (1,017 K23 competing and non-competing awards in total), thus exceeding its target of 120, in supporting the mentored, patient-oriented, career development experiences of young clinicians.

In FY 2005, the NIH made 76 competing K24 awards (264 K24 competing and non-competing awards in total) thus exceeding its target of 50.

In FY 2005, the NIH made 51competing K30 awards (53 K30 competing and non-competing awards in total), thus exceeded the target of 50.

Target 5. FY04 target target to increase by 1% over baseline the number of research training and career development positions occupied and enhanced opportunities provided to individuals from underrepresented racial and ethnic groups was MET. The original FY2004 target was extended in order to allow sufficient time to capture the necessary trainee appointment related information. The project period for many NIH institutional research training grants is from July 1 through June 30 of the following year, during which time trainee appointments are made. Information regarding these appointments is relayed to the NIH throughout this time period; however, the majority of information is available after June 30. The percentage of under-represented minorities rose by 2.4% in FY 2004, thus the FY 2004 target was met.

The revised FY 2005 target to provide enhanced opportunities to recruit and retain underrepresented racial and ethnic or disadvantaged groups to biomedical/behavioral research, beyond the required minority recruitment plans for all NIH institutional training grants, through the use of funding initiatives designed to increase research workforce diversity was also MET. The number of enhanced opportunities to recruit and retain underrepresented racial, and ethnic or disadvantaged groups to biomedical/behavioral research included:

	New	Continuations
Research Supplements to Promote Diversity	759	781
Minority Access to Research Careers (MARC)	140	516
Career Opportunities in Research Education & Training (COR)	29	142
Diversity Related Predoctoral Fellowship Awards	130	226

Target 6. The FY05 target to recruit and retain highly qualified extramural investigators to biomedical/behavioral research through the use of student loan repayment programs was MET.

The NIH received a total of 2,138 new and 1,152 renewal applications (3,290 total) for the 5 Extramural Loan Repayment programs in FY 2005. The NIH made 818 new (38%) and 782 (68%) renewal awards; therefore 49% of applicants were awarded loan repayment contracts.

Implementation Strategy Advances or Other Highlights

During fiscal year 2005, over fifty research training and career development funding opportunity announcements were updated. These revised announcements help ensure that the needs of the scientific research community continue to be served and will help facilitate the transition to electronic submission of training and career development grant applications projected to occur in fiscal year 2007.

The National Research Council of the National Academies issued two reports in fiscal year 2005 concerning the research training and career development of our Nation's next generation of biomedical, behavioral, and clinical research scientists. The reports evaluated needs for research personnel in the United States and provided recommendations to facilitate the transition of new investigators to become independent scientists with stable research support. Recognizing the importance of these issues, the Director of NIH formed the NIH New Investigators Committee. The Committee's objective is to review the reports' findings and to develop a list of action items that will facilitate an investigator's ability to receive a first independent R01 award earlier in his/her research career. The Committee is currently refining its recommendations for presentation to the Director of NIH.

Efficiency

The robust performance results reported for target 4 reflects NIH continued efforts to foster the research training and career development of patient-oriented research investigators.

CBRR-2	**Promote data sharing and provide information in real time by implementing and monitoring the NIH Business System. (By FY 2010, the NBS will be in an ongoing status.)**

BACKGROUND

The core mission of the NIH is to conduct and support biomedical research. After an extensive review of its administrative processes and current information technology support, the NIH began implementing an enterprise resource planning system known as the NIH Business System (NBS). The NBS Project will replace the NIH administrative and financial core operations systems, including the general ledger, finance, budget, procurement, supply, travel, and property management systems. The NBS will enable administrative/scientific support that is cost effective, provide more accurate and timely information, and facilitate the scientific mission of the NIH. The NBS will reduce the amount of time required by NIH scientists to complete administrative tasks (for example, related to travel requests or acquisition), thereby freeing these valuable resources in direct support of NIH's core research mission.

Rationale

Deployment of the NBS should position the NIH to meet the Chief Financial Officers (CFO) Act and Government Management Reform Act (GMRA) requirements and OMB's timeframes. The successful implementation of the NBS general ledger module for FY 2004 reduced the need for previously constructed adjustments required to prepare financial statements. This was a critical step for the NIH meeting the tighter timeframes for annual financial statements and other financial reporting while maintaining the accuracy of the reports. Implementation of the general ledger module and follow-on modules will strengthen the NIH's compliance with accounting standards for recording transactions in the appropriate ledger accounts, providing subsidiary ledgers for all appropriate general ledger accounts, and for identifying intra-governmental partners. Complying with accounting standards will help facilitate the reconciliation process and provide more effective analysis of general ledger account balances.

The NBS is an important component of the One HHS initiative and a major element of the DHHS Unified Financial Management System (UFMS). As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS. The NIH staff actively participates on DHHS UFMS teams to meet common goals, address Department-wide challenges, and ensure that the NBS will become an integral part of the UFMS.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NBS Implementation is a phased approach, as recommended by JFMIP, to incorporate individual modules as they are completed. Modules of the NBS will serve similar functions to the legacy ADB system. In FY 2006, the NBS is upgrading the general ledger/budgeting and travel modules already in production and plans to deploy the supply and replenishment modules. In FY 2007, the NBS plans to deploy the contracts/ acquisition, property, supply, accounts payable and receivables modules and

the agreement and real property solutions. Billing and cost accounting for Central Service and Supply operations will be deployed at a later date. Additional modules may be developed and implemented beyond the original seven functional areas of ADB.

The FY 2005, FY 2006 and FY 2007 NBS implementation and deployment activities that the functional, technical and change management teams will undertake include the ongoing design, configuration, and testing of the baseline system and the system at the integration phase including workflow management. An overview of the tasks follows:

a) identifying business rules to be applied and functionality that have policy change implications;
b) testing each function to assure that the configurations are accurate, that business rules are being applied properly and reporting test results for potential change management issues;
c) developing workflows for each function and identifying all interfaces with other functions;
d) testing integrated functionality to determine that business rules and workflow operate as expected and report the results
e) defining all existing integration with remaining ADB function(s) or other systems, as required;
f) developing acceptance test criteria and translating the acceptance test criteria into test scripts for the end user training and for the functions to be deployed;
g) collaborating with Change Management staff to develop technical training materials and user documentation for each function to be deployed;
h) training approximately 6200 users for an estimated 32 roles;
i) providing access to all authorized NIH users of each new function and providing pre and post deployment support to end users.

DHHS currently has a goal of deploying e-Travel throughout the Department. The intent is that the e-Travel system will provide functionality, integration with financial components and real-time support similar to that currently implemented by NIH. The NIH is currently analyzing the actions and resources necessary to include NIH travel needs into the consolidated eTravel system, while mitigating disruption or degradation to NIH travelers and administrators. The NBS roll-out phase will support integration activities to UFMS finance systems.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Deploy the property and contracts/acquisition/accounts payable and receivable/supply modules. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY06) FY06 Program steps h-I 'Final review' (Extended to FY07) *Previous Target:* Deploy the property module.	(FY03) NBS without contracts/acquisition/accounts payable/supply modules			→	→	◇
FY04	*Actual Performance:* (MET) Completed system design and configuration, unit beta testing and commenced CRP1 testing.					
FY05	*Actual Performance:* (EXT) The program steps a-g 'Integration' is being re-planned. Extended to 2006.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					

(Target 2) Deploy the service and supply fund activities module. FY04 Program steps a-e 'Development' FY05 Program steps a-g 'Integration' (Extended to FY08) FY06 Program steps h-I 'Final review' (Extended to FY09)	(FY03) NBS without service and supply fund activities module		◆	→	→	→
FY04	*Actual Performance:* (MET) Identified solutions for automated amortization for Real Property and Agency Agreements.					
FY05	*Actual Performance:* (EXT) The program steps a-g 'Integration' deployment for service and supply fund modules are being extended to 2008.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
(Target 3) Report critical elements of General Ledger and Travel Module performance.	(FY04) NBS performance with General Ledger and Travel Modules deployed				◇	◇
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 4) NBS roll-out and post deployment support.	(FY05) NBS without contracts/acquisition/accounts payable and receivable /supply modules					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 5) Commencement of NBS/UFMS migration activities.	(FY06) NBS without the UFMS migration					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY2005 Program steps a-g 'Integration' target to deploy the property and contracts/acquisition/accounts payable and receivable/supply modules was extended to FY2006. The property and contracts/acquisition/accounts payable and receivables/ supply modules are being re-planned for FY 2006 and FY 2007 from the FY2005 deployment timeline. The NBS completed an organizational impact assessment of changes to current business practices, built and executed CRP2 testing, continued development for the training and communication plans that support workforce transitions, began development of training materials and conducted a NIH-wide Town Hall meeting introducing the property and acquisition functions, including demonstrations of functionality. The project team also initiated proof of concept for the data collection component of data conversion and completed mock data conversions of master data. Deployment of the property and contracts/acquisition/accounts payable and receivable/supply modules are being extended to complete the second of two planned rounds of integrated testing and engage in regression testing of upgrades to Oracle, Prism, and Sunflower COTS packages required for needed functionality.

Target 2

The FY2005 Program steps a-g 'integration' target to develop the service and supply fund activities module was extended to FY2008. Deployment of the service and supply fund modules are being extended pending guidance on the most appropriate time for implementation given other HHS needs and government-wide mandates.

Implementation Strategy Advances or Other Highlights

The NBS Travel module is used daily by all NIH Travel administrative personnel. Approximately 300,000 records have been processed in the NBS Travel module since

deploying for FY 2004. For FY 2005, 137,334 travel authorizations and voucher transactions were entered online in real time. The NMC takes a proactive approach for intercepting document errors in both the travel and financial modules. The goal is to achieve "same-day resolution" for system and document errors that immediately affect user access and/or traveler reimbursements.

In addition, the NBS provides enhanced sponsored travel tracking and reporting. The process aids with the identification of outstanding receivables and allows for more efficient collection, as evidence by a significant reduction in sponsor-related billing requests since deployment of the NBS.

The NBS updates patient records every 5 minutes, seven days a week. This automated process coupled with real-time interfaces between the travel and finance systems enables Clinical Center staff to enter patient authorizations and pay travel vouchers as patients complete their stay at the Center. 26,925 patient trips were processed by the Clinical Center Travel Office during FY2005.

The NBS Management Center (NMC) supports the deployed General Ledger and Travel modules by employing standard escalation protocols for assisting users who are experiencing difficulty. In FY05 the NMC saw a 29% reduction in the number of user call assistance tickets, totaling 10,846 down from 15,178 in FY04. This can be largely attributed to system stability, continued user comfort with the system, and NMC education outreach efforts that include emails as well as supplementary training seminars. There were five such seminars in FY05, whose topics were derived from trend analysis from monitoring NBS user call assistance tickets as well as direct user feedback.

The NBS automated and linked the DHHS EHRP to the NBS Human Resources database for all employee-based transactions. This information is used to support portal access, travel manager transactions and review and approval processing flows. This solution has been adopted by the UFMS for their organization and people data base needs.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

After careful review of the GAO audit of the Department's UFMS project, the NBS data conversion strategy and the NBS project plans, the NBS has scheduled additional testing activities to assure system viability and acceptable product delivery. In reviewing the proposed delivery schedule, it has been decided to suspend the reporting of activities under track 3 beyond FY04, to avoid duplication of goals in this submission, and to place the reporting of such activities under track 4. The FY 2006 funding reflects this integration activity with funding which represents a 2% decrease from the FY 2005 level. Should additional funding reductions be necessary as a result of NIH FY 2006 appropriations, the deployment schedule will be analyzed to assess any additional impact.

CBRR-3	**Streamline business processes and automate data movement by implementing, monitoring and updating the clinical research information system (CRIS). (ongoing)**

BACKGROUND

The NIH Clinical Center has been a pioneer in the use of computer technology for the advancement of research and the improvement of care. The present Medical Information System (MIS) was implemented in 1975 and gave NIH physicians access to tools such as physician order entry and a point-and-click interface that are still not implemented in many academic health care settings. Unfortunately, the system was built around a proprietary database, and its capabilities no longer meet the needs of the institution for providing data in both the research and clinical care settings. For some functions such as pharmacy, surgical services, and consent management, no automation is currently in place.

To address the limitations of the present system and to fully automate clinical care information, NIH has embarked on the CRIS project. Specific functionality that will be provided by the CRIS includes:

- Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and regulations of the Privacy Act of 1974
- Interfacing with ancillary systems to provide integrated data and eliminate paper-and-pencil transfer of data among systems
- Reduction of potential medical errors through the implementation of a pharmacy and surgical scheduling, management, and documentation system
- Management and display of radiologic, anatomic, pathologic, and ultrasound images and other image-based data
- Interfacing to IC research databases
- Support for standardized medical vocabularies
- Support for analyzable electronic documentation (i.e., physician notes)
- Support for protocol-based provision of care
- Provision of management information for resource allocation and cost attribution
- Provision of longitudinal patient data
- Provision of historical patient data for research analysis
- Comprehensive support for patient appointing
- Support for bed management
- Support for nurse acuity assessments

Rationale

Historically, research data have been recorded in stand-alone systems or on paper. Because these research data could not be provided directly from the hospital system, they were typically copied from hospital system computer screens into the local electronic or paper-based research record. Such a process, when multiplied over the research enterprise of NIH, represents a substantial loss of productivity and a major risk of error. Implementation of the CRIS will reduce the life-cycle costs of these clinical information technology projects and obviate the need for IC-specific systems.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

CRIS includes several functional modules that will be phased in once they are completed. The core hospital system will be developed to include modules that streamline business processes and automate data movement among multiple systems. Staff time for redundant data entry was reduced with the implementation of the core system in FY 2004. In FY 2005, a surgery and anesthesia management system as well as an augmentation of the pharmacy system and patient registration system were implemented facilitating records management for Clinical Center staff. Additionally, a clinical data warehouse was developed and used across NIH. The warehouse directly supports the PMA goals of expanded electronic government and improved financial performance. The CRIS project represents the nucleus of clinical informatics for NIH, with the goal of collecting clinical information for patient care and research in one place. For centralized reporting and monitoring, the completed system will serve as a model for other health care organizations. The new goal for FY 2006 addresses the integration of clinical data systems across the Clinical Center and the NIH to help achieve the goal of collecting data centrally. Working together with CIT to identify multiple clinical systems, ensuring compliance with CHI standards, HL7 compliance and interoperability will ensure meeting the larger goals of the NIH Roadmap and DHHS.

The current CRIS project has delineated to OMB a five-year implementation strategy beginning in FY 2002 and entering a steady state phase after 2006. As with any information system, maintenance includes continual software upgrades and enhancements to ensure the best possible utilization and efficiency of a software system. The CRIS project will continue to add functionality in 2007 and beyond using existing resources within the Clinical Center and through maintenance contracts established through the acquisition and implementation phases of the project.

The development of the CRIS (Clinical Research Information System) is key to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). It is an ambitious undertaking and requires a number of enterprise process and system changes to deliver the long-term goal. The integration, in FY 2006, of clinical systems across NIH intramural programs (to eliminate redundancy) is a key milestone to successfully fulfill the requirement of cross-NIH standardization. The CRIS project will continue the process of integrating diverse clinical care systems into the CRIS. These types of integration are highly dependent on changing technologies and the ability to interface various data collection systems with the core CRIS.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Implement a core hospital system.	(FY03) 28 year old legacy system					
FY04	*Actual Performance:* (MET) The core hospital system, CRIS, went live and the legacy system was retired.					
Implement a surgery and anesthesia management system.	(FY03) No current system exists			◆		
FY05	*Actual Performance:* (MET) Surgery and anesthesia management system implemented; project is on task and within budget.					
Implement a clinical data warehouse.	(FY03) No trans-NIH clinical data warehouse currently exists			◆		
FY05	*Actual Performance:* (MET) Implemented a clinical data warehouse; project is on task and within budget.					

Integrate clinical systems across the NIH Clinical Center. *Previous Target:* Integrate clinical systems across the NIH to eliminate redundancy.	(FY04) Multiple clinical systems exist, but information is not retrievable in a central system.					◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
Integrate clinical research systems across the NIH Clinical Center. *Previous Target:* Integrate clinical care systems such as EKG, Echocardiograms.	(FY 05) The CRIS vision is to integrate all systems providing clinical data. Integration requires complex technical solutions based on HL7 standards.						◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 target to implement a surgery and anesthesia management system was MET. The project is on task and budget according to the CRIS master project plan, available on request. Weekly project updates are also available from the Clinical Center's Department of Clinical Research Informatics (DCRI) Project Management Office. The project has moved from contract signing to implementation. The configuration is currently approximately 90% completed. One section (Inventory Control) was moved to a separate activation in date in April 2006 because of resource constraints in the Department of Anesthesia and Surgical Services (DASS). It was deemed that separating this section would not have a deleterious effect on the performance or use of the rest of the system, and that there would be minimal if any budget consequence under the current contract.

Target 2

The FY05 target to implement a clinical data warehouse was MET. The project is in its preliminary phases. During the reporting period, the CRIS Steering Committee convened a users group that developed functional requirements for the Clinical Research Data Warehouse (CRDW) based on use cases proposed by several participating NIH Institutes. These requirements serve as the basis for an RFP that is currently being finalized. The final report of the user's group is available from the CRIS project, as is the current RFP.

Implementation Strategy Advances or Other Highlights

The development of use cases around clinical research was both a necessary project activity and a valuable learning experience for future users of the CRDW, demonstrating the need for standards as well as the development of better processes in the hospital information system for primary data collection.

CBRR-4	**Provide greater functionality and more streamlined processes in grants administration by developing and monitoring the NIH electronic Research Administration (eRA) system. (ongoing)**

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 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, the DHHS e-Grants storefront initiative, and ultimately to achieve the ability to execute end-to-end electronic processing between NIH and the external community using shared electronic resources.

Rationale

A significant goal for eRA is moving internal work flows from paper-based business processes to electronic processes. The electronic submission and receipt of grant applications through Grants.gov is currently an intense effort and when completed will permit a revitalized refocusing on the administration of grants from application through grant closeout. This will include substantial improvements to Receipt and Referral processes, peer review facilitation, and project oversight. The availability of applications on-line eliminates the need for multiple copies of applications for each reviewer. Financial and progress reporting can now largely be done electronically, and by the end of FY07 or FY08 it is anticipated that most aspects of the grant administration process will be done electronically, which will increase the efficiency of the process and lower the costs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Electronic reporting was implemented in institutions participating in the Federal Demonstration Partnership (FDP) through a Web-based progress-reporting system. A pilot of this system began in November 2002, and was tested throughout FY 2003 by making it available to FDP institutions that requested to use it. After ensuring acceptable performance of the progress reporting system once all FDP institutions have been invited to use it, its availability was expanded to all grantee institutions and a formal announcement was publicized on the NIH Commons during the third quarter of FY 2004. The ability for a grantee institution to submit progress reports through the Commons is now in the hands of the institution's business official. The next step for electronic progress reporting will be to develop the ability to receive reports for non-streamlined and multi-project grants by way of an XML data stream.

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. Efforts can now focus on extending and applying this existing infrastructure to an even broader array of services, such as the support of non-streamlined and multi-project progress reporting via XML data streams.

Migration of existing client/server applications will be completed by implementing an eRA J2EE Migration Plan. This plan stages the transition of proprietary client/server applications to a standard, multi-tier, component-based technology. The J2EE architecture complements the XML technology, transforming eRA into a non-proprietary, secure enterprise system.

The overall implementation strategy for the integration of electronic grant processing for HHS Operating Divisions (OPDivs) is to identify OPDiv integration requirements and, where there are gaps, determine whether OPDiv business processes need to be changed or whether eRA business processes/system modifications need to be made. To this end, a "fit/gap" analysis of OPDiv requirements has been completed for several of the OPDivs and nearing completion for the others; it was finalized in FY05. An eRA-led working group, with participation from the integrating OPDivs, meets bi-weekly and has finalized a list of issues that require changes to existing business processes or system modifications. Testing of OPDiv grant processing is ongoing, with AHRQ, FDA, and CDC (research) grants already being awarded through eRA. SAMHSA, HRSA, and CDC (non-research) began processing grants through eRA at the end of FY05. The anticipation is that full grant processing for OPDivs will occur in eRA during FY06, contingent upon the availability of resources to migrate legacy data and to perform any identified system modifications.

The transition from a paper-based business process to fully electronic processing has been part of the eRA vision for several years. The conversion of paper applications to electronic format has been fully implemented, and the system is capable of accepting electronic applications and doing "Internet Assisted Review". Other conversion activities are currently underway, and other processes will be converted as time, budget resources and other priorities allow. It will likely be several years before most of the conversion is completed. Even though NIH is targeting increased conversion to electronic processing of documents, it may not be cost-effective or desirable to expect a 100% conversion of the individual pieces that comprise end-to-end processing of grants. NIH plans to achieve most of this effort by FY08 or FY09. eRA continues to map electronic processes to existing business models, but as these continue to change, eRA efforts will require greater adaptability. These unknowns make it difficult to commit to a specific schedule for completion of paperless processing. Each year the NIH expects the capability for paperless processing to expand and this progress will be reported.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Implement electronic reporting with all 65 newly online institutions participating in the Federal Demonstration Partnership[3]	(FY99) No institutions using electronic reporting	◆e				
FY03	*Actual Performance:* (MET) Electronic reporting available to the 65 FDP participating institutions.					
(Target 2) Begin pilot-testing of progress reporting for multi-project mechanisms.	(FY99) 14 simple competing grant applications received	→	→	→	→	→
FY03	*Actual Performance:* (EXT) XML development needed. Extended to 2007.					
(Target 1) Expand availability of electronic progress reporting to all grantee institutions	(FY02) 145 FDP institutions given access to electronic reporting.		◆			
FY04	*Actual Performance:* (MET) 2,800 progress reports electronically and 102 grantee organizations are now registered to submit.					
(Target 2) Pilot-test extensible Markup Language (XML) transmission between extramural community and NIH.	FY03) Need for system to conform with OMB/Federal Enterprise Architecture		◆			
FY04	*Actual Performance:* (MET) Pilot-tested XML transmissions successful and technology incorporated into eRA architecture stack.					
(Target 3) Develop plan to integrate OPDIV's	No plans in place for OPDIV Integration.		◆e			
FY04	*Actual Performance:* (MET) eRA has developed plans for adding the FDA and components of the CDC.					
(Target 1) Integrate HHS OPDIVs as eRA users for administration of research grants by the end of FY 2006. Goals: FY05 – 50% of eligible HHS OPDIV's FY06 – 100% of eligible HHS OPDIV's	Integration plan has been developed. Limited use of eRA Grant System by two other HHS OPDIV's AHRQ and CDC/NIOSH			◆e	◇	
FY05	*Actual Performance:* (MET) The Target was exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) are using eRA to process new grants.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
(Target 2) Continue conversion of Business Processes: 80% of business processes being done electronically by FY2008 Goals: FY05 – 25% electronic business processing FY06 – 40% electronic business processing FY07 – 55% electronic business processing	10% of business processes being done electronically			◆e	◇	◇
FY05	*Actual Performance:* (MET) Approximately, 33% of business processes & financial status reports are done electronically.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

[3] Target was carried over from previous eRT goal and was met for FY 2003.

(Target 3) By the end of FY 2007 complete migration of existing client/server applications to Web-based technology. Goals: FY05 – 50% code conversion FY06 – 75% code conversion FY07 – 100% code conversion	(FY03) Migration plan developed. Current architecture is client-server mix with web			◇	◇

FY05	*Actual Performance:* (MET) 60%of the code has been converted. This efficiency was accomplished through a fixed price contract for the code conversion, which was substantially less than the originally estimated cost.
FY06	*Actual Performance:* Performance results will be reported in February 2007.
FY07	*Actual Performance:* Performance results will be reported in February 2008.

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

FY05 Target 1

The FY05 target for Integrating 50% of eligible HHS OPDIVs as eRA users for research grants was MET, and exceeded. 80% of eligible HHS OPDIVs (AHRQ, FDA, SAMHSA and CDC) were using eRA to process new research grants by the end of FY05. Operational reports for eRA will show the number of applications and grant awards processed by the OPDIVs in FY05.

FY05 Target 2

The FY05 target goal of 25% of the business processes being done electronically was MET, and exceeded. Approximately 33% of the business processes are now being done electronically. The pilot for electronic notification was implemented in FY05 and approximately 25% of the progress reports were submitted electronically, and about 75% of the FSRs were submitted electronically in FY 2005. Internet (electronic) Assisted Review has replaced the paper based review of applications. Although only a small percentage of applications are received electronically, all paper applications are converted to electronic format, and they are processed electronically. Operational reports for eRA will show the number applications and grant awards processed by eRA in FY05.

FY05 Target 3

The FY05 target for converting 50% of the client/server applications to J2EE code was MET, and exceeded. Seven of the eleven applications (64%), comprising about 60% of the applications code, have been converted to J2EE and are currently undergoing testing. J2EE code for the conversion of the remaining four applications is expected to be delivered for testing by November, 2005. Contractor reports and internal progress reports on testing will verify the reported results.

Implementation Strategy Advances or Other Highlights

The migration of existing client/server applications to web-base technology (J2EE) is ahead of schedule, and 100% of the code should be converted, tested and implemented in FY06 instead of FY07. The conversion of business processes from paper-based processing to electronic processing is also ahead of schedule. The implementation of electronic capabilities will now allow a high percentage of the business process activities to be done electronically. The actual use of the electronic capabilities is dependent on the ability and desire of the applicants and grantees to use those capabilities.

Efficiency

The conversion of the client/server applications to J2EE code is being accomplished through a fixed price contract for substantially less than the originally estimated cost. The increased use of electronic processing has increased the productivity of the people involved in the grants administration process. A detailed analysis of the increased productivity and cost savings has not been conducted at this time, but there are plans to conduct that analysis in FY06.

CBRR-5	**By 2007, expand by 15,000 the pool of researchers and clinicians NIH has trained in biomedical informatics, bioinformatics, or computational biology.**

BACKGROUND

The availability of high-powered, sophisticated computational tools and high-bandwidth communication networks is revolutionizing basic biomedical research, clinical practice, and public health administration. Organizing, linking, mining, and analyzing large heterogeneous data sets are fundamental to cutting-edge research in the biological sciences, public health services, and clinical medicine. The development, effective enhancement, and creative application of customized or general-use information tools requires sustained involvement of people who are trained in computational/information sciences as well as a biomedical/behavioral/biological science domain.

Biomedical informatics, bioinformatics and computational biology are terms that are often used interchangeably to describe scientific work that is the intersection of computational and informational sciences with an application domain in the biomedical, biological or biochemical sciences. The term "biomedical" is used in its broadest sense, encompassing health care and public health administration as well as basic fundamental research into the nature of the human body, its components and processes. In the text describing this goal, informatics training is used to mean any and all of these things.

Rationale

The potential value of informatics within clinical and basic biomedical sciences has been recognized for several decades. The need for at least two kinds of training has been identified: (1) training that expands the informatics knowledge of biologists, clinicians, and public health officials so that they can participate meaningfully in the design, deployment, enhancement, and evaluation of information tools and (2) training that expands the pool of research informaticians who can work at the nexus of informatics and a biomedical application domain. By supporting a range of informatics training opportunities, including short courses, internships, mentored research, and formal academic programs, NIH helps fulfill this important need and its mission to foster fundamental, creative discoveries that protect and improve health.

Often, the academic training of biomedical scientists, doctors, nurses, and public health officials may include hands-on "information literacy" training for the use of basic computers and software, but not an introduction to the concepts and methods of informatics or to the sophisticated computational systems and tools they will design, select, and use in professional settings. NIH sponsored training opportunities that address this deficiency include short courses, intensives, internships, and rotations.

There is a growing pool of graduate students whose academic interests center on informatics and computational biology. Additionally, as biomedical science becomes more information-technology intensive, scientists and clinicians already active in their careers may wish to expand the scope of their research to include informatics research questions. Core strategies used by NIH for meeting these informatics training needs include pre- and post-doctoral training mentored research awards.

As research in biomedical sciences increasingly involves the design and use of computational tools, modeling and simulation, it could be argued that the support of graduate students on individual research grants will meet informatics training needs, but that is not the case. That scenario would provide some hands-on experience with tools, experience that could eventually lessen the need for short-term training; it will not provide conceptual or methodological training in informatics and computational biology. Without a focused and continuing program of informatics training, NIH cannot assure that the information tools needed for science and medicine will be developed with speed and in a way that meets domain needs, or that the biomedical research workforce will include scientists whose discoveries are made in silico. At current funding levels, NIH short term training programs provide a solid starting point, reaching several thousand people each year. Current pre- and post-doctoral training programs bring more than fifty new graduate students, scientists, and clinicians each year into biomedical informatics, bioinformatics, or computational biology.

Research training in informatics or computational biology expands the research work force that advances knowledge in the biomedical computational and information sciences. Their research leads to important breakthroughs such as intelligent tools for clinical decision making, computational methods to organize and mine large, heterogeneous research data sets, and novel approaches for automated linking of clinical findings and genomic data. Short-term informatics training for scientists, clinicians and public health officials allows them to participate actively in the design and enhancement of tools they use, such as working with computer scientists to develop retrieval algorithms for microarray data gathered in their own research, guiding the design of a program for computer-aided surveillance of outbreaks in a local population, or evaluating effectiveness of new record system at a health center's pediatrics clinic.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH meets its informatics training goal through an array of annual training activities in two areas described below. Because the informatics and computational biology training needs of scientists and clinicians differ from those of individuals who seek research careers in informatics, an array of training opportunities is needed, including some that can be done without leaving one's home institution and some that allow short-term intensive "immersion" experiences elsewhere.

NIH will increase the number of clinicians and researchers who receive short-term informatics or computational biology training. NIH is committed to supporting short-term informatics training, including short courses, internships, summer programs or other intensive training opportunities for undergraduates, graduate students, scientists and clinicians, to provide them with basic knowledge of the concepts and methods of informatics.

NIH will increase the number of pre-doctoral and post-doctoral trainees who receive funding for formal academic coursework or mentored research training in informatics or computational biology. NIH is committed to increasing the pool of trained research informaticians, who work at the nexus of informatics and an application domain. These

opportunities involve acceptance into a training program, receipt of a fellowship or mentored research award. Many of these trainees spend several years in training.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Train people in short-term informatics or computational biology courses. (FY05) 1,950 people (FY06) 4,500 people (FY07) 4,500 people (goal completion)	(FY04) 6,134 people received short-term training in informatics or computational biology.			◆e	◇	◇
FY05	*Actual Performance:* (MET) NIH provided short-term training for 8,716 people in informatics or computational biology.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) Enroll people in pre- or post-doctoral training in informatics or computational biology. (FY05) 65 people (FY06) 220 people (FY07) 220 people (goal completion)	(FY04) 267 trainees enrolled in pre- or post-doctoral training in informatics or computational biology.			◆e	◇	◇
FY05	*Actual Performance:* (MET) NIH enrolled 365 people in pre or post-doctoral training in informatics or computational biology.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 targets were MET and exceeded. For Target 1, Short-term training, NIH provided short term training in biomedical informatics, bioinformatics or computational biology to 8,716 people in FY 2005.

For Target 2, Pre and Post-doctoral training, NIH enrolled 365 people in pre- or post-doctoral training in informatics or computational biology.

Implementation Strategy Advances or Other Highlights

Individuals who received short-term training were trained in a variety of settings, depending on the program and the type of course. The training techniques used included an informatics short courses at Woods Hole and Cold Spring Harbor; student rotations through informatics training centers; technical workshops and mini-courses sponsored at NIH or elsewhere; summer institutes; hands-on mini courses and individualized or small-group on demand training. Recruitment primarily takes place through list-serves, newsletters, word-of-mouth and web pages. For the NIH-based programs, advertising is done through the NIH calendar and email listservs.

For the pre- and post-doctoral training, some programs are university based and are housed at 18 different academic centers around the U.S.: Harvard-MIT Division of Health Sciences & Technology, Yale University, Columbia University Health Sciences, University of Pittsburgh at Pittsburgh, Johns Hopkins University, Medical University of South Carolina, Vanderbilt University, Indiana University - Purdue University at Indianapolis, University of Wisconsin Madison, University of Minnesota Twin Cities, University of Missouri Columbia, Rice University, University of Utah, University of California Irvine, Stanford University, Oregon Health & Science University, and

University of Washington. The approaches for pre and post-doctoral training also include individual fellowships (F series), and mentored research grants (K series).

Efficiency

NIH provided short-term training for 8,716 people in informatics or computational biology, well in excess of the target 1,950 people. This number may include individuals who take a course more than one time. Because interest in informatics training has not abated and even grew in FY 2005, NIH exceeded the target of training 1,950 individuals. Some of the interest is generated by new NIH emphasis on informatics via the Roadmap initiatives, but some reflects the belief of state and academic institutions that technology-enabled science and health care will lead to economic and social benefits. Given the current budget climate, it is unlikely that short-term informatics programs offered by NIH can continue to expand at this pace. The market for short-term informatics or computational biology training may saturate over time as well.

NIH enrolled 365 people in pre or post-doctoral training in informatics or computational biology, well in excess of the target of 65 people. Like the short term training courses, the interest in pre and post-doctoral training in informatics or computational biology has grown in recent years. The interest in informatics training at the pre-and post-doctoral levels is expected to continue, as NIH emphasis on informatics continues to expand. In addition to the National Centers for Biomedical Computing (NCBC) Roadmap initiative, other NIH Roadmap initiatives are likely to include informatics components (e.g., interdisciplinary centers and translational research centers). This could affect the number of trainees in future years.

EXPLANATION OF DIFFERENCES FROM PREVIOUS SUBMISSIONS

Target

Both of the FY06 and FY07 targets for this goal have been revised to reflect the increased demand for training in informatics and computational biology. NIH exceeded both the targets in FY 2005 and has adjusted the out year targets to reflect the increased demand for this type of training. The target of training 1,950 people in short-term informatics or computational biology courses has been increased to 4,500 people for FY06 and FY07. The target of enrolling 65 people in pre- or post-doctoral training in informatics or computational biology has been increased to 220 people for FY06 and FY07. Although it is hard to predict demand for either short-term or pre- and post-doctoral training in informatics and computational biology, NIH believes that interest will remain higher than originally anticipated and has revised the annual targets for this goal accordingly.

The goal itself has also been revised to reflect the new higher FY06 and FY07 targets. The original goal of training 5,000 researchers and clinicians by FY 2007 has been revised to train 15,000 researchers and clinicians by FY 2007.

STRATEGIC MANAGEMENT OF HUMAN CAPITAL

Performance-based results have become a central theme in human capital management efforts at NIH. NIH is developing a strategic, performance-based approach to workforce management by generating performance goals and measures that will (1) align individual performance with organizational goals, (2) provide seamless leadership continuity and succession planning, and (3) appropriately allocate rewards and incentives. Efforts are being invested to develop a clearly articulated workforce plan to address strategic alignment, results orientation, performance measurements, interdisciplinary team building, and workforce succession planning.

NIH is developing a methodical process that provides managers with a framework for making human resource decisions based on the organization's mission, strategic plan, budgetary resources, and a set of desired workforce competencies. Management is currently discussing longer-range resource priorities and staffing needs based on realistic resource improvement goals and staffing requirements. Plans are being developed to allocate funding to improve operating efficiencies and improve technical skills and competencies. NIH is in the process of determining current and future workforce needs, assessing how its current workforce and anticipated future workforce compare with these needs, and developing effective strategies to fill the gaps. The successful implementation of the plan will be critical to achieving program objectives, thus providing a basis for justifying budget allocation and workload staffing needs.

NIH values employees as an essential organizational asset and strives to provide them with the tools they need to be successful. The workforce plan is designed to match the right person with the right job by ensuring more efficient and effective recruitment, training, and retention. In high-performing organizations, employees see a direct connection between their work and accomplishing the organization's mission. Toward this end, NIH places a heavy emphasis on the education, development, and training of its employees. The plan will enable employees and managers to identify training and career development needs, link training with performance goals, provide meaningful performance incentives, and foster a diverse workforce.

To meet the challenge of workforce management, NIH has delayered management levels and consolidated human resource management functions. In addition, NIH has achieved great success in reaching competitive sourcing goals in a variety of commercial areas. While all these initiatives are under way, NIH managers are confronted with the need to balance the certainty of short-term requirements with long-term planning. The workforce plan is central to achieving NIH's long-term objectives and will be the foundation for policies that reshape the workforce over time.

In April 2003 the NIH Director formed the Administrative Restructuring Advisory Committee (ARAC) in response to Administration mandates to examine consolidation and restructuring as a means to provide more responsive, flexible, and efficient administrative services. Drawing on input from the ARAC, the NIH leadership prepared a restructuring plan and presented it to DHHS for consideration. Pending feedback from the Department, that plan will be the basis for a future GPRA goal.

SMHC-3	**Improve the strategic management of NIH human resources by developing and monitoring a comprehensive human capital plan based on the agency's programmatic objectives and projected future needs. (ongoing)**

BACKGROUND

The first item on the President's Management Agenda (PMA) is the strategic management of human capital, which seeks to create a more effective Government that depends on attracting, developing, and retaining top-quality employees from diverse backgrounds and ensuring that they perform at high levels. Strategic human capital management is the transformation of how to employ, deploy, develop, and evaluate the workforce. It focuses on results, not processes. It places the right people in the right jobs to most effectively perform the work of the organization.

Rationale

NIH is deeply committed to creating and sustaining a trained and motivated workforce to carry out the mission of the Agency and has taken a number of major steps to improve human capital management. NIH staff developed an initial strategic workforce plan; drafted a transition strategy to re-train and ultimately assign-employees who are not placed in new organizations as a result of competitive sourcing initiatives; consolidated human resource management functions; developed a major initiative to assess and modify the NIH infrastructure of key NIH administrative-management functions; implemented performance contracts for senior executives and managers; and initiated a major effort that will result in recommendations for improving the effectiveness of recruitment, development, and succession planning processes for key scientific positions within the NIH Intramural Research Program. The ongoing study of key positions within the NIH Intramural Research Program will provide a potential framework for the initiation of a future study of key positions within the NIH Extramural Research Program during FY 2006. All of these major activities demonstrate an unwavering commitment on the part of the NIH to the principles behind the PMA and DHHS management initiatives.

Ultimately, the strategic human capital management plan will capture the workforce needs based on NIH's scientific agenda, identify areas of staff expansion and contraction, address competencies and/or success profiles for key NIH Intramural and Extramural positions, incorporate succession planning and leadership development programs to ensure that viable candidates are available for critical positions, and fully integrate human resources policies to shape the NIH workforce according to the mission and direction of the Agency.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Key activities are underway to achieve the annual targets, improve the strategic management of human resources, and aid in the development of a comprehensive human capital plan. The NIH staff conducted a major study of key positions within the NIH Intramural Research Program (IRP), to include the identification and evaluation of industry best practices related to key IRP positions; development, piloting, conduct, and analyses of incumbent interviews regarding current IRP succession planning processes

and systems associated with eight categories of key IRP positions; development of competencies or success profiles of eight roles and four tiers of key IRP scientific roles; analysis and comparison of incumbent interview/competency criteria to industry best practices; and validation of the IRP competency model. An assessment of NIH strengths and weaknesses regarding succession planning for key IRP positions was conducted considering the scientific agenda and future workforce needs. A study of key IRP positions was also conducted to determine dynamics of the positions and associated competencies; gaps in positions were identified; and an assessment of the gaps will establish future impact. An additional framework of quantitative and qualitative information related to key IRP positions will also be derived from the conduct of annual studies of average age, years of service, retirement eligibility, retention, recruitment strategies and activities, and points of concern about the recruitment and selection processes. Findings from major and annual studies will be utilized to improve the strategic management of human resources. An associated system of performance indicators will be established to assess human capital management of key positions within the IRP.

An implementation plan will be developed to address the most significant challenges, gaps, policies, and systems needed to improve recruitment, development and succession planning processes for key IRP positions. Human capital needs of key positions within the NIH Intramural Research Program will be projected for 3 to 5 years. Findings, conclusions and initiatives will be incorporated into the NIH strategic workforce plan and other programmatic documents.

It is anticipated that the IRP human capital initiatives will serve as an initial framework for an overlapping study of key NIH Extramural Research Program positions while an assessment of newly instituted IRP methods is being accomplished. Additionally, NIH is currently co-chairing a Department-wide initiative to develop a leadership competency model and design competency based training and development opportunities for HHS leaders.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Intramural Research Program.	(FY01) NIH Workforce plan, June 2001		◆			
FY04	*Actual Performance:* (MET) Recommendations were identified, as potential initiatives, for improving human capital management; in key Intramural Research roles.					
(Target 2) Conduct a study to identify competencies needed by NIH leaders who will drive future development efforts.	(FY02) Administrative Restructuring Advisory Committee		◆			
FY04	*Actual Performance:* (MET) A major study to identify competencies and success profiles of key Intramural leaders was completed.					
(Target 1) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	Practices related to recruitment, retention and succession planning			◆		
FY05	*Actual Performance:* (MET) Methods were implemented that addressed recruitment, retention and succession planning for key IRP positions.					
(Target 2) Establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program.	Practices related to recruitment, retention and succession planning			◆		

FY05	*Actual Performance:* (MET) Performance indicators were established that addressed recruitment, retention and succession planning for key IRP positions.							
(Target 1) Develop recommendations for improving the effectiveness of recruitment, development, and succession planning methods and processes for key scientific positions within the NIH Extramural Research Program.	(FY04) Performance indicators to be determined from FY 2005 results					◇		
FY06	*Actual Performance:* Performance results will be reported in February 2007.							
(Target 2) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program. (Report on performance indicators and expected enhancements.)	(FY04) Performance indicators to be determined from FY 2005 results					◇		
FY06	*Actual Performance:* Performance results will be reported in February 2007.							
(Target 1) Assess the impact of utilizing adopted methods and processes for recruitment, development, and succession planning for key scientific positions within the NIH Intramural Program. (Report on performance indicators and expected enhancements.)	(FY 04) Performance indicators to be determined from FY 2006 results						◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
(Target 2) Implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the Extramural Research Program.	(FY 04) Performance indicators to be determined from FY 2006 results						◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.							
(Target 3) Establish performance indicators with baselines related to recruitment, development and succession planning for the NIH Extramural Research Program.	Performance indicators to be determined from FY 2006 results						◇	
FY07	*Actual Performance:* Performance results will be reported in February 2008.							

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 Target to implement methods to improve the effectiveness of recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program was MET. Office of Intramural Research (OIR) leadership began to implement new methods to improve the effectiveness of recruitment, development, and succession planning for key intramural scientific positions. The new methods include: (a) new initiatives for trainees, including development of interdisciplinary training programs for both graduate students and postdoctoral fellows; (b) a course for tenure-track investigators to enhance their leadership skills and tenurability; and (c) leadership training for senior investigators, to enable them to move into intramural leadership positions. Training of fellows has also rested heavily on the quality of mentoring in the NIH intramural laboratories. To better enhance recruitment and retention methodologies for key intramural positions within the IRP, the NIH fully utilizes the pay flexibility associated with Title 42 and has developed a compensation plan that provides for fair and appropriate use of this special administrative employment authority. Furthermore, the OIR has purchased ad space in two of the leading scientific magazines for recruitment of new scientific staff. The tenure track program has been established as a succession planning tool to ensure the availability of high quality senior investigators.

Target 2

The FY 05 target to establish performance indicators with baselines related to recruitment, development, and succession planning for key scientific positions within the NIH Intramural Research Program was MET. Training is being assessed through survey methodologies, along with independent course evaluations and will be updated to reflect

the survey findings. Furthermore, in order to track the effectiveness of the journal recruitment ads, applicants are asked, when they apply online, how they became aware of the job vacancy announcement. Additionally, the number of tenure track scientists who become tenured is also tracked.

Implementation Strategy Advances or Other Highlights

The NIH Intramural Research Program received the highest rating of "effective" during FY 2005. Highlights of PART reporting and evidence demonstrated that the NIH Intramural Research Program (IRP) has unique characteristics that set it apart and above all other programs elsewhere; is unparalleled in the breadth of its biomedical research portfolio; is generally regarded as setting a "gold standard" for the rigor of its independent scientific reviews, the quality of its management, and abundant research and training productivity; and is widely admired and emulated worldwide.

The regular, independent evaluations conducted by outside experts (i.e., Boards of Scientific Counselors, Blue Ribbon Panels) and accrediting bodies demonstrate and certify that programs are of high quality and effective in the conduct of research at the NIH. The Office of Intramural Research (OIR), under the leadership of the Deputy Director for Intramural Research oversees evaluation of management performance of the overall intramural program. Scientific Directors within the IRP assure effective program design, execution, evaluation, and resource allocation.

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 2013, 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.

Consistent with the Department's commitment that affected employees will have a job, NIH will be using all tools at its disposal to retrain, counsel, and place affected employees within NIH, HHS, other federal agencies or alternate employers. Use of VERA and Voluntary Separation Incentive Payments should help reduce the number of affected employees who will need to be placed.

Rationale

The HHS views competitive sourcing as a method to "achieve excellence in management services and thereby improve overall Department management," (goal number 8 in the HHS strategic plan). Like consolidation and centralization, improved financial management, and electronic commerce, competitive sourcing aims to improve efficiency, in order that HHS may more effectively deliver health and human services. For this reason HHS has taken a highly strategic approach to institutionalizing competitive sourcing - one that carefully reflects the needs of the Department.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with the PMA, NIH plans to carry out annual competitive sourcing reviews. The bases for the reviews are the number of full time equivalent staff in particular functional areas as identified in the annual FAIR Act inventory process,

supplemented by annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. Subsets of the identified functional areas that are deemed appropriate for review are then reviewed. The A-76 requirement is met once the reviews are completed.

For FY 2004, the preplanning step identified 14 potential functional areas for review, and of these, eleven were deemed appropriate for review. All eleven have been completed.

As each review is completed, NIH develops transition plans to move to the new organizational structures and to fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards.

For FY 2004 the NIH Transition Center delivered career transition services to employees impacted by the two FY 2003 competitive sourcing studies. In FY 2005, an evaluation of those services was performed; thereby, concluding the implementation of services. Consequently, this performance target will terminate in FY 2006.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Identify annually commercial activities for competitive sourcing comparison.		(FY02) Preplanning initiated for identifying functional areas	◆[e]	◆	◆	◇	◇
FY03	*Actual Performance:* (MET) Extramural Administrative Support Services and Real Property Management groups identified for competitive sourcing comparison.						
FY04	*Actual Performance:* (MET) Nine streamlined and two standard studies conducted in FY 2004.						
FY05	*Actual Performance:* (MET) Thirteen streamlined and one standard studies conducted in FY 2005.						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 2) Complete negotiated competitive sourcing reviews annually.		(FY02) Functional areas identified as appropriate for review	◆[e]	◆[e]	◆	◇	◇
FY03	*Actual Performance:* (MET) Competitive sourcing reviews completed for Extramural Administrative Support Services and Real Property Management groups.						
FY04	*Actual Performance:* (MET) Nine streamlined studies completed, with 8 work awards placed with NIH.						
FY05	*Actual Performance:* (MET) Eleven streamlined studies completed. Two streamlined and one standard study will be completed in March 2006.						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 3) Implement transition services for employees annually displaced due to prior year's competitive sourcing.		(FY03) Transition plans developed for employees		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) Career transition services provided for out-placed staff as a result of competitive assessments/studies.						
FY05	*Actual Performance:* (MET) Career transition services were provided to employees displaced.						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						
(Target 4) Evaluate transition services provided to employees.		(FY03) Career transition services provided to employees impacted by one of the FY 2003 studies			◆	◇	◇
FY05	*Actual Performance:* (MET) Evaluation conducted during FY 2005.						
FY06	*Actual Performance:* Performance results will be reported in February 2007.						
FY07	*Actual Performance:* Performance results will be reported in February 2008.						

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

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 target 'Identify annually commercial activities for competitive sourcing comparison' was MET. For FY 2005, the pre-planning step identified 15 potential functional areas for review, and of these, 13 were deemed appropriate for a streamlined review and one for a standard review. The one remaining review was not studied because during pre-planning, 99% of the work identified for the function was either Inherently Governmental or Commercial Core.

Target 2

The FY05 target “Complete negotiated competitive sourcing reviews annually” has been MET in part. Eleven of the 13 streamlined reviews have been completed. The remaining two streamlined reviews and one standard review will be completed in March 2006.

Target 3

The FY05 target “Implement transition services for employees annually displaced due to prior year's competitive sourcing” was MET. Career transition services were provided to employees displaced.

Target 4

The FY05 target “Evaluate transition services provided to employees” was MET. An assessment of transition services was conducted during FY 2005 by the NIH Office of Strategic Management Planning. It resulted in some modifications to the applicability, depth, budget and duration of transitions services. These modifications, while still in the proposal stage, were presented to the NIH Management and Budget Working Group and the NIH Steering Committee. A final policy for transition services was approved by these groups. No further evaluations are contemplated.

Implementation Strategy Advances or Other Highlights

In accordance with the President’s Management Agenda, NIH plans to carry out annual commercial sourcing reviews. The bases for the reviews are the number of full time equivalent staff in particular functional areas and the annual guidance from the Department. To accomplish this task each year, NIH carries out a preplanning step in order to identify potential functional areas for review. Subsets of the identified functional areas are then deemed appropriate for review through a negotiation process with the Department and OMB and then are reviewed. The A-76 requirement is met once the reviews are conducted and awards are made.

For FY 2005, the preplanning step identified 15 potential functional areas for review, and of these, fourteen were deemed appropriate for review. To date eleven reviews have been completed and the remaining three are nearing completion.

After each review is completed, NIH will develop transition plans to move to the new organizational structures and fill positions as proposed in the respective Most Efficient Organizations (MEOs) awards.

SMHC-5	**Improve and monitor the use of human resource services by providing real-time access to tools via the NIH portal. (ongoing)**

BACKGROUND

The NIH Portal is the next generation intranet for the NIH community. It employs a document directory to organize loose documents by subject, regardless of source, in one logical taxonomy and can be used as a launch pad for enterprise systems and access to information that pertains to the NIH mission. The Portal uses approximately 100 "gadgets" to launch or interact with enterprise systems such as ITAS, Employee Express and the NIH Manual Chapters database. 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.

Currently, Human Resources information relevant to the NIH community is posted on a variety of websites (OHR, ICs, OPM, HHS, etc.), leading to confusion among users, duplication of effort, and a cumbersome search process. 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. Subject matter experts have found it difficult to maintain the currency of HR information. The portal technology will allow for distributed content management, so that subject matter experts can take greater control of their documents and content and self-publish them to the HR Community. By making the HR Community of the NIH Portal the primary site for NIH HR guidance, NIH can greatly improve service to users and subject matter experts alike.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

Beginning in 2002, CIT worked with NIH focus groups to develop a logical taxonomy and identify documents and applications to be accessed through the NIH Portal. OHR helped identify human resources documents and applications that should be included on the NIH Portal. Dozens of HR and HR-related applications were made accessible through the NIH Portal and over 10,000 HR documents were reviewed from over 20 websites. Their relevance, currency and appropriate placement were considered in determining which ones would be accessible through the Portal. Duplicates and obsolete versions were discarded and the remaining 4,000 to 5,000 documents were categorized in the document directory.

In 2003, OHR assumed management of its own content and committed to launching all new HR systems through the NIH Portal. In 2004, the Strategic Programs Division (SPD), OHR began maintaining these documents by "crawlers," which automatically check their target websites for new or revised information. If changes are detected, the new or revised document is automatically crawled to the Portal. The same is true for deleted documents. If a document has been deleted from its host website, the crawler will

automatically remove it from the Portal. Subject matter experts have merely to review new documents and approve them before they are published to the document directory. OHR has 107 crawlers that check their designated sites nightly.

NIH achieved Target 1 which was to develop an HR Community on the NIH Portal. This has become the primary site for NIH HR information, systems and resources. The target to identify HR critical elements and tools to monitor use and quality of the HR information was also realized. In fiscal year FY 2005, SPD launched the HR Community area of the NIH Portal, trained users on accessing the Portal and the Community, marketed the Community's availability, and eliminated where feasible and appropriate, access to HR systems, information and resources through means other than the Portal.

Also in FY05, SPD established the HR critical elements and identified methods to measure them. For example, assuming usage of the HR Community site is one of the critical elements, SPD worked with CIT to determine methods to greater quantify and define usage as distinct hits on the HR Community site. SPD can subsequently demonstrate the increased usage (expressed as percentage of the NIH population) of the HR Community area by measuring the number of HR documents and systems available on the HR Community and the number of people accessing HR systems available only through the HR Community.

Target 3 is to establish baselines for the HR critical elements to monitor over time, and Target 4 is to develop a plan for corrective strategies to improve usability and quality of HR information. In fiscal year FY 2006, the SPD will determine the baselines for the HR critical elements and establish a plan to manage and continuously improve the quality and features of the HR Community.

Building upon prior activities, in building a portal-based Human Resources (HR) system, current goals detail a task to measure the success of the tool in readily providing users with access to HR related policies, publications and guidelines. Current activities explore and establish baselines for the HR system to be monitored over time, with the development of corrective strategies where applicable.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources.	(FY04) Multiple means of access to HR systems; multiple websites for HR information and resources.			◆		
FY05	*Actual Performance:* (MET) Developed HR Community on the NIH Portal as primary site for accessing HR information and resources					
(Target 2) Identify HR critical elements and tools to monitor use and quality of the HR information.	Inconsistent quality and currency of HR information.			◆		
FY05	*Actual Performance:* (MET) Worked with CIT to evaluate products for measuring usage of HR information on HR Community Portal.					
(Target 3) Establish baselines for the HR critical elements to monitor over time.	(FY05) HR critical elements and tools identified.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
(Target 4) Develop plan for corrective strategies to improve usability and the quality of HR information.	(FY05) HR Community established.				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					

(Target 5) Implement corrective strategies with subject matter experts and customers.	(FY 06) A plan for corrective strategies to improve usability and quality of HR information has been established.	◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.	

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 target to develop an HR Community on the NIH Portal to become the primary site for NIH HR information, systems and resources was MET. A Human Resources Community was developed on the NIH Portal that serves as the primary site for NIH employees to access HR information and self-service applications - http://hr.od.nih.gov/hrcommunity.htm (NIH Only). The Community was launched on 3/21/2005 and consists of 5 pages (NIH Employee, HR Professional, Managers, HR Calendar and Community Knowledge Directory). The HR Professionals page provides access to all HR-related projects (online collaboration area) for OHR employees while the HR Calendar page is a "rolled-up" view of all of the calendar items from any project for which the viewer is a member or guest.

Content from several internet websites were moved to the centralize HR Community portal for easy access of HR information. Having HR information on one site has made the management of HR information more efficient for the web/portal team. A specific example of improved efficiency is the "Who Are My HR Contacts" and the "Update Your Information" portlets on the NIH Portal. OHR staff can update their own contact information and assignments using the 'Update Your Information" portlet. These updates are immediately effective on the "Who Are My HR Contacts" portlet. NIH employees can access an up-to-the-minute listing of OHR staff who services them and OHR can use the "Who Are My HR Contacts" portlet as an online staff roster.

HR content on the NIH Portal includes 20 portlets, 2 Admin portlets (HR Contacts Admin and HR Navigator Admin); 2 Excel portlets (New Hires by Mission-Critical Category and NIH New Hires, Separations and FTE Usage); 4 Launch portlets with SSO (Enterprise HR & Payroll (EHRP), HRIBS, ITAS and WiTS Launch Pad); 4 Link portlets (Benefits Quicklinks, E-HR, E-HR Professional and HHS Careers (QuickHire)); 3 Snapshot queries (Human Resources News & Events , Latest Human Resources (HR) Documents and New HR Standard Operating Procedures (SOPs)); Federal Government Operating Status; HHS Employee Search, HR Navigator, Update Your Information and Who Are My HR Contacts.

NIH network users can access statistics on the NIH Portal by logging into the portal at http://my.nih.gov. Navigate to the "Portal Info Center", to view statistics on the Top Portal Communities and Top Portal Searches of which the HR Community Portal is part.

URL for NIH Portal Top Communities	https://my.nih.gov/portal/server.pt?space=CommunityPage&cached=true&parentname=CommunityPage&parentid=2&in_hi_userid=1321966&control=SetCommunity&CommunityID=247&PageID=502#
URL for Top Portal Searches	https://my.nih.gov/portal/server.pt?space=CommunityPage&cached=true&parentname=CommunityPage&parentid=2&in_hi_userid=1321966&control=SetCommunity&CommunityID=247&PageID=504#

Target 2

The FY05 target to identify HR critical elements and tools to monitor use and quality of the HR information was MET. The critical elements identified are, freshness of human resources information; relevance of human resources information to the NIH audience; and usability of the HR tools. HR worked with the Center for Information Technology (CIT) to evaluate products that could measure the usage and distinct hits on HR content in the NIH HR Community Portal. The Portal Interaction Analytics product was launched on the NIH Portal in September 2005. This product provides statistics on the usage of the Human Resources community, collaboration on the NIH Portal, human resources portlets as well as providing metrics on the documents most accessed on the NIH Portal and key search terms.

Prior to the deployment of the Portal Interaction Analytics tool, HR had basic information on how many people used the NIH Portal. Now, there are specific information on which HR portlets were used, how many people are using the HR community and what topics and documents were accessed most frequently. HR can use this knowledge to better direct the NIH Community to HR resources more intelligently. HR is currently reviewing tools and resources that are accessed most frequently in order to plan for future development. Tools used to monitor quality of HR information consist of:

- Tracking of questions that come into HR Systems Support (through phone, e-mail, etc.).
- HR Content Manager Group that monitors HR content in their areas of expertise.
- HR Content Stoplight Report produced quarterly to identify areas that need review.
- The Portal Interaction Analytics product measures what search terms our audience is using – which we can use to guide and modify the way we present HR information.
- Survey.
- Usability Testing.

One immediate accomplishment was to review the top HR-related search terms and to associate each search term with a "best bet" of which resource should be listed first in the search results. OHR worked with the Center for Information Technology (CIT) to evaluate products that could measure the usage and distinct hits to HR content in the NIH Portal. HR reviewed several products and provided feedback to CIT on the type of metrics that would be beneficial to HR.

Implementation Strategy Advances or Other Highlights

HR formed a Web/Portal project team consisting of SPD staff. This team worked with HR Content Managers throughout OHR to determine the HR content to display on the HR Community portal and how to best present the information. Some major accomplishments on the project for FY2005 include:

- Successfully updated the HR Navigator with seven new topics.
- Created an OHR & OSMP Employee Toolbox using a Content Canvas portlet. Made the Toolbox a subcommunity of the HR Community on the NIH Portal.
- Drafted HR Systems Handouts for new OHR/OSMP employees as well as regular NIH employees.
- Released HR Navigator and Who Are v. 2.0 to the OHR Community.
- Announced new & updated HR portlets to OHR community.
- Sent out instructions to all of OHR for updating their contact information and assignments using the "Update Your Information" portlet on the NIH Portal.
- Trained pilot group of HR Content Managers to use Contribute. The pilot has been a great

success. HR Content Managers are successfully updating their own content.

- Reviewed/revised/instructed OHR staff on updating their contact information on the "Who Are My HR Contacts" portlet on the NIH Portal.

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 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, linkage of employee performance contracts with organizational objectives, and performance of proactive, compliance site visits to grantee institutions.

POI-1	**By 2007, ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an earned value analysis and management system (EVAMS).**

BACKGROUND

NIH is committed to efficient and effective management and oversight of its real property capital projects. The Earned Value Analysis and Management System (EVAMS) will provide a means to do this. EVAMS is a project data analysis framework that links cost and schedule estimates to actual results.

Earned Value Management (EVM) provides an early warning system for deviations from project plans and quantifies technical problems in cost and schedule terms, providing sound and objective basis for considering corrective actions. EVM helps flag and develop strategies to mitigate the risk of cost and schedule overruns while also providing a forecast of final cost and schedule outcomes. The EVAMS will provide NIH Project Managers with a management system, tools and the information needed to improve their ability to manage, report on, track project performance, and intervene as necessary when the risk to successful completion of a project increases.

Rationale

Earned Value Management (EVM) is an integrated project management system that will significantly improve NIH's ability to actively track capital project performance management.

This goal is consistent with the philosophy of the Federal Real Property Executive Order that recommends establishment of clear goals and objectives to improve agencies accountability for real property and with OMB Circular No.A-11, Part 7 that references EVM as a project management system required to support facility budget submissions.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

In accordance with OMB Circular No.A-11, Part 7, NIH implemented a project management review system based on the EVAMS. This is used to monitor and manage the performance of the design, acquisition, construction, and commissioning of capital facility projects. As a first step in the implementation of the EVAMS, NIH integrated existing project management data from Lab 33, and the Northwest Parking Garage, into a "proof-of-concept" version of an NIH EVAMS. NIH used information generated by EVAMS data reports and analysis to evaluate and redesign work processes to improve the efficiency and effectiveness of its capital project delivery systems.

The NIH established preliminary EVMS policies and procedures in June 2003 as a management tool to improve the delivery of capital projects. Projects in design and proposed for construction were selected to pilot the system and be a source for collection of data to validate its effectiveness and flag areas needing enhancements.

Evaluation and assessment of existing project management systems and their integration into a proof-of-concept version of an EVAMS took between nine and 12 months. The first draft of the development of EVAMS policies and procedures began in late June 2003. Implementation of a revised project management system that incorporates EVAMS took place within 16 months after the evaluation and proof of concept were completed.

Further, NIH will continue review of its project management systems, benchmark with public and private sector organizations, and pursue a grant under the NIH One Percent Evaluation Set Aside Program to assist in the evaluation, assessment, and validation of proposed EVAMS methodology.

Concurrent with this action, Office of Research Facilities (ORF) will begin initial implementation of its proposed EVAMS, beta test the system using a minimum of one (1) design and up to two (2) construction projects, and provide top management and Project Manager level training on the use of the EVM management system to enable better management and facilitation of on time, within scope, and within budget delivery of projects.

The NIH will continue data analysis and collection to enhance the EVMS. The services of a consultant, recognized as an EVAMS specialist, will be obtained to review, analyze and further validate the proof of concept version. Data will be verified using information from the Office of Research Facilities Quality Management System and the earned-value analyses that are performed for pilot projects. The lessons-learned from the pilot test, the benchmark results and the observations of consultants was used to fully launch the NIH EVAMS in FY 2005.

By the end of FY 2006, conduct Earned Value Analyses for major capital acquisition projects using the information as a baseline for future year analyses.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Evaluate and assess existing project management systems and implement into a proof-of-concept version of the NIHs Earned Value Management System (EVAMS).	(FY03) Policies and procedures in place to identify data needed for evaluation		◆			
FY04	*Actual Performance:* (MET) Project Management Systems were evaluated and assessed by ORF staff and EVMS external experts.					
Implement a revised project management system that incorporates earned value analysis and management.	(FY03) EVAMS proof-of-concept version			◆		
FY05	*Actual Performance:* (MET) Project Management System was modified to reflect management and contracting procedures suitable for the project acquisition method used.					
Fully launch the Earned Value Management System (EVMS) and conduct Earned-Value Analyses to evaluate and assess major capital acquisition projects included in the NIH Real Estate Portfolio.	(FY05) Earned Value Management System (EVMS) is incorporated into the project management system				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Complete goal of ensure that approved design and construction projects are executed on time, on scope, and on budget by implementing and monitoring an earned value analysis and management system (EVAMS).	FY06 results					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY2005 target to implement a revised project management system that incorporates earned value analysis and management was MET. The Office of Research Facilities (ORF) integrated the principles of the Office of Management and Budget (OMB) Circular A-11, Part 7 into its practices and applied them to the various acquisitions methods used in the delivery of facilities.

Implementation Strategy Advances or Other Highlights

The gap analysis undertaken during the assessment and evaluation stage and subsequent review of current practices resulted in formulation of earned value operational metrics suitable for use with firm-fixed price contracts.

PART

This goal was included in the FY2007 PART for the NIH Buildings and Facilities Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

POI-2 Utilize performance-based contracting (PBC). (ongoing)

BACKGROUND

One of the major challenges for Federal Government management and administration is improving the efficiency and effectiveness of contracting and procurement activities. Historically, Government policies, regulations, and attention have been directed at acquisition of supplies rather than services. A 1997 OMB 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

The Office of Management and Budget/Office of Federal Procurement Policy (OMB/OFPP) has placed an increased emphasis on PBC. 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, OMB established annual targets. NIH's PBC GPRA goals for FY 2004 and FY 2005 were based on achieving the OMB targets. In a September 7, 2004 memorandum, the OMB stated its plan to reevaluate the target achievement levels for future years based on agencies' FY 2005 Performance.

The strong endorsement of PBC stems from the Government's emphasis on managing for results: by linking payments to results rather than to effort or process. PBC provides NIH with useful indicators of contactor performance and allows vendors to be innovative in responding to requirements for specific products and services.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

The NIH strategy to utilize PBC incorporates three basic elements: 1) promoting the value of PBC in acquisition and contract administration/management planning; 2) ensuring that PBC planning takes place on individual requirements and contracts; and 3) making certain that NIH acquisition staff is properly trained and aware of guidance on PBC.

Under the Office of Acquisition Management and Policy's (OAMP) leadership, the acquisition and project officer community have attended training sessions promoting PBC. By fostering and facilitating these sessions as well as disseminating information about Government and industry sponsored events focused on PBC, the NIH has raised awareness and improved our ability to apply PBC methods to our requirements.

To ensure that PBC planning occurs, the OAMP/Division of Acquisition Policy and Evaluation (DAPE) stresses the implementation of PBC as required by the Federal Acquisition Regulation (FAR). Through publications such as the Seven Steps to Performance-Based Services Acquisition Guide, the acquisition community is reminded of the importance for considering PBC during the acquisition-planning phase. In addition, the Head of the Contracting Activity reviews solicitations submitted for Board of Contract Award reviews thereby providing the necessary oversight regarding the applicability of PBC.

As stated previously, PBC training opportunities continue to be offered to the acquisition and project officer community. In addition, consultant support has been identified to assist both contracting and project officers on their individual requirements. This effort has increased the familiarization of the community to PBC and eased the transition from traditional contracting methods to performance based contracting methods.

The monitoring of PBC activity is accomplished by the submission of monthly reports from the contracting offices and through reports of PBC funding activity from the Departmental Contract Information System. IC contracting offices are being reminded of the Government-wide move toward increased use of PBC and that PBC is an NIH GPRA target. Contracting staff will be continually reminded that the FAR requires that contracting officers include in their acquisition plans for service contracts or orders, a description of the strategies they will use for implementing performance-based contracting methods, or provide a rationale for not using these methods. The planned strategy for performance-based contracting is to meet the OMB/OFPP target set annually.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Allocate $226 million of available NIH contracting dollars to PBC-eligible contracts.	(FY02) $207 million projected for contracted work with requirements tied to performance	◆				
FY03	*Actual Performance:* (MET) Obligated $557 million of eligible service contracting dollars through performance-based contracting.					
Obligate 40% of eligible service contracting dollars through PBC.	Obligate 40% of eligible service contracting dollars through performance-based contracting		◆[E]	◆[E]		
FY04	*Actual Performance:* (MET) Obligated $654 million of eligible service contracting dollars through performance-based contracting.					
FY05	*Actual Performance:* (MET) Obligated 44% of eligible service contracting dollars through performance-based contracting.					
Obligate FY 2006 OMB/OFPP Goal of eligible service contracting dollars through PBC.	FY 2006 OMB/OFPP Goal				◇	
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
Obligate the FY 2007 OMB/OFPP goal of eligible service contracting dollars to PBC.	FY 2007 OMB/OFPP Goal					◇
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY2005 target to obligate 40% of eligible service contracting dollars through PBC was MET and exceeded by 4%. Forty four percent of the total eligible dollar 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.

Implementation Strategy Advances or Other Highlights

PBC activity is tracked monthly through submission of reports from the contracting offices and through reports of PBC funding activity to the DCIS. Training opportunities for PBC continue to be offered to the acquisition and project officer community to ensure that they are properly trained in the use of PBC. Furthermore, information about Government and industry sponsored events focused on PBC is regularly disseminated.

Efficiency

The FY2005 target was exceeded by approximately 4%.

POI-4 By 2005, ensure proper stewardship of public funding for research.

BACKGROUND

With the receipt of NIH grant awards or other types of public funding for research, principal investigators and grantee institutions accept the responsibility to conduct scientific studies ethically and honestly and to provide proper stewardship of NIH funds. Because of the nature of the assistance relationship, which is predicated largely on trust between the sponsor (NIH) and the recipient (grantee institution), the need for effective internal and external compliance programs is essential. One of the 10 Department-wide program objectives, "Advance science and medical research," lists as one of its components the strengthening of mechanisms for ensuring the protection of human subjects and the integrity of the research process. Although these are only two of the many research compliance issues of concern to NIH, the Agency complemented the objectives of the DHHS Offices of Research Integrity and Human Subjects Research by supporting and establishing programs in these two areas. NIH support of research on Research Integrity and the Human Subjects Research Enhancements Program are two such examples, and underpin Objective 4.5 in the DHHS Strategic Plan for FY 2003-2008.

Rationale

To minimize the risks associated with noncompliance, NIH established a goal in FY 2001 to ensure proper stewardship of public funding for research. This crosscutting goal involves ICs working in partnership with grantee institutions and national professional organizations to improve institutional compliance with NIH requirements.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

A significant NIH strategy for enhancing compliance is to develop a proactive grants compliance program. The program currently focuses on the following major activities: (1) enhancing administrative oversight by creating a new organizational component within NIH with the capacity to perform annual proactive compliance site visits, (2) increasing educational outreach by providing compliance seminars and providing Web-based information and tools to help grantees understand their stewardship role and improve their institutional compliance programs, and (3) creating an internal NIH compliance program to provide management control and exercise oversight for implementation of grant-related policies.

The compliance program involved a newly established management controls compliance program. A subset of grants administration policies was reviewed in order to assess the risk level of each policy. After this was accomplished, NIH began the internal compliance reviews which were planned for 2004. The latter helped to determine if the policies are correct, clear, and/or if training is needed to address any instances of noncompliance. These activities serve to enhance NIH's oversight of sponsored research. By the end of FY 2005 NIH had developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, completed the goal of developing a strong program to ensure proper stewardship of public funding for research.

PERFORMANCE MEASURES		BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
Conduct five proactive compliance site visits.		(FY02) Criteria in place for selecting institutions for site visits	◆				
FY03	*Actual Performance:* (MET) Five proactive compliance site visits conducted.						
Perform a risk assessment and develop a plan for reviews of compliance with grant-related policies.		(FY03) Framework in place for risk assessment	◆				
FY03	*Actual Performance:* (MET) Initial risk assessment of 35 grants administration policies performed; ten policies selected for compliance review.						
Provide Internet-accessible resource information and/or tools for implementing institutional compliance programs.		(FY02) Web site in place for grants compliance and oversight under the Office of Extramural Research	◆				
FY03	*Actual Performance:* (MET) Internet-accessible resource information posted on enhancing institutional compliance programs.						
Begin internal compliance reviews.		(FY03) Ten policies selected for compliance reviews		◆			
FY04	*Actual Performance:* (MET) Compliance reviews grants-administration policies were initiated.						
Implement recommendations from the internal compliance reviews held in 2004. By the end of FY 2005 NIH will have developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, will complete the goal of developing a strong program to ensure proper stewardship of public funding for research.		(FY04) Completed compliance reviews			◆		
FY05	*Actual Performance:* (MET) Recommendations from the internal compliance reviews held in 2004 were implemented.						

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

The FY 2005 target to implement recommendations from the internal compliance reviews held in 2004 was MET. By the end of FY 2005 NIH had developed an ongoing program for internal compliance reviews which, combined with other continuing efforts, has completed the goal of developing a strong program to ensure proper stewardship of public funding for research. Two grants policy assessments were initiated in FY 2004, and one was completed - Evaluation of Progress Reports by Program Officials. The results of the assessment were analyzed and problem areas identified. The Division of Grants Compliance and Oversight (DGCO) provided individualized feedback to each of the ICs which included a report describing observations and findings and the specific compliance issues requiring corrective action. Information designed to enhance compliance was also provided. Each IC was asked to respond to the findings and to develop an implementation plan of appropriate correction actions with a timeline; this information is reviewed and approved by DGCO. The results of the evaluation were shared with the Grants Management Advisory Committee, an NIH-wide committee of grants management officers from each IC that concerns itself with those activities designed to insure compliance with fiscal and administrative policy requirements. No policy clarification issues were identified.

Goal Achievement

NIH achieved the three objectives: 1) enhancing administrative oversight by creating a new organizational component within NIH with the capacity to perform annual proactive compliance site visits, (2) increasing educational outreach by providing compliance

seminars and providing Web-based information and tools to help grantees understand their stewardship role and improve their institutional compliance programs, and (3) creating an internal NIH compliance program to provide management control and exercise oversight for implementation of grant-related policies. Also, NIH has achieved all annual targets for this goal. In fiscal year (FY) 2003, five proactive compliance site visits were conducted and risk assessment was performed for 35 grants administration policies; in 2004, NIH initiated compliance reviews on grants administration policies; and in 2005, NIH implemented recommendations from the internal compliance review held in 2004. NIH has established an effective, on-going compliance program to ensure proper stewardship of public funding for research by achieving all the established objectives and targets. This ongoing program includes management control compliance assessments, proactive compliance site visits and rigorous outreach programs designed to promote effective compliance by grantees as well as by extramural grants staff.

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 be taking specific steps to enhance its ability to demonstrate benefits resulting from extramural research investments. These steps include: (1) making policy changes to formally recognize co-principal investigators, which will allow NIH to characterize better the scientific workforce; (2) making organizational changes to more closely coordinate information systems development and reporting needs with strategic planning efforts; (3) implementing the research and related (R&R) data set to standardize the capture, tracking, and analysis of data across research agencies; and (4) positioning NIH to utilize sophisticated analytical tools, such as knowledge management, and continuing to enhance public access to the results of NIH research as well as improve the ability to analyze the NIH portfolio.

There are four general and related areas under this Goal:

- Permitting and collecting information on more than one Principal Investigator (PI) on a research grant.
- Implementing the collection of electronic grant applications using the Standard Form 424 Research and Related (R&R) dataset.
- Positioning NIH to be able to utilize sophisticated analytical tools such as Knowledge Management to characterize and analyze better the NIH research portfolio. New targets will be added as the process materializes and the other targets are completed.
- Enhance public access to NIH-sponsored research findings.

Rationale

The NIH as a federal agency needs to understand, the nature of the science being funded, how that science addresses the health-needs of the nation, and the community that conducts 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 new information available electronically from scanned applications and electronic grants and progress reports will help with setting priorities as well as identifying gaps and areas of common interest across the ICs.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

At this time, planned approaches involve the following activities.

Multiple Principal Investigators: The scale and complexity of biomedical research problems increasingly require collaborative teams of scientists that frequently combine the disciplines of the physical, biological and social sciences. This approach is specifically encouraged by the NIH Roadmap Initiative Research Teams of the Future. A critical part of this involves the recognition of all key contributors on NIH projects. Accordingly, the NIH has initiated an effort to permit more than one PI on an NIH

funded research project. This change in policy will not only encourage the development of interdisciplinary approaches, it will allow the NIH to recognize and acknowledge the contribution of all PIs. The White House Office of Science and Technology Policy issued a directive to all federal agencies on January 4, 2005 to begin planning to allow and recognize more than one PI. Under the NIH plan, it will be possible for more than one PI to share the responsibility for a research grant. Once implemented, grant applications will identify all PIs involved with a particular project. All the PIs will be listed on the notice of grant award and in reports related to that particular grant. Adapting to multiple PIs will require 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. The NIH issued an RFI during the spring of FY 2005 to probe institutional preferences. This will help define the electronic design to be finished in FY 2006 and the collection of information on more than one PI to be in place by FY 2007. Collection of information on other key collaborators should be available by FY 2008.

Research and Related Dataset: The SF424 R&R dataset is a set of application data elements and instructions that Federal Agencies involved in Research and Related (R&R) funding have agreed to use. This common data set will theoretically replace the OMB-cleared data collection instruments (applications) currently maintained by each research agency. The goal is to create a consistent application for research grant support that can be used across the government. For NIH, this will essentially replace most of the data currently collected under the OMB cleared PHS Form 398. NIH efforts have involved negotiating a common dataset for all federal research agencies and then identifying agency-specific items that are not in general use. A pilot using "dead data" with the R&R forms was completed this year. A phased, controlled, live pilot is expected during FY 2006. Ramp-up to larger pilots is expected during FY 2006 and FY 2007 with an expected transition to broad use of the R&R in May 2008. Since these goals depend largely on other federal agencies, the expected implementation dates should be considered preliminary.

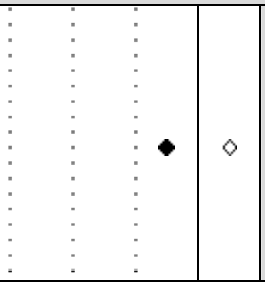
Knowledge Management for Disease Coding: Knowledge Management (KM) software tools can be used to systematically find, select, organize, distil and present information from complex sources. These methods have been used in problem solving, dynamic learning, strategic planning, and decision making. This approach has been used in limited ways to mine text from grant applications, summary statements, publications and other documents to help select reviewers based on areas of expertise and improve the reliability and consistency of disease coding across the NIH as a way to facilitate budget reporting. Unlike the use of simple index terms, KM searches documents for concepts such as fever, fatigue, breast neoplasm, etc. It then assigns a weight to specific terms or concepts in a document depending on the frequency of appearance, distinctiveness and juxtaposition to other concepts. Weighting factors for the searched terms can then be displayed as a "fingerprint". Document fingerprints can then be compared to fingerprints established for a particular disease category and the quality of the match can be scored. A pilot that involves 20 disease categories and 12 institutes and centers was completed by September 2005; it determined whether this technology is sufficiently reliable for disease coding.

Public Access to Information on NIH-Sponsored Research: The NIH is using information technology systems within the NIH Commons and the National Library of

Medicine's (NLM) PubMed Central (PMC), to archive publications resulting from NIH-funded research. This policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The policy is intended to: 1) create a stable archive of peer-reviewed research publications resulting from NIH-funded research to ensure the permanent preservation of these vital published research findings; 2) secure a searchable compendium of these peer-reviewed research publications that NIH and its awardees can use to manage more efficiently and to understand better their research portfolios, monitor scientific productivity, and ultimately, help set research priorities; and 3) make published results of NIH-funded research more readily accessible to the public, health care providers, educators, and scientists. The Public Access Policy was implemented in 2005. NIH-funded investigators were requested to submit to the NIH NLM PMC an electronic version of the author's final manuscript using the NIH Manuscript Submission (NIHMS) system after it has been through the publication peer review process and accepted for publication.

By storing research publications from diverse sources in a searchable, electronic archive with a common format, PMC facilitates greater integration with related resources in other NLM databases thus providing the opportunity to develop unprecedented scientific search and analysis capabilities for the benefit of science. This searchable archive will enable NIH program officials to manage their research portfolios more efficiently, monitor scientific productivity, and ultimately, help set research priorities. This strategy also will enable NIH to advance its goal of creating an end-to-end, paperless grants management process. Finally, it will make the publications of NIH-funded research more accessible to and searchable for the public, health care providers, educators, and scientists.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Recognize Multiple Principal Investigators on Research Grants (FY2007 accomplished) (FY05) - Address signature and regulatory issues associated with Multiple PIs. Develop plans for application forms and data systems that accommodate multiple PIs. (FY06) - Complete Modifications of forms and data systems to accommodate multiple PIs. (FY07) - Accept applications that include information on more than one PI.	In FY 2004, all research grants had only one Principal Investigator			◆	◇	◇
FY05	*Actual Performance:* (MET) Addressed signature and regulatory issues, and develop plans for application forms and data systems associated with multiple PIs.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) Accept Electronic Grant Application through the Grants.Gov Portal Using the 424-R&R dataset. (FY 2008 accomplished) (FY05) – Mock Pilot 424-R&R forms using "dead data" to assess utilization of common data sets. (FY06) – Conduct phased, controlled pilot of the 424-R&R dataset using live data to assess the transmission of common data elements. (FY07) – Conduct expanded Pilot of the 424-R&R dataset using live data to assess the expansion of common data elements.	Paper grant applications currently received			◆	◇	◇
FY05	*Actual Performance:* (MET) A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use.					

FY06	*Actual Performance:* Performance results will be reported in February 2007.	
FY07	*Actual Performance:* Performance results will be reported in February 2008.	
(Target 3) Create and Implement a Policy to Enhance Public Access to Archived Publications Resulting from NIH-Funded Research (FY 2006 accomplished) (FY05) – Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators (PI). (FY06) – Expand NIHMS system capabilities by 1. Linking submissions to PI Progress Reports 2. Receiving third party manuscript uploads to facilitate submissions.	(FY 04) No mechanism exists to receive manuscripts	
FY05	*Actual Performance:* (MET) NIH developed and launched the NIHMS system was May 2, 2005.	
FY06	*Actual Performance:* Performance results will be reported in February 2007.	

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 target "Address signature and regulatory issues associated with Multiple PIs and develop plans for application forms and data systems that accommodate multiple PIs" was MET.

Regulations: Regulations need to be modified at 42 CFR 52 to accommodate more than one Principal Investigator (PI). Planning for this modification has involved several meetings with the NIH Legal Advisor, the Workgroup on Multiple PIs, the Interdisciplinary Roadmap Committee, and the Extramural Program Management Committee. These discussions have permitted the development of a draft modification of the rule with changes at 52.2 and 52.6 to accommodate a definition that allows more than one PI and the possibility that more than one award might be made in response to a single application. A package will be approved within weeks for submission to DHHS and OMB and publication in the Federal Register for comments.

Signatures: Discussions with the NIH Legal Advisor have indicated that signatures on grants are occasionally valuable in legal procedures involving PIs on NIH grants. Discussions have revealed that other federal agencies receive grant applications without PI signatures and that PI signatures are not included in electronic applications on SF 424 (R&R) forms. The migration to electronic receipt of applications on the SF 424 (R&R) will mean that signatures will be discontinued as a normal course of business. Additional discussions are currently underway with the NIH Compliance Office to see if there are compelling policy reasons to retain PI signatures as part of the phase-out package for the PHS 398 form.

Application Forms: The SF 424 (R&R) forms already include provisions for more than one PI. NIH data systems will accommodate more than one PI from those forms beginning on May 1, 2006. Since the NIH will be mid-way in the transition to electronic applications using the SF 424 (R&R), The NIH will revise the PHS 398 to accommodate more than one PI. The PHS 398 will be sent to the Office of Management and Budget for interim Paperwork Reduction Act approval.

Data Systems: A plan with a detailed timeline has been deliver to update NIH data systems to receive, process, track, and report information on more than one PI. Systems are scheduled to be in place by May 1, 2006.

Target 2

The FY05 target "Mock Pilot 424-R&R forms using "dead data" to assess utilization of common data sets" was MET. The goal of this exercise was to prepare a sample package of 424-R&R forms and instructions that would be representative of a typical NIH 'apply' posting in Grants.gov, and elicit the feedback of actual applicants. This was referred to as a 'dead data' pilot, since the applicants were instructed to use data from applications which had been previously submitted to the NIH. The ultimate objective was to determine relative areas of strength and weakness in the forms and instructions, so that appropriate adjustments could be incorporated into these instruments prior to the first production 'apply' posting in Grants.gov in December 2005.

This target was accomplished on schedule, with the participation of applicant representatives from the NIH Commons Working Group. A 424-R&R forms sample was developed, and a draft set of instructions posted with this package for applicants' use. An on-site computer lab session was facilitated, at which time the pilot was conducted and feedback on forms, process, and instructions was collected.

Target 3

The FY05 target 'Build and launch the NIHMS IT system on PubMed Central to receive peer-reviewed manuscripts submitted by Principle Investigators' was MET. Public Access to Information on NIH-Sponsored Research: As a result of the release of the Public Access Policy, 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. To meet the goals of the policy, the NIH developed a comprehensive manuscript submission system (NIHMS system) to allow NIH-funded investigators, including NIH intramural investigators, the opportunity to submit their peer reviewed, accepted for publication, author manuscripts to NIH. The manuscripts are then posted for public accessibility on PMC. The NIHMS system was launched on May 2, 2005. Enhancements are periodically added to the system to make it easier for authors to submit their manuscripts to NIH. For example, on July 6, 2005 third parties (e.g., publishers, libraries, assistants, etc.) were able to upload manuscripts on behalf of the authors. Therefore authors need only approve and finalize the submission.

Implementation Strategy Advances or Other Highlights

The mock 424-R&R pilot was conducted on schedule. It was an important milestone in our progress toward electronic submission in Grants.gov and provided valuable feedback. While we were unable at that time to perform full end-to-end testing with the NIH Commons, it was a very valuable experience and provided vital information for our ongoing forms and instruction development.

POI-6	**Provide responsible stewardship over existing federally owned real property assets. (Ongoing)**

BACKGROUND

Responsible stewardship over federally owned real property assets addresses the issue of deferred maintenance risks. Deferred maintenance compromises the life safety and health of the occupants in the facility. It may prevent the facility from meeting all or part of its stated mission and reduces the intrinsic and market value of a real estate asset.

Facility Condition Index (FCI) is an industry best practice for assessing and measuring the state of individual facilities and the portfolio of facilities by objectively quantifying deferred maintenance and non-compliance with recognized codes and applicable standards. Facility Condition Index (CI) is a mathematic way of expressing the relationship between the cost of deferred maintenance and the capital replacement value of a facility or portfolio of facilities.

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

Rationale

For NIH to assure its facilities are capable of supporting its biomedical research mission, NIH must have an objective way to measure the state of its real property assets and to plan for and to monitor the capital maintenance and repair program. The FCI is one of the required measures under the President's Management Agenda Real Property Asset Management initiative.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

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

- Update the facility condition assessment data
- Modify the prior year's capital repair plan in light of actual funds appropriated
- Execute the funded plan
- Develop next year's annual capital repair plan based on the facility condition data, the work funded in prior years, and other criteria that optimizes the use of available capital repair funds in pursuit of the goal

Through this annual process NIH will be able to maintain the condition of the portfolio so the average CI is 85 and not less than 95% of occupied facility gross square feet (GSF)

has a CI greater than 65, which are the criteria for optimum performance. By monitoring these measures annually, NIH can demonstrate good stewardship.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Maintain the condition of the portfolio so the average CIwa = 85*	(FY04) CIwa = 85 (FY05) CIwa = 85		◆	◆[e]	◇	◇
FY04	*Actual Performance:* (MET) The condition of the portfolio was maintained so that the average CI was 85.					
FY05	*Actual Performance:* (MET) The condition of the portfolio improved so that the average CI for 2005 was 87 which met and exceeded the 2005 target of 85.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) By 2010, not less than 95% of occupied GSF will have a CI greater than 65 FY04 (target = 86.0%) FY05 (target = 87.0%) FY06 (target = 88.5%) FY07 (target = 90.0%) FY08 (target = 91.5%) FY09 (target = 93.0%) FY10 (target = 95.0%)	(FY04) 86.0% (FY05) 87.0%		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) 86% of occupied GSF had a CI greater than 65.					
FY05	*Actual Performance:* (MET) 87% of the occupied space had a CI greater than 65.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY05 target to maintain an average facility Condition Index (CIwa) of 85 was MET and exceeded. The average CI for 2005 was 87. Throughout the fiscal year, facility repairs and improvements were conducted to correct structural deficiencies, improve the facade of buildings, and to provide efficient building equipment and systems to enhance operations.

Target 2

The FY05 target to ensure that not less than 87% of occupied GSF will have a Condition Index (CI) greater than 65 was MET. In FY05, 87% of the occupied space had a CI > 65. Repairs and improvements focused on a wide range of structural, architectural, mechanical, plumbing and electrical systems to improve operations and reliability within available resources.

Implementation Strategy Advances or Other Highlights

A Repair and Improvements Board (R&IB) consisting of management representatives from each organization responsible for facilities operations and maintenance is used to review and prioritize the program requirements to ensure the best return on investment and utilization of available resources for overall improvement of the condition of NIH facilities portfolio.

Efficiency

Target 1

The FY05 target was met through use the NIH Facility Condition Assessment Program which prioritize repair and improvements program requirements utilizing a management cadre familiar with the unique maintenance and operations of NIH research and supporting facilities.

PART

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

POI-7	**Manage design and construction of capital facility projects funded by the Building and Facilities Appropriation (B&F) so the HHS and congressionally approved scope of work is delivered within the approved budget. (Ongoing)**

BACKGROUND

The design and construction processes are complex, imprecise, and vulnerable to many outside influences including changing requirements, changing standards, weather, material shortages, and market forces. Thus, managing capital facilities design and construction so the planned scope of the project is completed within the approved budget and schedule is always an ambitious goal. Under current practice as defined by OMB A-11, federal construction projects are to be fully funded in advance. In this situation, it is critically important to manage each project identified in the B&F request (so-called line item projects) within appropriated amounts because, short of reducing the scope of work, reprogramming from other capital projects, or requesting additional appropriations, there is no more money to cover cost overruns, if they occur.

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 on an annual cycle must manage funded projects to meet schedule and cost management targets. This involves development and execution of specific project management plans for each project that will include as a minimum:

- Formation of an Integrated Project Team that includes stakeholders
- Pre-project planning to manage potential project risks
- Development and approval of a program of requirements as a basis for design
- Design management to include peer reviews and approvals
- Acquisition planning
- Construction management and quality assurance programs
- Commissioning to validate that the facility is fully operational for the intended use

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

- Manage all B&F line item projects so they are completed within 100% of the final approved total project cost.
- No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

This goal is to monitor and track on time, on scope and within budget delivery of facilities to be good stewards of the limited resources received to support the research

mission of the NIH and to comply with OMB Circular A-11. Earned Value Management is one of the key tools that will be used to accomplish this objective.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Manage all B& F line item projects so they are completed within 100% of the final approved project cost. (FY04) 19 active projects (FY05) 21 active projects (FY06) TBD active projects (FY07) TBD active projects	(FY04) 19 active projects (FY05) 21 active projects		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) All 19 projects were managed within the approved budget.					
FY05	*Actual Performance:* (MET) All twenty-one (21) projects were managed within the approved budget.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) No more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope. (FY04) 19 active projects / 10% ≤ 2 (FY05) 21 active projects / 10% ≤ 2 (FY06) TBD (FY07) TBD	(FY04) ≤ 2 (FY05) ≤ 2		◆	◆	◇	◇
FY04	*Actual Performance:* (MET) No projects required scope adjustments.					
FY05	*Actual Performance:* (MET) All projects were managed within the approved scope.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1

The FY2005 target to manage all B&F line item projects so they are completed within 100% of the final approved project cost was MET. The twenty-one (21) active project goal set for FY2005 were all managed within the approved budget. This included management of projects on the NIH Bethesda, North Carolina, Hamilton, Montana, Poolesville, Maryland, and Frederick, Maryland campuses within the funding levels approved for those projects.

Target 2

The FY2005 target, no more than 10% of the projects may incorporate plus or minus 10% adjustments of the approved scope, was MET. For FY05, there are 21 projects; therefore, 10% is less than or equal to 2. One project experienced a scope variance greater than 10%. However, the project did not exceed budget. The scope variance resulted from re-evaluation of construction site options proposed for the project. Findings concluded that the most viable option was to relocate the facility to the central portion of the campus. This shift provided opportunities to consolidate administrative functions displaced by the new facility into the project, accounting for the greater than 10% scope increase without a budget increase.

Implementation Strategy Advances or Other Highlights

The Office of Research Facilities (ORF) Earned Value Management system will be one of the tools used to support evaluation of the delivery of the portfolio of capital assets within approved cost and scope.

PART

This goal was included in the FY2007 PART for the NIH Buildings and Facilities Program. NIH will continue to achieve this goal's annual requirements as indicated by the PART Improvement Plan.

POI-8	**Protect NIH's interest in real property supported under the extramural construction grant program throughout each phase of the project. (ongoing)**

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 pre-award, award, and post award requirements that are unique to the program.

The additional pre-award requirements are associated with the availability of matching funds, the applicant's compliance with additional public policy requirements and ensuring sufficient title to site. 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. Target 1 for this goal consists of these pre-award requirements. The baseline is the number of awards issued during the target year.

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 subordinated to those of non-Federal parties unless a deviation is approved. Target 2 consists of these award requirements. The baseline is the number of projects that began construction during the target year.

Lastly, after construction is complete, the awardee 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, an awardee is required to provide a certification that the property is adequately insured against physical destruction or provide a certification that the awardee 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 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. Target 3 consists of these post-award compliance measures. The baseline is the number of projects completed in the 20 years prior to the end of the target year (e.g. FY05 baseline is number of projects completed during October 1, 1985 to September 30, 2005).

NIH staff also provides additional oversight related to environmental impact issues, design specifications, and financial management of construction projects.

NIH's grants compliance program works to ensure that the ICs adhere to NIH construction-specific grants oversight policies through a management controls initiative that examines IC policies and procedures, their compliance with NIH policy, and if IC staff follow the required procedures.

PERFORMANCE ANALYSIS

Planned Implementation Strategies

NIH has collected data on IC compliance with certain policy requirements including monitoring the use of research space supported by NIH construction grants for the 20 year period specified in the Notice of Grant Award. Based on the findings of the data analysis, NIH staff will work closely with ICs to ensure that they have systems in place that meet policy requirements. NIH will reevaluate IC systems by re-administering a management controls questionnaire self assessment tool to validate continued compliance.

PERFORMANCE MEASURES	BASELINE	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007
(Target 1) Meet 100% of pre-award requirements for construction grants or implement corrective strategies. • Ensured the Availability of Matching Funds, when applicable • Ensured Compliance with Public Policy Requirements • Ensured Sufficient Title to Site	No. of Awards: (FY05) 21 issued (FY06) TBD (FY07) TBD			◆	◇	◇
FY05	*Actual Performance:* (MET) 100% of awards met the pre-award requirements or are implementing corrective strategies.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 2) For projects under construction, have met 100% of award requirements or implement corrective strategies. • Approved Design and Construction Documents • Ensured the Notice of Federal Interest has been Recorded	No. of Projects: (FY05) 35 active (FY06) TBD (FY07) TBD			◆	◇	◇
FY05	*Actual Performance:* (MET) 100% of projects under construction met the award requirements or are implementing corrective strategies.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					
(Target 3) Meet 100% of post-award compliance measures, as defined by NIH Policies and Procedures, for completed construction grant projects or implement corrective strategies. • Ensured Adequate Protection Against Physical Destruction • Monitored the Use of Grant-supported Space	No. of Projects occupied in past 20 years: (FY05) 322 active (FY06) TBD (FY07) TBD			◆	◇	◇
FY05	*Actual Performance:* (MET) 100% of projects completed in the past 20 years met the post-award requirements or are implementing corrective strategies.					
FY06	*Actual Performance:* Performance results will be reported in February 2007.					
FY07	*Actual Performance:* Performance results will be reported in February 2008.					

◇ Active	◆ Met	→ Extended	× Not Met

SUMMARY OF 2005 PERFORMANCE RESULTS

Target

Target 1:

The FY 2005 performance target was MET. Awardees met the pre-award requirements to

1) ensure the availability of matching funds; 2) ensure compliance with public policy requirements; and 3) ensure sufficient title to site; or are implementing corrective strategies. Fully meeting the pre-award requirements is difficult since a number of the requirements are not easily obtained without a promise of construction support. For example, when the awardee organization is state owned, many of the requirements need levels of approval above that of the awardee in order to buy the land and/or to enter into a lease agreement. This situation can create insufficient time between when the awardee was selected for funding and received funding and when the awardee received approval to negotiate the purchase of the designated land. In this case, the corrective strategy taken includes the issuance of a provisional *Notice of Grant Award*, which indicates that the project must ensure sufficient title to site by a certain time period or the award will be terminated.

Target 2:
The FY 2005 performance target was MET. NIH-funded projects which began construction in FY 2005 have met the construction requirements to have 1) approved design and construction documents; and 2) ensured that the *Notice of Federal Interest* (NFI) had been recorded; or are implementing corrective strategies.

Award requirements are challenged by issues that are often beyond the agency's and/or the awardee's control. For example, there is a reporting gap between the time the design documents are approved and ground breaking, which is the trigger for the NFI requirement. Also, it may take up to three months between the time the awardees submit their NFI to when it is returned by their County or State Recording Office(s). NIH must work diligently with awardees to assist in achieving the award requirements in a timely manner.

For corrective strategies, each individual IC Grants Management Office will send formal letters to the noncompliant awardees requesting the status of the documents that need to be filed. Once all documents are received, a revised *Notice of Grant Award* is issued or a letter is sent to reflect both approved design and construction documents as well as receipt of NFIs. For those awardees who do not respond to the letters, a follow-up letter will be sent. Those awardees not responding to the follow-up letter is sent a letter from the Chief Grants Management Officer from each Institute or Center detailing corrective action to be taken should the awardee fail to respond. In addition, NIH staff members may conduct site visits to ensure compliance with all of the regulations.

Target 3:
The FY 2005 performance target was MET. Post-award compliance requirements have been instituted to 1) ensure adequate protection against physical destruction; and 2) monitor the use of grant-supported space; or NIH has implemented corrective strategies.

To monitor compliance, all awardees must submit required documents. When non-compliant, awardees are reminded, by either a phone call or a formal letter, of the reporting requirements. If additional corrective strategies are needed, NIH sends formal letters to all awardees in the monitoring phase that indicate what information is required of them. When all required information is received from the awardee, the Grants Management Office sends acceptance letters. At the end of the 20 year monitoring period,

a final acceptance letter is sent to the awardee with the encouragement to continue to use the space for the purpose(s) of the award.

For those awardees who do not respond to the monitoring letters, a follow-up letter is sent. The Chief Grants Management Officer sends a follow-up letter to those awardees not responding detailing corrective action(s) to be taken. In addition, NIH staff members may conduct site visits to ensure the compliance of all of the regulations.

Implementation Strategy Advances or Other Highlights

Over the last several years, NIH has experienced a significant expansion of its construction and modernization programs due to biodefense activities. Therefore, NIH recognized the need to revise the construction grant section of the NIH Grants Policy Statement (external document) modify the requirements, clarify certain policies, and emphasize polices that require increased attention by awardees. The NIH Grants Policy Statement includes policy requirements that serve as the terms and conditions of NIH construction grant awards.

NIH is developing a NIH Manual Chapter (internal document) applicable to Construction, Modernization, or Major Alteration and Renovation of Research Facilities. This chapter will provide guidance to NIH program and grants management staff on the administration of construction and modernization grants and cooperative agreements. The chapter will include responsibilities of NIH staff for the administration of the extramural construction grant program as well describe pre-award, award, and post award procedures. The manual chapter will also include standard checklists, letters and terms and conditions of award that will be used by NIH staff to ensure the consistent documentation and administration of the program by all NIH awarding components with construction or modernization grant authority. The NIH expects to submit the manual chapter to the Department for review and approval by spring 2006.

In order to provide additional oversight of this program, the Office of Extramural Research, NIH, administrated a targeted Management Control Self-Assessment tool specifically related to this program to those ICs who are actively awarding construction grants. This evaluation tool was used to evaluate and/or validate the ICs compliance with the specific elements identified in the GPRA goal. The tool helped ICs identify potential areas for improved compliance with grant regulations, NIH policy, and their own established policies and procedures. NIH will re-administer an expanded evaluation tool to cover the areas related to the pre and post award administration of construction grants that will be addressed in the forthcoming NIH manual chapter.

Changes and Improvements over Previous Years

The current Plan/Report contains 48 goals and 68 targets for the Initial FY 2007 Plan; 53 goals and 76 targets for the Final FY 2006 Plan; and 56 goals and 79 targets for the FY 2005 Report. Of these goals, the majority fall under the Scientific Research Outcome category. Goals in the remaining functional areas (Communication and Transfer of Results, Capacity Building and Research Resources, Strategic Management of Human Capital, Program Oversight and Improvement) address objectives described in the PMA and the management objectives in the One DHHS Plan. These latter goals underscore NIH's commitment to responsible management of its research dollars.

Changes/Improvements in GPRA Goals and Targets

In the SRO section, two goals were achieved in FY 2004 and, thus, eliminated from the plan. Since many goals will be achieved in the next two years, ten SRO goals were added to the plan. These changes are described in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
SRO-4.1	Goal achieved and therefore dropped.		
SRO-7.1	Goal achieved and therefore dropped.		
SRO-2.4	New goal added to the plan.		By 2009, the Laboratory of Symptom Management will develop and test multidisciplinary biobehavioral interventions to prevent/attenuate disease- and treatment-related symptoms such as pain, fatigue, and psychological distress, to reduce related symptom burden and to increase functional status and quality of life.
SRO-3.5	New goal added to the plan.		By 2013, identify and characterize at least 2 human candidate genes that mutually influence risk for substance use disorders and risk for comorbid psychiatric disorders using high-risk family, twin, and special population studies.
SRO-3.6	New goal added to the plan.		By 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.
SRO-5.6	New goal added to the plan.		By 2009, identify 1 or 2 new medication candidates to further test and develop for the treatment of tobacco addiction.
SRO-5.7	New goal added to the plan.		By 2010, validate and compare 4 imaging methods of assessing lung cancer response to therapy.
SRO-5.8	New goal added to the plan.		By 2010, improve device(s) to measure hot flashes and test device(s) in clinical trials.
SRO-5.9	New goal added to the plan.		By 2010, establish the role of genetic factors in three major diseases for which health disparities are noted between populations.
SRO-6.4	New goal added to the plan.		By 2014, identify and characterize two molecular pathways of potential clinical significance to serve as the basis for discovering new medications for preventing and treating asthma exacerbations.
SRO-8.6	New goal added to the plan.		By 2011, develop stable national estimate of vision impairment by extending the vision component of the National Health and Nutrition

			Examination Survey (NHANES).
SRO-9.3	New goal added to the plan.		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.
SRO-1.1	Goal ending date extended.	By 2005, 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.	By 2007, conduct medications development using animal models and begin conducting Phase I and II human trials of two potential treatments for alcoholism: the cannabinoid antagonist rimonabant and the corticotropin-releasing hormone antagonist antalarmin.
	FY06 target added.		(FY06) Conduct toxicology studies as required by FDA.
	FY07 target added.		(FY07) Obtain IND approval from FDA to begin phase I/II trials.
SRO-3.2.1	Goal revised.	By 2013, demonstrate the feasibility of islet transplantation in combination with immune tolerance induction for the treatment of type 1 diabetes in human clinical studies.	By 2015, evaluate islet transplantation in combination with immune modulation strategies for the treatment of type 1 diabetes in clinical trials.
	Targets revised.	(FY06) Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY06) Establish uniform cGMP manufacturing process for preparation of pancreatic islet cells across CIT centers.
		(FY07) Enroll patients for Phase I trial to evaluate anti-CD3 to promote immune tolerance induction in patients with transplanted pancreatic islets in the absence of immunosuppressive drugs.	(FY07) Develop 2 clinical protocols.
SRO-1.2.3	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-2.3	New Goal Identifier: SRO-1.2.3
SRO-2.3.2	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-3.2	New Goal Identifier: SRO-2.3.2
SRO-2.3.4	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-3.4	New Goal Identifier: SRO-2.3.4
SRO-4.5.1	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-5.1	New Goal Identifier: SRO-4.5.1
SRO-4.5.4	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-5.4	New Goal Identifier: SRO-4.5.4
SRO-7.8.1	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-8.1	New Goal Identifier: SRO-7.8.1
SRO-7.8.3	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-8.3	New Goal Identifier: SRO-7.8.3
SRO-8.9.1	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-9.1	New Goal Identifier: SRO-8.9.1
SRO-8.9.2	Moved in SRO matrix as nears completion date.	Previous Goal Identifier: SRO-9.2	New Goal Identifier: SRO-8.9.2

For the non-scientific functional areas, six new goals were added to the plan because several goals will be achieved in the next two years. The changes are summarized in the table below.

GOAL IDENTIFIER	DESCRIPTION OF CHANGE	PREVIOUS WORDING	NEW WORDING
CTR-3	Goal revised from ongoing to ending in FY 2006.	Through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products. (ongoing)	By 2006, through education and technical assistance, strengthen the capacity of developing countries to identify technologies and pursue their development into products.
CTR-4	Goal revised from ongoing to ending in FY 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. (ongoing)	By 2008, increase the percentage of Small Business Innovation Research (SBIR) program award recipients who are successful in identifying the resources and/or partners necessary to further the development of their SBIR projects toward commercialization.
CTR-5	New goal added to the plan.		By FY 2013, improve marketing and management of NIH intellectual property assets by building text mining capability.
CBBR-5	New goal added to the plan.		By 2007, expand by 15,000 the pool of researchers and clinicians NIH has trained in biomedical informatics, bioinformatics, and computational biology.
POI-5	New goal added to the plan.		By 2010, enhance NIH's ability to demonstrate benefits for extramural research investments through changes to policy and information systems.
POI-6	New goal added to the plan.		Provide responsible stewardship over existing federally owned real property assets. (ongoing)
POI-7	New goal added to the plan.		Manage design and 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. (ongoing)
POI-8	New goal added to the plan.		Protect NIH's interest in real property supported under the extramural construction grant program throughout each phase of the project. (ongoing)