About NIH

Statement of the Director

It is my privilege to present to Congress the Biennial Report of the Director of the National Institutes of Health (NIH) for Fiscal Years (FYs) 2008 and 2009. Thanks to ongoing congressional support, NIH continues the 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. Indeed, the contributions of NIH to improved health are countless and have touched the lives of not only all Americans, but also of millions of people around the world.

Unique Resources and Opportunities

It is an extraordinary time to be chosen to direct the world's largest biomedical research enterprise. The power of the molecular approach to health and disease has steadily gained momentum over the past several decades, and is now poised to catalyze a true revolution in medicine—ultimately with profound consequences for diagnosis, prevention, and treatment of virtually all diseases. The success of the Human Genome Project and several other major projects that followed quickly afterward have provided a powerful foundation for a new level of understanding of human biology, and have opened a new window into the causes of disease. That includes the revelation of hundreds of previously unknown risk factors for cancer, diabetes, heart disease, hypertension, and a long list of other common illnesses. In the area of cancer, a new ability to achieve comprehensive understanding of the mechanisms responsible for malignancy has already provided insights into diagnostics and pointed to a whole new array of drug targets. Advances in stem cell research—now poised to move forward at an accelerated pace after the President's signing in March 2009 of Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*—hold great promise for applications to diseases such as Parkinson's disease, type 1 diabetes, and spinal cord injury. New partnerships between academia and industry promise to revitalize the flagging drug development pipeline. An era of personalized medicine is emerging where prevention, diagnosis, and treatment of disease can be individualized, instead of using the one-size-fits-all approach that all too often falls short. Vigorous U.S. support of biomedical research in all these areas promises to save lives, reduce the burden of chronic illness, stimulate the economy, empower new and more effective prevention strategies, and reduce health care costs.

NIH Research Works!

Over the years, NIH research has contributed enormously to the remarkable increase in health and life expectancy in the United States. For example, we have gained 7.4 years of life expectancy from 1961 to 2004. Infant mortality has decreased from 26 deaths per 1,000 live births in 1960 to 6.9 in 2005. Two decades ago, the 5-year survival rate for women diagnosed with breast cancer was 84.3 percent and the annual mortality rate was 32.2 per 100,000. Due in large part to NIH research, the 5-year survival rate has risen to more than 90 percent. Breast-conserving surgery followed by local radiation therapy has replaced mastectomy as the preferred surgical treatment. New non-surgical therapies include combination chemotherapies, hormonal treatments, and new monoclonal antibodies.

In the 1990s, the discovery and development of antiretroviral drugs transformed HIV infection for many infected individuals from a death sentence into a chronic disease. Recently, researchers found that beginning antiretroviral therapy early in children infected with HIV significantly improves their immune systems. Because of this evidence, the HHS Panel on Pediatric Antiretroviral Therapy and Management Guidelines has modified recommendations on when to start HIV antiviral treatment in children.

Just a few decades ago, 30 percent of patients died within 25 years of a diagnosis of type 1 diabetes.

One in four diabetics developed kidney failure, and diabetic retinopathy was responsible for 12 percent of new cases of adult blindness. The concept of controlling blood sugar tightly to prevent diabetes-related eye disease, nerve damage, and kidney failure was untested. In 1989, enrollment of 1,441 people with type 1 diabetes was completed in the landmark Diabetes Control and Complications Trial (DCCT). The trial showed that intensive blood sugar control reduced risk for eye, kidney, and nerve complications by 50 to 75 percent. Upon completion of the DCCT, intensive therapy rapidly became the standard of care nationwide. Nearly all DCCT participants continue to be followed in an ongoing successor study. Now, based on new results from this pivotal study, we see not only continued dramatic reductions in eye, kidney, and nerve complications, but also that heart disease and stroke are cut by more than 50 percent. We also see improved long-term health outcomes: 30 years after their initial diagnosis, fewer than 1 percent of the intensively controlled DCCT participants have become blind, required kidney replacement, or had an amputation. Thus, people with type 1 diabetes are living longer, healthier lives than ever before, largely due to long-term NIH-supported research.

Importantly, as the Nation is in the midst of debating ways to reduce increasing health care costs dramatically, NIH research has resulted in remarkable U.S. gains in health and longevity, often with surprisingly modest investments and often accompanied by significant cost savings. A recent analysis of the trajectory of U.S. population health[1] shows substantial correlation of NIH funding with improved life expectancy, reduced disability rates, and economic benefits. For example, deaths from coronary heart disease have declined by 63 percent in the last 30 years, thanks to a host of new insights about prevention and treatment. These dramatic advances have come about with an investment of just $3.70 per American per year in NIH research support. Another example of savings we have seen over time is the development of a vaccine against *Haemophilus influenzae* type b (Hib), which has resulted in a 99 percent decline in the incidence of this leading cause of bacterial meningitis in children under age 5. This has achieved an estimated medical cost savings of $950 million per year, as well as another $1.14 billion per year in avoidance of lost earnings due to disability of the patient and uncompensated caregivers.[2]

[1] Manton KG, et al. *PNAS* 2009;106:10981-6. PMID: 19549852. PMCID: PMC2700155.
[2] Zhou F, et al. *Pediatrics* 2002;110(4):653-61. PMID: 12359777.

ARRA: Jumpstarting a New Era

It was because of this remarkable synergy between the health and economic impacts of NIH-supported research that Congress directed an extraordinary $10.4 billion to NIH as part of the American Recovery and Reinvestment Act (ARRA). Annually, about 85 percent of the NIH budget is dispersed by grants and contracts through the 50 states and territories, with a significant impact on the local economies. Economic input-output studies found that through a multiplier effect each Federal dollar of NIH funding generates more than twice as much in state economic output.[3] Moreover, estimates for FY 2007 indicated that NIH grants and contracts supported more than 350,000 jobs, in full or in part.[4] Due to the ARRA funding, we estimate that approximately 50,000 jobs (full or in part) will be created or retained. It is important to note that 2-year ARRA funds will provide job creation and retention as well as longer-lasting impacts from advances in health science. Therefore, this unprecedented infusion of funds has been an excellent opportunity for sustaining our critical investment in medical research while creating jobs, stimulating related economic activity, and also buttressing the competitiveness of the Nation's biomedical research enterprise. The astounding number of applications that we received for ARRA funding (more than 20,000 Challenge Grant applications and 2,000 Grand Opportunity Grant applications)[5] revealed an untapped pool of innovative research ideas and projects with the potential for future breakthroughs and discoveries that address some of the Nation's and world's most pressing health problems. Clearly, NIH serves a unique role as the critical stimulus for the entire U.S. biomedical R&D enterprise.

[3] FamiliesUSA. In Your Own Backyard: How NIH Funding Helps Your State's Economy. Washington, D.C.: 2008. Available at: http://www.familiesusa.org/issues/global-health/publications/in-your-own-backyard.html
[4] Ibid.
[5] Data as of October 26, 2009.

Five Exceptional Opportunities for Biomedical Research at NIH

The investment in NIH research has certainly paid off. However, we are continuously faced with serious challenges in the fight against disease and disability. I see five major thematic areas that build on NIH's recent advances and that could reap substantial downstream benefits for the diagnosis, prevention, and treatment of a long list of diseases, both rare and common.

First Thematic Area: Applying the unprecedented opportunities in genomics and other high-throughput technologies to understand fundamental biology, and to uncover the causes of specific diseases

In the past, most basic science projects in biomedicine required investigators to limit the scope of their studies to some single aspect of cell biology or physiology. The revolution now sweeping biomedical science is an emphasis on comprehensive approaches that identify *all* of the genes, *all* of the proteins, and *all* of the pathways involved in a disease process. Technologies contributing to these advances, many of which only recently have become practical to use on a routine basis, include DNA sequencing, microarray technology, nanotechnology, small molecule screening capabilities, new imaging modalities, and computational biology.

Cancer is a prime example of the potential of high-throughput approaches. Although a lot of information has been gleaned in the past from targeted efforts with certain tumors, the first complete cancer genomes are now becoming available (for leukemia and brain tumor). Stunning revelations are emerging about the genetic lesions that are involved in malignancies. Due partly to ARRA funding, The Cancer Genome Atlas is poised to derive comprehensive information about the causes of 20 major tumor types. It is virtually certain that this information will force a complete revision of diagnostic categories in cancer, and will usher in an era when every cancer will be evaluated in this comprehensive way, allowing an individualized matchup of the abnormal pathways in that specific tumor with the specific drug or therapeutic known to target that pathway.

Another example is the exciting new opportunity to understand how interactions between our bodies and the hundreds of trillions of microbes that live on us and in us (the so-called "microbiome") can influence health and disease. The inability to culture most of the species that make up the human microbiome severely limited earlier investigations. But all of these organisms have DNA and/or RNA—and so it is now possible to categorize the vast array of species that are present in various body sites, in both healthy and ill individuals. The consequences for our understanding and treatment of a long list of diseases are likely to be profound. Currently, Human Microbiome Project investigators are studying microbial involvement in a range of diseases including psoriasis, Crohn's disease, ulcerative colitis, and obesity.

Second Thematic Area: Translating basic science discoveries into new and better treatments

Often the path from molecular insight to therapeutic benefit has not been easily or quickly discernible for many disorders. That is changing now. The major factors propelling this change include the discovery of the fundamental molecular defect in hundreds of diseases, new resources that allow the screening of hundreds of thousands of compounds for drugs that target the defective molecule or molecular pathway, and the partnering of academia and industry to bring the strengths of each to the drug development pipeline.

The NIH Therapeutics for Rare and Neglected Diseases (TRND) program, established in FY 2009, is an

example of a critical step in the direction of a truly integrated partnership for drug development between NIH and the private sector. TRND will combine experienced, high-level experts from pharmaceutical and biotechnology organizations and academic researchers. These scientists will work together to translate basic research findings into candidate drugs for patients with rare and neglected diseases. This program will allow promising compounds to be taken to the preclinical phase—often referred to as the "Valley of Death" because it is the place where good ideas often die—by modeling its infrastructure and staffing on best practices in the pharmaceutical and biotechnology industries while also capitalizing on the many human, intellectual, and technological resources available at NIH that are not easily accessed by industry.

Another major area that is ripe for major translational advances is the application of various types of stem cells to treatment of human disease. FDA recently approved the first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs), and the potential for increased Federal support for human embryonic stem cell research will bring into this field many investigators who have been reluctant to participate due to uncertainties regarding Federal funding of research in this area. The recent revelation that skin fibroblasts can be transformed into induced pluripotent stem cells (iPSCs) opens up a powerful new strategy for therapeutic replacement of damaged or abnormal tissues, without the risk of transplant rejection. While much work remains to be done to investigate the possible risks of this approach, there is much excitement about the potential. The development of the iPSC approach stands as one of the most breathtaking advances in basic science in the last several years, and NIH will be making every effort to pursue with maximum speed the therapeutic consequences of iPSCs, hESCs, and adult stem cells.

Third Thematic Area: Putting science to work for the benefit of health care reform

NIH can make substantial contributions to health care reform. For example, in comparative effectiveness research (CER), NIH has supported clinical studies for many years that rigorously evaluate the outcomes of different medical treatment options. Examples include the Diabetes Prevention Program, which demonstrated substantially better benefits of exercise and lifestyle changes over medication in preventing the onset of diabetes, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared older, cheaper antipsychotic drugs with newer ones, demonstrating that the older drugs worked just as well and had a better side-effect profile.

Prevention and personalized medicine is another area where NIH can widely contribute to health care reform. Advances in pinpointing individual genetic and environmental risk factors for disease now make it possible to focus prevention strategies more effectively on those who need them most. For example, including newly derived information about individual genetic risks for colon cancer or prostate cancer in determining the timing of colonoscopy or PSA screening could save lives and save money. Behavioral research focusing on how personalized information about disease risk actually alters health behaviors and clinical outcomes will be a critical component of this program.

Pharmacogenomics is another important area where research can inform health care. Already there is compelling evidence of a correlation between genotype and drug response for more than a dozen drugs, and that number is growing. But prospective studies will be needed for many of these applications, such as the one for warfarin (a widely prescribed anticoagulant), currently underway at NIH. The opportunity to choose the right drug at the right dose for the right person holds great promise for better health, both by avoiding treatments that are not going to work, and by reducing the incidence of adverse drug reactions.

One of the most tragic aspects of our health care system is the widespread presence of disparities in health. The health of racial and ethnic minorities, people living in poverty, people living in rural and remote locations, and other disadvantaged groups in the United States is worse than the health of the overall population. National concerns for these health disparities repeatedly have been expressed as a high priority in national health status reviews (including Healthy People 2010), and attention to this issue will be a critical component of any successful reform of the U.S. health care system. Now, new opportunities are emerging to define the causes and potential solutions for many health disparities, and these call for

integration of research on the multifactorial nature of health disparities, including biological and nonbiological factors, and an understanding of the causes of disparities in access to and delivery of health care.

Fourth Thematic Area: Encouraging a greater focus on global health

NIH has a long tradition of supporting research on global health, and recent seminal scientific advances position NIH to make even more important contributions. Examples already in hand include the development of a vaccine against Ebola virus (proven effective in primates) and the recent discovery by NIH researchers of the first new potential drug in 50 years to treat the parasitic disease schistosomiasis.

Much of recent global health research justifiably has been focused on AIDS, tuberculosis, and malaria, given the enormous human toll from these common and life-threatening disorders. NIH is ideally positioned to play a major role in ramping up the discovery phase for these infections, by applying new technologies such as RNAi, high-throughput screening, proteomics, and metabolomics, and tapping into the talents of highly motivated young researchers with a deep understanding of pathogen-host interactions. Combining these technological and human resources will inform future vaccine development and potentially open a vast new range of targets in pathogens and hosts for prevention, diagnostics, and therapeutics. It also is critical to go beyond the focus on the “big three” diseases to apply some of these same strategies to neglected diseases of low-income countries (e.g., roundworm, hookworm, leprosy, African sleeping sickness).

Importantly, we also must respond to the growing challenge of chronic noncommunicable diseases and injuries, which are now responsible for more than half of deaths in the developing world. Studying the causes of diseases such as diabetes and cancer in countries with limited resources can shed important light on pathogenesis and suggest interventions that can be implemented in low-resource settings.

Fifth Thematic Area: Reinvigorating and empowering the biomedical research community

The lifeblood of biomedical research in the United States rests on the talent and dedication of its scientists and an emphasis on innovation—both factors are considered in NIH’s peer review system. The two-level peer review process is much admired and copied by other research agencies around the world. However, the increasing breadth, complexity, and interdisciplinary nature of modern research pose challenges to the traditional review process. To enhance peer review, NIH recently undertook an extensive examination of its review process, and in June 2008, announced a series of concrete steps for improvement. Those include recruiting the best reviewers; shortening proposals to reduce the burden on both applicants and reviewers; adapting the review process to make it as thorough, reliable, fair, and transparent as possible; and focusing more on impact than on methodological details. The effects of these new steps will be closely monitored, and additional reforms that encourage innovation will be undertaken as needed.

NIH-wide innovation now is fostered by the NIH Common Fund, which is designed to support crosscutting innovative projects that require participation of at least two or more Institutes or Centers. Established in law by the NIH Reform Act of 2006, the Common Fund provides a unique opportunity to support research that otherwise might not find a natural home at NIH.

Finally, the success of biomedical research rests squarely on the robustness of NIH training programs for the next generation of basic, translational, and clinical scientists. Multiple issues must be explored including adequacy of support, our role in training foreign scientists, and how best to diversify the scientific workforce. We need to provide the most exciting and positive environment for new scientists possible, where their enthusiasm and creativity will be nurtured in a way that optimizes their scientific creativity and independence.

Conclusion

There are unprecedented opportunities in front of us. The current acceleration in the pace of discovery was unimaginable only a decade ago. We need to capitalize on this moment of great opportunities for biomedical science in order to tackle the maladies that afflict millions of Americans and people around the world. Strong leadership by NIH, in collaboration with the many research organizations in the country and around the world, is a precious asset to the global community to move forward and secure better health and better lives for all.

Overview of NIH Structure and Organization

NIH is the primary Federal agency for leading, conducting, and supporting medical and behavioral research. Its mission is 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 for all Americans and for people worldwide. Composed of the Office of the Director (OD) and 27 Institutes and Centers (ICs), NIH employs close to 19,000 people and is the steward of a $30 billion budget (Fiscal Year [FY] 2009). The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our Nation and the world.

Institutes and Centers

The 27 NIH ICs are organized with a focus on and expertise in a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), life stage (e.g., children, the aging population), an overarching field of science (e.g., human genome, nursing), or a technology (e.g., biomedical imaging, information technology). The ICs *support* research and research training through extramural activities and most also *conduct* research and research training through intramural activities.

The NIH Reform Act of 2006 reaffirmed certain organizational authorities of agency officials to: 1) establish or abolish national research institutes; 2) reorganize the offices within NIH OD; and 3) reorganize divisions, centers, or other administrative units within an NIH IC. The Act also mandated the establishment of a Scientific Management Review Board (SMRB) to advise the NIH Director and other appropriate agency officials on the use of these organizational authorities, through reports to the NIH Director, at least once every 7 years. Also, any SMRB report that contemplates a specific organizational issue will be submitted to appropriate congressional committees. The SMRB held its first meeting in April 2009 and members were briefed on two topics put forth by senior NIH leadership for their consideration: 1) optimizing research at NIH into substance use, abuse, and addiction; and 2) whether organizational change within the NIH Clinical Center and/or the NIH intramural research program could further optimize those programs. The SMRB unanimously agreed to consider both topics through corresponding workgroups, and to form a workgroup to develop criteria for use in assessing whether specific organizational changes within NIH are warranted. The Board also is required by the NIH Reform Act to seek input from the public. The first two public forums were held in September and October 2009. Workgroup findings will be brought back to the full SMRB for deliberations at future meetings in FY 2010.

Office of the Director

The Office of the Director (OD), NIH, is composed of several offices that provide expert advice to the NIH Director and his leadership team, coordinate policy across the NIH research community, and administer centralized support services essential to the NIH mission. With 229 government-owned buildings in 6 locations, the facilities infrastructure maintained by the NIH Office of Research Facilities is the literal foundation for a successful research program. The facilities necessary to support 21st century science are far more sophisticated than yesterday's bricks, mortar, pipes, and lines. From biosafety to a secure and robust information technology infrastructure, the requirements of today's research create greater demands for a safe, healthy, and functional environment for employees and patients.

The NIH Office of Extramural Research (OER) provides the corporate framework for NIH administration of research grants and contracts, ensuring scientific integrity, public accountability, and effective stewardship of the NIH extramural research portfolio. Offices within OER include the Office of Laboratory Animal Welfare, the Office of Policy for Extramural Research Administration, the Office of Extramural Programs, the Office of Research Information Systems, and the Office of Administrative Operations. The Office of Intramural Research (OIR) is responsible for oversight and coordination of intramural research conducted within NIH laboratories and clinics. Offices within OIR include the Office of Intramural Training and Education, the Office of Technology Transfer, the Office of Human Subjects Protection, and the Office of Animal Care and Use. (Also see the section in this chapter on *Extramural and Intramural Research Programs* for more information regarding OER and OIR).

The OD Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) was established by mandate of the NIH Reform Act of 2006. DPCPSI's role is to identify emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research; assist NIH in effectively addressing identified areas; and develop and apply resources (databases, analytic tools, and methodologies) that will support priority setting and analyses of the NIH portfolio. In addition, DPCPSI manages the NIH Demonstration Projects in High Risk/High Reward Research—an initiative to test new ways of fostering innovation that also was authorized through the Reform Act. Finally, DPCPSI plans, supports, and provides technical assistance for NIH-wide program and project evaluations and manages NIH planning and reporting required by the Government Performance and Results Act and other government-wide performance assessment endeavors. (Also see the section on *NIH Strategic Planning and the NIH Roadmap and Common Fund* later in this chapter). DPCPSI now incorporates the functions of the former Office of Portfolio Analysis and Strategic Initiatives. The primary components within DPCPSI are the Office of Strategic Coordination, which manages the NIH Common Fund (including the Roadmap), and the four OD program offices—the Office of AIDS Research, the Office of Behavioral and Social Sciences Research, the Office of Disease Prevention, and the Office of Research on Women's Health. Within the Office of Disease Prevention are three offices covering the areas of dietary supplements, rare diseases research, and medical applications of research. The OD program offices fund research using IC award-making authorities. Often, ICs partner with a program office to supplement their funding for a specific program or project.

Other OD offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination include the Office of Communications and Public Liaison, the Office of Science Policy, the Office of Legislative Policy and Analysis, the Office of Management, the Office of Equal Opportunity and Diversity Management, the NIH Ethics Office, and the Office of the Chief Information Officer. The policies and activities of some of these offices are highlighted in later sections of this chapter.

Links to IC and OD Office Website Home Pages

Following is a list of NIH ICs and select OD program offices. In the electronic version of the report, the names of the ICs and offices are linked to the home page on the respective websites. The ICs are

presented in the order in which they appear on the appropriation table in the Congressional Justification. Appendix B provides brief descriptions of the missions of the ICs and OD program offices and in the electronic version, live links to IC and office strategic plans. The mission statements and strategic plans provided in Appendix B classify and justify NIH priorities. Historical information about NIH, including the establishment of the categorical Institutes, Centers, and specialized offices, is maintained by the NIH Office of History, a component of OIR that preserves records of significant NIH achievements, innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.

Institutes and Centers

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of General Medical Sciences (NIGMS)
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- National Eye Institute (NEI)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute on Aging (NIA)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute of Mental Health (NIMH)
- National Institute on Drug Abuse (NIDA)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Nursing Research (NINR)
- National Human Genome Research Institute (NHGRI)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Center for Research Resources (NCRR)
- National Center for Complementary and Alternative Medicine (NCCAM)
- National Center on Minority Health and Health Disparities (NCMHD)[6]
- John E. Fogarty International Center (FIC)
- National Library of Medicine (NLM)
- NIH Clinical Center
- Center for Information Technology (CIT)
- Center for Scientific Review (CSR)

[6] With enactment of the Patient Protection and Affordable Care Act, on March 23, 2010, the National Center for Minority Health and Health Disparities became an institute—the National Institute for Minority Health and Health Disparities (NIMHD).

Office of the Director

- Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI)
  - Office of AIDS Research (OAR)
  - Office of Behavioral and Social Sciences Research (OBSSR)
  - Office of Disease Prevention (ODP)
    - Office of Dietary Supplements (ODS)
    - Office of Medical Applications of Research (OMAR)
    - Office of Rare Diseases Research (ORDR)

    - Office of Research on Women's Health (ORWH)
    - Office of Strategic Coordination (OSC)
- Office of Extramural Research (OER)
- Office of Intramural Research (OIR)

Extramural and Intramural Research Programs

As noted above, NIH *supports* research and research training through extramural activities and *conducts* research and research training through intramural activities. The sections below provide overviews of the extramural and intramural programs.

Extramural Program

More than $8 of every $10 appropriated to NIH is awarded by the ICs to the extramural biomedical and behavioral research community through grants and contracts. The extramural research community is composed of scientists, clinicians, and other research personnel affiliated with more than 3,100 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad. In FY 2009, NIH funded more than 37,000 principal investigators on research grants, with many thousands more personnel supported by the projects. With NIH support, these investigators, with their research teams, conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability.

OER is led by the Deputy Director for Extramural Research (DDER), who provides leadership and coordinates policy, guidance, and oversight for IC grant and programmatic management operations and is a conduit for extramural policy issues with the biomedical research community beyond NIH. OER is where grants policy, program coordination, compliance, and services converge to support and sustain the NIH extramural research program.

A primary service OER provides for the NIH grants program is the electronic Research Administration (eRA) system. eRA supports the grant administration functions for grantees and Federal staff from the submittal of applications to close out of awards. eRA also provides services to other operating divisions of the Department of Health and Human Services (HHS) and other Federal agencies. eRA has more than 215 registered users (of which more than 150,000 are principal investigators) at 16,500 research institutions worldwide.

Grants Overview

NIH announces the availability of funds for grant programs by issuing funding opportunity announcements (FOAs)[7] in the *NIH Guide for Grants and Contracts* and on www.Grants.gov. The majority of NIH grant funding is investigator-initiated, submitted through omnibus parent announcements that span the breadth of the NIH mission. NIH uses program announcements (PAs) and requests for applications (RFAs), and other types of FOAs, to express interest in particular areas of research. Because many FOAs are trans-NIH opportunities, considerable collaboration can be involved in their preparation. During 2008 and 2009, NIH refined and further developed an internal electronic document/content management system in support of the *NIH Guide* publication process that facilitates communications, collaborations, and the

exchange of documents and information among ICs and within the NIH OD, thereby providing a more efficient and cost-effective means of developing and publishing NIH FOAs.

The main types of grant funding provided by NIH are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), and Program Projects/Centers Grants (P series). Activity codes that incorporate the funding series differentiate the wide variety of research and research-related awards made by NIH. The most commonly used activity code is the R01, which designates a grant for a discrete, specified research project, generally awarded for 3 to 5 years. Receipt of an R01 traditionally is the mark of a scientist achieving scientific independence, and a faculty member's track record with R01 awards normally is a significant factor in university promotion and tenure decisions. Examples of other activity codes are:

- R41/R42 and the R43/R44 for the Small Business Technology Transfer program and the Small Business Innovative Research program, respectively;
- R24 for research projects that will enhance the capability of biomedical research resources;
- R25 for research education projects;
- F32 for postdoctoral individual fellowships under the National Research Service Award;
- T32 for enabling institutions to make National Research Service Awards for both pre- and postdoctoral training;
- K08, a career development award for providing support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience;
- P01 for research program projects that are broadly based, multidisciplinary, often long-term research, which have a specific major objective or a basic theme;
- P30 for shared resources and facilities at research centers; and
- P40 for animal model and biological materials resources.

ICs vary in the extent to which they use various activity codes.

[7] An FOA is a publicly available document by which a Federal agency makes known its intentions to award grants or cooperative agreements. Funding opportunity announcements may be known as program announcements, requests for applications, solicitations, or parent announcements.

NIH Peer Review Process

All grant applications and contract proposals for research and development funding undergo evaluation through peer review, in which external expert panels determine which applications or proposals are the most scientifically and technically meritorious—the first tier of peer review—and are most programmatically relevant and therefore should be considered for funding—the second tier of peer review. The NIH peer review process is designed to evaluate the scientific, technical, and programmatic merit of each application for potential research funding with processes that are fair, equitable, timely, and free of bias. The NIH dual (two-tier) peer review system is mandated by statute (section 492 of the PHS Act) and by Federal regulations governing "Scientific Peer Review of Research Grant Applications and Research and Development Contract Proposals" (42 CFR Part 52h).

CSR is the portal for receipt and referral of NIH grant applications and for most applications is the locus for the first level of review. Applications relevant to the NIH mission receive two assignments. One assignment is to an IC that has a mission encompassing the aims and objectives of the application and thus potential interest in funding the application. The other assignment is to the group or panel that will conduct the first level of review, i.e., evaluation of scientific and technical merit. The assignment may be to either a Scientific Review Group (SRG) or a Special Emphasis Panel (SEP). If the application is in response to an RFA, the SRG or SEP most often will be convened by the IC(s) responsible for the

initiative. NIH uses established referral criteria to determine the appropriate SRG to carry out review and the IC(s) most suitable to potentially fund the project.

As noted above, the first level of review is conducted by SRGs or SEPs that evaluate and give expert advice on the overall scientific and technical merit of the research proposed in the application, as well as the protection of human subjects, vertebrate animal welfare, and the budget and period of support requested. SRGs and SEPs conducting the first level of review are composed primarily of non-Federal experts qualified by training or experience in particular scientific or technical fields, or as authorities knowledgeable in the various disciplines and fields related to the applications under review. No more than one-fourth of the members of any SRG or SEP may be Federal employees.

The second level of peer review is performed by the National Advisory Councils (or Boards) of each IC, which are composed of scientific and public members chosen for their expertise, interest, or activity in matters related to a specific area of health and disease. The vast majority of SRG- or SEP-reviewed applications assigned to an IC go to the respective Council,[8] which then recommends those applications that should be considered for funding. Identifying applications that further specific program priorities is a particularly important function of this second level of peer review. Advisory Councils recommend projects for funding, but do not make funding decisions.

An ongoing trans-NIH effort to optimize the efficiency and effectiveness of the NIH Peer Review system is discussed in *Enhancing Peer Review*, under the section below on *Improving Research Management.*

[8] An application may be designated "Not Recommended for Further Consideration (NRFC)" at the first level of peer review, if it lacks significant and substantial merit; presents serious ethical problems in the protection of human subjects from research risks; or presents serious ethical problems in the use of vertebrate animals, biohazards, and/or Select Agents. Applications designated as NRFC do not proceed to the second level of peer review (National Advisory Council/Board) because they cannot be funded.

Funding Decisions

Applications that are scientifically meritorious, based on SRG or SEP review, and favorably recommended by an IC's National Advisory Council, are considered for funding. The score given to an application during the initial peer review process is important, but not the sole factor determining an IC's funding decision. Other considerations are portfolio balance, requirements specified in congressional appropriations, programmatic relevance, IC priorities, and availability of funds. (Also see the section later in this chapter on *Enhancing Peer Review* for information on recent changes in the scoring of applications during initial review.)

Many ICs establish a "payline"—a percentile-based[9] funding cutoff point determined at the beginning of the fiscal year by balancing the projected number of applications assigned to an IC with the amount of funds expected by NIH and the IC to be available for such projects. Applications that score within the payline are most likely to be funded. However, Advisory Councils consider, evaluate, and make recommendations on specific applications that score both within and beyond the payline.

In addition to setting paylines, many ICs establish procedures for funding applications that scored beyond the payline. Terms used for this category of awards vary by IC, but include "select pay," "exception pools," "high program-priority," and "special emphasis." What is consistent is the use of these funds, with strong justification, to support highly innovative or high program-priority applications that score beyond the payline.

Prior to award, NIH ensures that the planned research meets all requirements for safe and responsible conduct. This includes making sure that the research has undergone all necessary reviews and has obtained required approvals from boards and committees charged with protection of human subjects; inclusion of minorities, women, and children; humane animal care and use; biosafety; and other matters as appropriate. NIH also ensures that the institution where the research takes place has necessary and appropriate policies in place for avoidance of financial conflicts of interest in research. (Also see the section on *Ensuring Responsible Research* later in this chapter).

[9] Percentile represents the relative position or rank (from 1 to 100) of each overall impact/priority score.

Post-Award Administration

NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and provide oversight to ensure responsible conduct of research. Scientific monitoring includes reviewing yearly progress and financial reports submitted by grantees, the publications generated by the research, and any invention reports. NIH also monitors compliance with Federal laws and policies pertaining to protection of human subjects, the care and use of vertebrate animals used in research, data sharing, the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and tracking of inclusion of women and minorities in research. (Also see the sections on *Capitalizing on Discovery* and on *Ensuring Responsible Research* later in this chapter).

Intramural Research Program

Approximately 10 percent of NIH funds support research and training activities carried out by NIH scientists in NIH laboratories on its campuses in the Bethesda (including the NIH Clinical Center), Rockville, Frederick, and Baltimore, Maryland, areas; Research Triangle Park, North Carolina; Detroit, Michigan; Phoenix, Arizona; and the Rocky Mountain Laboratories, Montana. Approximately 1,150 principal investigators lead intramural research projects that involve more than 6,000 trainees ranging from high school students to postdoctoral and clinical fellows. OIR is responsible for trans-NIH oversight and coordination of intramural research, human subject protections, animal welfare, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. OIR is led by the NIH Deputy Director for Intramural Research (DDIR), and each IC intramural research program is led by an IC Scientific Director; OIR oversight is carried out in conjunction with the IC Scientific Directors. A summary of policies governing intramural research can be found in the ***Intramural Research Sourcebook***.

Research Programs and Priorities

The NIH intramural research programs conduct basic, translational, and clinical research. Organizationally, the individual laboratories and clinics report to their respective IC and are responsible for conducting original research consistent with the goals of the parent IC. Most ICs have an intramural program, the exceptions being NIGMS, CSR, FIC, and NCRR. As with the extramural program, intramural research proposals are generated by scientists. In the intramural research program, however, program directions and research priorities are not shaped primarily through grant awards,[10] but rather through professional hiring and promotion decisions, external reviews, and the allocation of resources to

laboratories and branches.

Each intramural research program has a promotion and tenure committee that evaluates all recommendations for professional appointment or promotion, and tenured and tenure-track scientists undergo formal, annual, internal reviews. Resource allocations and promotions are determined from these reviews. In addition, at least every 4 years, an external expert Board of Scientific Counselors reviews the work of each tenured/tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (budget, space, personnel). Moreover, IC Scientific Directors are evaluated by an external committee every 5 years, and each IC intramural research program is reviewed, in its entirety, by a "blue ribbon" panel approximately every 10 years. These panels assess and make recommendations concerning the impact of the research program, program balance, and other significant matters that play a role in the success of the program.

Two offices manage research training for OIR. The Office of Intramural Training and Education (OITE) is charged with helping trainees in the intramural research program, including graduate students in partnership with universities in the United States and abroad, develop scientific and professional skills to become leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education (OCRTME) deals with all aspects of clinical training. Many training programs were developed or updated during 2008 and 2009 (also see the section on *Research Training and Career Development* in Chapter 3).

[10] The exception is that intramural investigators are eligible to compete for most NIH Roadmap initiatives to allow qualified intramural researchers to contribute to the goals of Roadmap programs.

NIH Clinical Center

The Clinical Center is the Nation's largest hospital devoted entirely to clinical research. Research at the Clinical Center is conducted with access to cutting-edge technologies in an environment of compassionate care. This world-class national resource promotes translational research—that is, the transformation of scientific observations and laboratory discoveries into applications for diagnosing, treating, and preventing disease that benefit patient health and medical care. Composed of two facilities—the Mark O. Hatfield Clinical Research Center (2005) and the original Warren Grant Magnuson Clinical Center (1953)—the Center houses 234 inpatient beds, 82 day hospital stations, an ambulatory care research facility, 12 operating rooms, critical care facilities, advanced radiology and imaging capabilities, and research laboratories. The unique design of the facility locates patient care units in close proximity to laboratories conducting related research. This design facilitates interaction and collaboration among intramural clinicians and researchers. More than 1,400 studies are in progress at the Clinical Center, bringing 21,000 patients per year from all 50 states and throughout the world. The Center has more than 90,000 outpatient visits a year and 6,000 inpatient admissions. Approximately 1,200 credentialed physicians, dentists, and Ph.D. researchers, 660 nurses, and 630 allied health care professionals, such as pharmacists, dietitians, and medical technologists, work at the Center. As a research facility, generally only a patient with the precise kind or stage of illness under investigation and meeting other inclusion criteria of a protocol is enrolled as a subject in a study. However, in May 2008, NIH launched the Undiagnosed Diseases Program, a clinical research program in collaboration with NHGRI and the NIH Office of Rare Diseases designed to provide answers to patients with mysterious conditions that have long eluded diagnosis by their health care providers. Within its first 6 months, more than 1,000 potential subjects sought to participate in the new program-a tangible reminder that the NIH Clinical Center truly is a "house of hope."

NIH Strategic Planning and the NIH Roadmap and Common Fund

Strategic Planning

Strategic planning at NIH takes place at many levels. The U.S. Congress, through the NIH authorization and appropriations processes, sets NIH and IC funding levels and directs NIH attention to particular areas of research interest or emphasis.[11] The Administration establishes specific priorities for improving the health of the Nation, such as those in Healthy People 2010, a comprehensive set of disease prevention and health promotion objectives aimed at increased quality and years of healthy life and the elimination of health disparities for the Nation. Through progress reviews, HHS tracks trends in data that measure advancement toward the plan's objectives. NIH efforts are contributing toward Healthy People 2010 objectives, ranging from reducing uncorrected visual impairment due to refractive errors to increasing the proportion of persons with arthritis who have had effective, evidence-based arthritis education as part of management of their condition. Healthy People 2020 objectives are now in development, and will reflect assessments of major risks to health and wellness, changing public health priorities and emerging issues related to our Nation's health preparedness and prevention that also will need to be addressed by NIH. In addition, NIH establishes its own goals and priorities fully cognizant of the framework of the *HHS Strategic Plan Goals and Objectives* - FY 2007-2012, which sets the stage for individual performance plans and outcome measures across NIH.

Strategic planning at NIH is a highly consultative process involving many constituencies that generate and provide input on public health needs and research gaps, opportunities, and priorities. Importantly, strategic plans can serve as a framework for ICs to measure and report on portfolio balance and progress relative to their missions. NIH stays constantly tuned to twin touchstones for priority-setting—public health need and scientific opportunity.

The majority of strategic planning at NIH is IC-based. IC strategic plans function as guideposts to the investigative and NIH communities. Each NIH IC has unique processes for generating and disseminating its strategic plans, but by developing and articulating consensus on today's most pressing health needs and research questions, all IC strategic plans influence the research directions and methods proposed by investigators in their applications. By the same token, strategic plans inform IC decisions about areas of research that require stimulation—achieved through a variety of means including meetings, workshops, conferences, and various FOAs—to move science planning into the implementation stage. Finally, strategic plans influence IC priority-setting and funding decisions.

While each of the 24 grant-making ICs has a broad strategic plan that clearly states its mission and priorities, many of the ICs also have disease- and program-specific strategic plans and research agendas as well as reports from workshops, "blue ribbon" panels, and other expert working groups that contain recommendations for research goals or priorities within the IC mission.

NIH also has a significant tradition of trans-NIH strategic planning, which has been strengthened through the creation of DPCPSI in the NIH OD. DPCPSI was created to identify important areas of emerging scientific opportunity, rising public health challenge, and knowledge gaps that deserve special emphasis and would benefit from strategic coordination and planning or the conduct or support of trans-NIH research that involves collaboration between two or more national Institutes or Centers. As noted above, DPCPSI is the organizational home for the NIH Common Fund (see section below on *Common Fund Strategic Planning Processes*). Another important facet of DPCPSI's role in support of NIH-wide planning and coordination is its development and application of resources (e.g., databases, analytic tools, and methodologies) in support of portfolio analyses and priority setting.

Trans-NIH strategic plans focus on areas that are best addressed by involving multiple ICs in identifying

research goals and priorities. A prominent example is the annual *Trans-NIH Plan for HIV-Related Research* to guide the NIH investment in biomedical and behavioral AIDS-related research and to provide the framework to translate critical research findings into improved prevention and treatment strategies. The development of the plan is led by OAR, using a collaborative process involving broad input from scientists across NIH, other government agencies, and non-governmental organizations, as well as community representatives and other experts from the United States and abroad. Another example is the March 2009 Report, *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*—a 10-year plan for digestive diseases. The Commission was led by NIDDK and was composed of 16 members, including academic researchers, medical professionals, and patient advocates, who were appointed by the NIH Director, and 22 representatives of NIH ICs, as well as other Federal agencies involved in digestive diseases research, who served as *ex officio* members. Other trans-NIH research plans address goals and objectives in areas that include neuroscience research, liver disease, diabetes, health disparities, muscular dystrophies, autoimmune diseases, and more. (Lists of both IC and trans-NIH strategic plans appear at the end of each disease/disorder topic section of Chapter 2).

[11] For more information see http://officeofbudget.od.nih.gov/pdfs/FY09/Significant%20Items%20Final.pdf and http://officeofbudget.od.nih.gov/pdfs/FY10/Significant%20Items.pdf.

Common Fund Strategic Planning Processes

The NIH Common Fund was established by the 2006 Reform Act to support the mission of NIH. The trans-NIH strategic planning for the Common Fund occurs continually and on many levels. The most visible activity occurs every 3 to 5 years and was first initiated before the Common Fund existed as a process to address fundamental barriers to research or unique opportunities that affect the NIH mission as a whole. The programs that resulted from these early planning processes are known collectively as the NIH Roadmap for Medical Research. With the establishment of DPCPSI and the Common Fund, the goals for the Roadmap have been maintained, but the planning activities have been expanded to increasingly foster inter-IC collaboration and coordination and to allow the NIH Director added flexibility to develop new programs continually rather than only on a 3- to 5-year schedule.

NIH uses iterative planning processes, involving NIH stakeholders and NIH leadership, to generate, select, prioritize, and develop recommendations for Common Fund initiatives. Various assessments and portfolio analyses, supported by new and evolving databases, analytic tools, and evaluation methodologies, inform the planning processes. NIH solicits ideas for new initiatives from the intramural and extramural scientific community, patient advocates, and the general public to help senior NIH staff identify crosscutting challenges in biomedical research that meet criteria established for Common Fund initiatives (see text box). This solicitation is conducted formally every 3 to 5 years through an expanded process involving brainstorming workshops, Requests for Information, and widespread staff involvement. In other years, ideas are presented to the NIH Director through continual interaction with IC directors and leaders in the scientific and lay communities. As required by the Reform Act, on a biennial basis, NIH issues a Common Fund Strategic Planning Report. The latest such report, issued in June 2009, is provided in Appendix C.

To facilitate the prioritization of ideas, NIH conducts a programmatic review of the ideas that are gathered—assessing their responsiveness to the Roadmap initiative criteria, as well as conducting a preliminary assessment of the currently funded NIH portfolio of research related to the broad areas highlighted by the ideas presented. Informed by this analysis and following scientific discussion with IC directors, the NIH Director selects areas that are to be pursued. Trans-NIH Working Groups then form to develop funding announcements and to implement programs in the selected areas.

A Council of Councils,[12] also established by the Reform Act, advises the NIH Director on scientific areas pursued through the Common Fund and considers concepts for new Common Fund programs.

Criteria for Common Fund Initiatives

The goals established for Common Fund initiatives by the 2006 Reform Act include identifying research that:

- Represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps
- Deserves special emphasis
- Would benefit from conducting or supporting additional research that involves collaboration between two or more national research institutes or national centers, or otherwise benefit from strategic coordination and planning.

In addition to these criteria, NIH expects Common Fund programs to:

- Have the potential for exceptionally high impact and accepts a high level of risk that may be associated with innovation and creativity
- Catalyze research funded through the ICs and to synergize with IC program

[12] The Council of Councils is composed of approximately 30 members selected from the IC National Advisory Councils and nominated by the OD program offices, as well as broad lay representation, including a member of the NIH Council of Public Representatives. The Council advises the NIH Director on matters related to the policies and activities of DPCPSI, and acts as an external advisory panel to the IC directors during the "concept approval" stage of the Common Fund/Roadmap initiative review process through its recommendations to the NIH Director and DPCPSI Director.

NIH Implementation of the American Recovery and Reinvestment Act of 2009 (Recovery Act)

The American Recovery and Reinvestment Act (ARRA) of 2009 (Pub. L. No. 111-5) was signed into law by President Obama on February 17, 2009. The legislation provided NIH with an unprecedented level of additional funding—$10.4—billion to help stimulate the U.S. economy through the support and advancement of scientific research.[13] Although NIH has broad flexibility to invest in many types of grants programs, the ARRA-funded projects aim to stimulate the economy and create or retain jobs, and have the potential for making scientific progress in 2 years. The impact of NIH ARRA funding is expected to extend beyond the investigators who receive the funds to also reach allied health workers, technicians, students, trade workers and others who will receive the leveraged benefits. Beyond the immediate economic stimulus, the long-term impact from the science projects, research training, and research facilities funded by the Recovery Act will have a positive impact on the health of the Nation for years to come.

NIH quickly developed implementation and spending plans for the $10.4 billion in 2-year ARRA funding initiatives, and between March 4 and September 18, 2009, published 22 Recovery Act FOAs. The response from the scientific community was extraordinary. Typically the CSR reviews 16,000 applications

with the help of about 8,000 reviewers in each of NIH's three annual rounds of review. In 2009, in one round, CSR assessed about 40,000 applications (including ARRA applications), relying on the assistance of about 28,000 reviewers.

The bulk of the ARRA funds—$8.2 billion—will be used for extramural awards for scientific research. In FY 2009, NIH funded $4.73 billion in grants and contracts to universities, medical centers, hospitals, and research institutions throughout the country. Nearly 60 percent of ARRA funds are supporting new science, while approximately 40 percent of funds are accelerating the science of existing projects. Because of ARRA funds, over two summers approximately 5,000 students and science educators will gain hands-on experience in top research laboratories. Approximately $137 million in ARRA funds were transferred from the NIH OD to the Common Fund to support and expand existing Roadmap programs and to address cross-cutting emerging needs and opportunities outside the Roadmap. (See also the section of this chapter on *Strategic Planning and Common Fund/Roadmap*.) One billion dollars in NIH Recovery Act funds was provided to NCRR specifically for the Extramural Construction program. Other approximate allocations are: $500 million for NIH buildings and facilities; $300 million for the shared instrumentation grant program; and $400 million for comparative effectiveness research (CER),[14] which can be awarded through a variety of mechanisms including Grand Opportunity Grants, Challenge Grants, R01s, and supplements. (Also see the section on *Clinical and Translational Research* in Chapter 3 for more information about CER).

[13] Information about NIH ARRA-funded projects and their impact on the economy in terms of jobs created and retained is available at www.hhs.gov/recovery.

[14] Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and sub-groups. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.

ARRA Funding for Extramural Scientific Research

For the $8.2 billion in Recovery Act funds for extramural research projects, NIH is implementing a strategy that focuses on:

1. Expansion of the payline to support peer-reviewed and approved, highly meritorious, grant applications from investigators across the Nation for whom funding was not available in FY 2008, as well as grant applications not otherwise likely to be funded in FY 2009 or FY 2010 because of budgetary limits.
2. Revision Applications/Administrative Supplements to expand the scope and accelerate the tempo of ongoing science through support of additional infrastructure and personnel on existing awards for additional activities that fit the intent of ARRA.
3. Challenge Grants to focus on health and science problems in 15 broad areas of scientific interest where significant progress can be made in a 2-year timeframe. Within each area, specific Challenge Topics were identified. NIH spent more than $380 million in FYs 2009/2010 ARRA

funds to support more than 800 grants.

4. Grand Opportunity Program or "GO grants" to support high-impact ideas that lend themselves to short-term, non-renewable funding, and may lay the foundation for new fields of investigation. The GO program supports large-scale research projects costing more than $500,000 each that accelerate critical breakthroughs, early and applied research on cutting-edge technologies, and new approaches to improve the synergy and interactions among multi- and interdisciplinary research teams. NIH spent more than $600 million in FYs 2009/2010 ARRA funds to support more than 350 grants.
5. Signature Initiatives to support new, exceptionally creative, innovative, and potentially transformative scientific opportunities in major research challenges, such as nanotechnology, health disparities, autism, genetic risk for Alzheimer's disease, and HIV vaccine research.
6. New Faculty Awards to support the recruitment of faculty to conduct research at U.S. institutions.
7. Summer Research Experiences for Students and Science Educators to provide summer jobs for high school/college students and teachers to work in science laboratories. These supplements encourage students to seriously pursue research careers in the health-related sciences and support student research experiences in NIH-funded laboratories. Awards were made to approximately 350 institutions (including small businesses), supporting 1,300 mentors, and providing about 5,100 summer research positions for 4,400 students and 700 teachers.

NIH began making Recovery Act awards in April 2009. About half of the ARRA funding available for the extramural scientific research was obligated in FY 2009, with the rest to be obligated in FY 2010. NIH grant awards funded by the Recovery Act have been made in all 50 States, the District of Columbia, and Puerto Rico.[15]

[15] See http://report.nih.gov/recovery/index.aspx for a listing.

ARRA Funding for Extramural Construction

Recovery Act funds for extramural construction ($1.0 billion) are building the Nation's capacity to conduct biomedical and behavioral research by providing support to domestic health professional schools, other academic institutions, hospitals, health departments, and research organizations. Funds are being used to improve facilities to meet the biomedical or behavioral research, research training, or research resource needs of an institution. Awardees must consider the use of "green" technologies and design approaches, and certain projects must obtain certification from the U.S. Green Building Council's Leadership in Energy and Environmental Design (LEED) or the Green Building initiative's Green Globes System Certification rating. NIH ARRA funding for extramural construction supports two main activities:

1. The Extramural Research Facilities Improvement Program to expand, remodel, renovate, or alter existing facilities, or to construct new facilities, for biomedical and behavioral research.
2. The Core Facility Renovation, Repair, and Improvement activity awards to renovate, repair, or improve core facilities, which are centralized shared resources that provide access to instruments or technologies or services, as well as expert consultation to multiple investigators supported by the core.

ARRA Funding for Shared Instrumentation

The Recovery Act Shared Instrumentation program ($300 million) aligns with the existing Shared Instrumentation program, and provides grants to NIH-supported research institutions to provide multiple

investigators with technologically sophisticated equipment to enable the conduct of federally sponsored research. The Shared Instrumentation program consists of two main activities:

1. The Shared Instrumentation Grants program supports grants to groups of three or more NIH-supported investigators for the purchase of commercially available instruments, such as confocal and electron microscopes, biomedical imagers, mass spectrometers, DNA sequencers, biosensors, and cell sorters costing from $100,000 to $500,000.
2. The High-End Instrumentation Grants program supports grants to groups of three or more NIH-supported investigators for the purchase of a single major item of biomedical research equipment costing from $600,000 to $8,000,000. Examples of such equipment include high-resolution mass spectrometers, cryoelectron microscopes, and supercomputers.

Awards are made to public and non-profit domestic institutions only, including health professional schools, other academic institutions, hospitals, health departments, and research organizations.

ARRA Funding for NIH Buildings and Facilities

The intended recipients of ARRA funding for NIH buildings and facilities ($500 million) are construction contractors. Awards are made through new or existing competitive contracts. Several major projects will be supported with Recovery Act funds:

1. John Edward Porter Neuroscience Research Center Phase II to complete the consolidation of neuroscience researchers into one facility from 10 Institutes and multiple disciplines.
2. Building 10 F Wing Renovations to support translational research for 9 of the 12 ICs that have clinical research programs in the new Clinical Research Center.
3. Build-Out of Building 3 to transform an unused, vacant building that could not be reoccupied as laboratory space into useable office space.
4. Conversion of Building 7 at the Rocky Mountain Laboratories in Hamilton, Montana, to convert unused mechanical space to laboratories, providing critical space for NIAID research.
5. Other Repair and Improvement Projects to improve the reliability and condition of NIH facilities.

Examples of specific ARRA funded activities are highlighted throughout the report in the topic sections that follow in Chapters 2 and 3.

Oversight

NIH implementation of ARRA is accompanied by an unprecedented level of oversight and reporting to ensure that Recovery Act funds are being used in accordance with legal and administrative requirements, and to provide the public with up-to-date data on the expenditure of funds. NIH activities include:

Performance Measures

NIH fully complies with all Recovery Act monitoring and reporting requirements, including monthly and quarterly reports. Moreover, NIH has established performance measures for the Recovery Act programs in extramural construction, buildings and facilities, shared instrumentation, and extramural scientific research. The measures are posted as part of the implementation plan for each funding area under "Strengthening Scientific Research and Facilities" on the HHS page of the Recovery Act website. In addition, NIH has developed scientific research outcome and output goals for its ARRA funding. Details

and data regarding the goals will be included in the FY 2011 and FY 2012 NIH Budget Requests.

Monitoring

In addition to established NIH policies, procedures, and oversight practices that monitor NIH grants, cooperative agreements, and contracts in accordance with established law and policies,[16] the NIH Office of Management Assessment (OMA) and the Office of Financial Management will use the established NIH risk management framework for identifying, assessing, and testing of operational and financial risks and internal controls associated with implementing Recovery Act requirements.[17] OMA will work with NIH offices responsible for implementing programs receiving Recovery Act funding, and report on the risks and controls to NIH and HHS leadership. The Division of Environmental Protection in the NIH Office of Research Facilities reviews the environmental plans and monitors compliance for all extramural construction awards. All Recovery Act funds are awarded separately from normal appropriations funds, and all awards issued with Recovery Act funds have special accounting numbers and codes to track the funds and awards.

[16] Guidance includes OMB Circular A-110, OMB Circular A-123, *Management's Responsibility for Internal Control,* sections of the Recovery Act including Section 1512, and the *Updated Implementing Guidance for the Recovery Act of 2009.*
[17] Assessments will be done consistent with the statutory requirements of the Federal Manager's Financial Integrity Act, the Improper Payments Information Act, and the OMB circular A-123 *Management's Responsibility for Internal Control*.

Transparency

Recipients are kept informed of their reporting obligations—both existing NIH and Recovery Act reporting requirements—through special terms and conditions of award, administrative notices in the *NIH Guide* FOAs, contract solicitations, and program guidance. Further technical assistance is available to grantees and contractors from project officers and OER to ensure compliance with reporting requirements. Beginning in October 2009, recipients of ARRA funds are required[18] to submit quarterly reports through the www.FederalReporting.gov website. These reports contain detailed information on the projects and activities funded by the Recovery Act.[19] These reports are available to the public on www.Recovery.gov. NIH developed and provided outreach, oversight, and data quality reviews for the quarterly recipient reports required by the Recovery Act.

[18] Section 1512 of the Recovery Act.
[19] OMB Memorandum M-09-21, Implementing Guidance for the Reports on Use of Funds Pursuant to the American Recovery and Reinvestment Act of 2009. June 22, 2009. Available at: http://www.whitehouse.gov/omb/assets/memoranda_fy2009/m09-21.pdf.

Accountability

In addition to the monitoring and oversight actions described above, the NIH performance appraisal system for program and business function managers incorporates Recovery Act program stewardship responsibilities, as appropriate, to ensure that managers are held to high standards of accountability in achieving program goals under the Recovery Act.

Providing the Platform for Discovery

Science Education and Literacy

NIH takes an active role in pre-college (K-12) science education and in science literacy activities. These activities aim to improve the science knowledge and skills of students, attract young people to biomedical and behavioral science careers, lay the groundwork for advanced study, enhance public understanding of health science, and empower the public as consumers of science and health information.

Curriculum supplements—ready-to-use, interactive teaching units—are one of NIH's most popular and effective science education efforts. Crafted through a unique partnering of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with State education standards and are consistent with the National Science Education Standards. NIH has shipped nearly 350,000 curriculum supplements upon request to K-12 educators across the Nation. Topics covered include "The Science of Healthy Behaviors," "Cell Biology and Cancer," and "The Brain: Understanding Neurobiology through the Study of Addiction." The newest addition is "Exploring Bioethics" for high school biology classes.

NIH provides other types of school resources as well. *Findings* is a semi-annual magazine targeted to high school and early college students to convey the excitement of cutting-edge research, the interesting people who pursue science careers, and the enjoyment they get from this work. A companion website offers videos, podcasts, and interactive games expanding on the printed material. NIH also offers topical publications and school resources such as slide kits, online quizzes, and science puzzles that are used by teachers across the country to augment textbooks and enrich the classroom experience. Subject areas include cell biology, genetics, structural biology, chemistry, pharmacology, and computational biology. Classroom posters linked to selected publications also promote interest in science and research careers, and continue to be tremendously popular.

NIH aims to engage students and the public in the wonders of biology and biomedical research through other programs as well. For those who are interested in a career in the life sciences, NIH provides resources such as LifeWorks®, a career exploration website for middle and high school students, and their parents, teachers, and career guidance counselors. Users can search the site for in-depth information on more than 100 health and medical science-related careers, and generate a customized list of careers that match their skills and interests. SciLife is an annual health and biomedical career planning workshop for parents and high school students. NIH also sponsors a speakers' bureau that provides engaging science professionals to talk to school groups and local and national organizations.

NIH's Science Education Partnership Award (SEPA) program enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with K-12 students and the general public. SEPA generates resources such as curricula, exhibits, films, and after-school and summer hands-on science programs. The SEPA website provides access to the educational materials and expertise produced through these efforts.

Information and Information Technology

The goal of Information and Information Technology (I&IT) at NIH is to provide a platform for discovery through advanced tools, systems, and IT infrastructure, so that knowledge creation, discovery, and collaboration are commonplace through the NIH biomedical community. NIH has evolving research and business needs, which require effective and responsive design, management, and implementation of I&IT

assets so that the most benefit is gained pursuant to the NIH mission.

In January 2008, in an effort to foster improved I&IT efficiencies, integration, and oversight, the Office of the Chief Information Officer (OCIO) was established in the NIH OD, and the functions of the Chief Information Officer (CIO) were transferred from the NIH Center for Information Technology (CIT). OCIO develops IT-related strategy, services, and policy to ensure that all NIH IT infrastructure is secure, cost-effective, responsive, and benchmarked against industry standards.

CIT functions as the operating arm of the CIO, and provides expertise and support for OCIO program activities. CIT supports NIH research and management programs with efficient, cost-effective, administrative and high-powered scientific computing, software development, networking, and telecommunications services. CIT directs Business Intelligence Services (known as nVision) to provide a central data reporting repository for data extracted from systems that manage the day-to-day operations of NIH. nVision provides reporting tools to meet NIH business needs, including ARRA reporting and monitoring capabilities.

From supercomputing to management of an Image Processing Facility, CIT provides the NIH intramural community with invaluable tools and resources, such as bioinformatics support, and CIT's scientists, engineers, and mathematicians, as partners in the discovery of biomedical knowledge, contribute to advances in computational science. CIT also deployed and now manages the NIH Federated Authentication Identity Service (known as iTrust), which facilitates access to NIH research applications, databases, and scientific information, by authorized collaborators from government agencies, national laboratories, universities, hospitals, and pharmaceutical and biotechnology medical research centers, using the same sign-in as their home institution. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

Infrastructure and Capacity-Building

Many research resource, infrastructure, and capacity-building activities are addressed in the chapters that follow. These include investments in informatics and research resources such as data repositories and disease registries; funding of shared instrumentation; funding of programs that support development and use of animal models; clinical research networks and centers for clinical and translational research; and efforts to increase and enhance capacity for research on minority health and health disparities (see respectively the sections on *Disease Registries, Databases, and Biomedical Information Systems; Technology Development; Molecular Biology and Basic Sciences;* and *Clinical and Translational Research* in Chapter 3 and the section on *Minority Health and Health Disparities* in Chapter 2). However, several important additional infrastructure and capacity-building activities are cross-cutting and do not fit neatly into these sections of the report so are noted here.

The Institutional Development Award (IDeA) program broadens the geographic distribution of NIH funding for biomedical and behavioral research. By supporting faculty development and research infrastructure enhancement, the program enhances the competitiveness of investigators at institutions located in States that historically have been less successful in competing for NIH funds. IDeA also serves unique populations, such as rural and medically underserved communities where it is active—currently 23 states and Puerto Rico.

NIH's interest in capacity-building extends beyond our Nation's borders. For example, there is a growing recognition of the scientific imperative and mutual health benefit of a stronger research environment in Sub-Saharan Africa. To address the need to build stronger and more sustained partnerships with African institutions, in November 2008, NIH held a summit on Sub-Saharan Africa. This seminal meeting provided a forum for discussing key opportunities for expanding research activities between NIH and Sub-Saharan Africa institutions, with the goal of identifying prospects for enhancing NIH research, while working to

stimulate the scientific research enterprise in Sub-Saharan Africa, bolstering the growth of centers of excellence in Sub-Saharan Africa, and encouraging the development of a cadre of African investigators able to advance a research agenda for the region. As follow-up to this summit, and in an effort to expand its support of research and research training involving African institutions and scientists, NIH published a notice in the NIH Guide for Grants and Contracts encouraging African scientists and institutions to become involved in its various research and research training programs that offer the opportunity to contribute to science while building research capacity at African scientific institutions.

Core facilities are increasing in number, complexity, and cost. At the same time, there are academic institutions that are in need of the services of core facilities but cannot readily access them. To address these issues, NIH launched efforts directed toward the efficient management and utilization of core facilities, including a 2-day meeting held in July 2009. NIH already is taking steps to implement the recommendations made by scientists and administrators who attended the meeting.

Public-Private Partnerships

The NIH Program on Public-Private Partnerships

The NIH Program on Public-Private Partnerships (PPP), within the NIH Office of Science Policy, was established in 2005 as an NIH Roadmap initiative to facilitate collaborations to improve public health through biomedical and behavioral research. As the central NIH resource on public-private partnerships, the program staff provide guidance and advice to ICs and OD offices and to potential partners on the formation of collaborations that leverage NIH and non-NIH resources to achieve synergy. Program staff work with ICs and OD offices to review existing partnership mechanisms and to recommend policies or legal authorities needed to achieve NIH objectives, manage intellectual property, achieve data access and sharing, and address human subject protections and other critical and complex concerns in the setting of PPPs. NIH PPPs are science-driven, aim to improve the public health, and are structured to uphold the principles of transparency, fairness, inclusiveness, scientific rigor, and compliance with Federal laws and NIH policies. The PPP Program is responsible for the NIH Manual Chapter on Public-Private Partnerships—a reference guide to using the various available mechanisms to create public-private partnerships.

Partnerships can be established directly between NIH (as a whole or through one or more ICs) and any of a wide range of other organizations, including patient advocacy groups, foundations, pharmaceutical or biotechnology companies, academic institutions, and the Foundation for the NIH (FNIH) (see below for more information on FNIH). One example of a PPP is the Genetic Association Information Network (GAIN)—a combined private sector, FNIH, and NIH effort to provide genome-wide association data for common diseases. GAIN completed its work in 2008 and posted genotypes and phenotypes from the 18,000 samples it mapped to the NLM database of Genotypes and Phenotypes (dbGaP). Another PPP example is the Biomarkers Consortium—a complex partnership involving NIH, the U.S. Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services, FNIH, the Pharmaceutical Research and Manufacturers of America, and the Biotechnology Industry Organization. The Biomarkers Consortium is dedicated to discovery, development, and regulatory qualification of biomarkers[20] in any area of biomedicine.

The PPP Program also is involved in the development of international partnerships in several ways: international memberships and participation in the Biomarkers Consortium; membership and active participation in the National Academies Government-University-Industry Roundtable International Agreements group; providing advice and best practices in consultation with other governments seeking to establish PPP policies and programs (Canada and others); and ongoing conversations with leadership in the European Union's Directorates-General of Research as well as Enterprise and Industry. The expected outcome of these activities is to increase the involvement and harmonization of global activities in

biomedical research consortia and collaborations.

[20] Biomarkers are any characteristic that can be objectively measured to indicate (that is serve as a surrogate of) normal biological processes, disease processes, or responses to therapeutic intervention. Biomarkers are the foundation of evidence-based medicine, promising to revolutionize the development and use of therapeutics, and to make the practice of medicine more personalized, predictive, and preemptive.

The Foundation for the NIH (FNIH)

FNIH is an independent, private, charitable foundation established by Congress to support the NIH mission. A non-profit, 501(c)(3) corporation, the foundation works to engage the private sector, public and patient advocacy organizations, and researchers in cross-sector and multidisciplinary activities for a broad portfolio of unique programs that complement and enhance NIH priorities and activities. As a non-governmental entity, FNIH is not subject to a variety of policies and regulations that NIH as an agency of the U.S. Government is bound by, thus allowing FNIH to have a unique role in PPPs including raising funds for NIH initiatives and activities.[21] This enables NIH to leverage private sector partners' energy, ideas, and other resources in many promising research collaborations that might not otherwise be undertaken by any of the partners alone due to cost, risk, or other reasons. Although some FNIH partnership initiatives involve one specific IC, many involve two or more with a trans-NIH focus, including efforts on cancer, neuroscience, proteomics, informatics, and imaging.

FNIH manages large-scale programs, such as the Grand Challenges in Global Health Initiative, as well as highly focused programs such as special fellowships, lectures, and conferences. Much of the foundation's focus is on identifying partners (including organizations and individuals) and matching donors' interests to specific NIH needs. However, corporations, individuals, or foundations can bring an idea to FNIH, which then works with donors to assess which of the extraordinary array of existing and prospective programs within NIH's priorities would be most relevant to their interest.

All FNIH activities support the NIH mission, and include activities that, for example, help in developing new trial methodologies or tools, or new datasets. NIH's OSP serves as the official NIH liaison to FNIH, and maintains a record of each Memorandum of Understanding between NIH ICs and FNIH.

[21] In 2008, for the third consecutive year, Charity Navigator gave a coveted four-star rating to the Foundation for NIH and recognized it as the #1 health charity.

Improving Research Management

Enhancing Peer Review

Starting in 2007, NIH conducted a year-long, formal self-assessment of its peer review system. This assessment aimed to maintain the hallmarks of objectivity, fairness, and maximum competition that form its foundation, while accommodating the growing breadth, complexity, and interdisciplinary nature of modern research. The assessment involved recommendations from external and internal working groups, feedback from advocacy groups and regional town hall meetings, and consultation with professional societies. The final report, issued in March 2008, outlined broad challenges, and recommended transformative enhancements of the NIH peer review system. Subsequently, NIH convened internal committees to outline strategies and timelines to achieve implementation goals in four broad priority

areas:

- Engage the best reviewers
- Improve the quality and transparency of review
- Ensure balanced and fair reviews
- Engage in continuous review of peer review

Figure 1: Timeline for Enhancement of the NIH Peer Review Process

In spring 2008, NIH engaged in a detailed, intense, and rapid planning process (see Figure 1) to implement and launch the enhancements. The first changes—adjustments to recognize early stage investigators—were launched in less than a year. The changes began rolling out quickly thereafter and were accompanied by extensive training sessions and communication efforts. Remarkably, the advent of ARRA funding sped rather than slowed implementation. NIH used the new shorter application form for ARRA research grant applications in advance of the scheduled NIH-wide implementation of this enhancement. Other planned enhancements launched on their original timelines.

The peer review enhancement process entailed numerous policy announcements (see Table 1).

Table 1: Enhancing NIH Peer Review: Selected Policy Announcements

NOT-OD-09-024	NIH Announces New Scoring Procedures for Evaluation of Research Applications Received for Potential FY 2010 Funding
NOT-OD-09-025	NIH Announces Enhanced Review Criteria for Evaluation of Research Applications Received for Potential FY 2010 Funding
NOT-OD-09-003 and **NOT-OD-09-016**	New NIH Policy on Resubmission (Amended) Applications
NOT-OD-09-013	Revised New and Early Stage Investigator Policies

---

Following are highlights of the enhancements made within each priority area.

Engage the Best Reviewers

- New members of scientific review groups were given additional flexibility regarding their tour of duty. They now can expand their period of service preparing for and attending fewer meetings per year over a longer period of time. NIH expects that this option for flexibility will make it easier for reviewers to serve on scientific review groups.
- The Scientific Review Officers who staff SRGs and SEPs now have guidance on best practices for recruiting reviewers.
- NIH is conducting pilot tests of the use of high-bandwidth technological support for review meetings (such as virtual participation via videoconference) to provide reviewers with alternatives to in-person meetings, which require considerable time investments for travel.
- NIH implemented a policy for continuous submission of certain applications from appointed members of chartered NIH advisory groups and frequent temporary members (SRGs and Advisory Councils). Under the continuous submission policy, eligible applicants can submit their R01, R21, and R34 applications continuously (without regard to deadlines). The applications are reviewed by a SRG or SEP no later than 120 days after receipt and then are referred to the appropriate Advisory Council for the final level of review at its next meeting. This benefit is provided as part of the NIH continuing commitment to recognize outstanding peer review service. The first use of the continuous submission policy, in February 2008, was so successful that, in July 2009, it was extended to ad hoc members of advisory groups.

Improve the Quality and Transparency of Review

- NIH began using enhanced review criteria to evaluate research grant applications submitted for potential FY 2009 funding. The enhanced review criteria emphasize the potential impact of the work proposed and de-emphasize details of the experimental design with the intention of improving the quality of review. The enhanced review criteria form the basis for ongoing efforts to align the application format with the review criteria, which will greatly facilitate the transparency of the review process.
- NIH implemented a new 1-9 scoring system, in lieu of the current 41-point scale. Moreover, instead of giving the application just one score, each assigned reviewer also gives a numerical score for each of the now enhanced review criteria. For most applications, the criteria are significance, investigator(s), innovation, approach, and environment. Additional review criteria may be added for applications submitted in response to RFAs and certain Program Announcements. The nine-point scale is designed to provide an optimum range for making reliable and meaningful distinctions among applications.
- Reviewers are using structured templates to compose their critiques of the applications they review. The template focuses the review on the application's strengths and weaknesses relative to each criterion and fosters more concise and clear communication of the reviewer's assessment.
- Applications have been shortened and restructured. Applications submitted on and after January 25, 2010, are organized to align with the structure and content of the enhanced review criteria. This helps ensure that review and applicant expectations coincide for a more efficient and transparent process. At the same time, NIH shortened the page limits for certain sections of applications. This both reduces burden and focuses applicants and reviewers on the essentials of proposed research plans.

Ensure Balanced and Fair Reviews across Scientific Fields and Career Stages, and Reduce Administrative Burden

- To ensure that the largest number of high-quality and meritorious applications receive funding earlier and to improve system efficiency, NIH decreased the number of allowed grant application resubmissions (amendments) from two to one.
- Where possible, NIH is clustering New Investigator and Early Stage Investigator[22] applications during review, and the same approach was extended to clinical research applications.
- The standard review criteria used by reviewers to evaluate applications for research grants and cooperative agreements were enhanced (see *Improve Quality and Transparency of Review* above) to include consideration of the investigator's career stage.

[22] New Investigators lack previous, major NIH funding. Early Stage Investigators are New Investigators within 10 years of completing their terminal degrees or residencies.

Continuous Assessment of Peer Review

- Ongoing evaluation is critical to the health of the NIH peer review system and assuring that the system embodies the core values of competence, fairness, timeliness, and integrity. To achieve this end, NIH operationalized a dynamic effort to assess the cumulative outcomes of the changes being brought about by the peer review enhancements. This is part of a larger effort to develop appropriate measures and indicators for future monitoring efforts.

Launching RePORT: A Central Portal for Information on NIH Research Activities

NIH is committed to promoting a high level of public accountability for its investment of public funds. As part of that effort, NIH strives to provide extensive, detailed, and accurate information on its research funding in a user-friendly format. To that end, the Research Portfolio Online Reporting Tool (RePORT) was created by OER. RePORT serves as the central repository for all NIH external reports and as a public access point for comprehensive information, data, and analyses of NIH research activities. This includes information on NIH expenditures and the results of NIH-supported research, as well as a section on reports specific to recent issues of interest, such as the Recovery Act. To facilitate and encourage public use of RePORT, a tutorial introducing the major features of RePORT is presented on the site.

The RePORT home page provides links to frequently requested information and to major sections of the site, including:

- The NIH Data Book, which provides basic summary statistics on extramural grants and contract awards, grant applications, the organizations NIH supports, the scientific workforce, and trainees and fellows supported through NIH programs. NIH Data Book charts and tables are generated and updated automatically from a database of NIH statistics and can be exported to PowerPoint or printed in a printer-friendly format.
- NIH Strategic Plans, a site that provides links to strategic plans including IC, NIH-wide, topical, and HHS and inter-agency plans, with information on plans in the process of being updated.
- Categorical Spending, which provides the link to and information about the NIH Research, Condition,

and Disease Categorization (RCDC) system. (See section immediately below for more information.)
- RePORT Expenditures and Results (RePORTER), NIH's new and improved searchable database of funded research projects. (See section below—RePORTER: Expanded Information on Scientific Projects—for more information.)
- The Reports page, which provides access to a searchable database of reports. Each report has been categorized by topic, IC, the portfolio being reported on, the budget mechanisms and activities through which the programs included in the report are funded, and the years covered by the report. There are several drop-down menus that can be used to narrow the search further, which reduces the database containing hundreds of reports to a small set that matches the selected criteria.
- Other information, including this report—*The Biennial Report of the Director, National Institutes of Health.*

Research, Condition, and Disease Categorization (RCDC) System

In mid-January 2009, NIH launched a new process for providing detailed funding information, by fiscal year, for 215 major research categories, as part of its extensive efforts to keep the American people informed about how their tax dollars are used to support biomedical and behavioral research. The process, known as Research, Condition, and Disease Categorization (RCDC), uses a computerized approach to mine the descriptive text associated with NIH research projects and match it to standardized parameters to categorize the NIH research projects. The public can access the resulting categorical spending reports on the RePORT website.

NIH developed RCDC because it needed a more consistent system for reporting on its research spending and saw that advances in computer technology for data and text mining would enable the agency to modernize its systems. About the same time, the National Academies, an organization that provides scientific advice to the Federal government, issued two reports recommending a change in the way NIH categorizes its research portfolio. Subsequently, the U.S. Congress, through the NIH Reform Act of 2006,[23] mandated that NIH build a tool to categorize the agency's research.

Hundreds of NIH technical and scientific experts helped create the RCDC categorization methods and identify key terms and concepts. RCDC provides increased consistency of reporting, and in turn, enhances NIH's capacity for portfolio analysis and strategic planning. RCDC also provides improved transparency through the RePORTER database, and improves NIH's accountability for its spending and ability to respond to public inquiries.

The 215 categories reported through the RCDC process are the same categories that historically have been requested by and reported to Congress and the public at the end of each fiscal year. Some of the research funding amounts that the RCDC system reports may differ from NIH reports issued in the past. That is because the RCDC process applies a uniform definition, for each category, across all NIH's research projects. Individual research projects can be included in multiple categories, so the sum of all research/disease categories does not add up to 100 percent of NIH-funded research for a given fiscal year. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. Despite the changes in categorizing NIH research using the RCDC system, NIH's methods for budgeting and spending tax dollars remain the same.

[23] NIH Reform Act of 2006, Pub. L. No. 109-482, Sec. 402B.

RePORTER: Expanded Information on Scientific Projects

For many years, one of the most common ways for the public to find information on NIH research programs was to search for projects in NIH's Computer Retrieval of Information on Scientific Projects (CRISP) system. Now a new system that provides much more detailed information about projects is on-line. The new system, accessed through the RePORT website, is called RePORTER (RePORT Expenditures and Results). Like its predecessor CRISP, RePORTER allows users to locate and view NIH awards using their own search criteria. However, RePORTER also gives users access to budget award information, research results, and other research outcomes such as patents and publications. RePORTER includes data from 1985 through to the present—including projects funded through ARRA—and project lists can be sorted and downloaded to Excel. New features will continue to be added to RePORTER in several releases throughout FY 2010.

Capitalizing on Discovery

Technology Transfer

Technology transfer is essential to ensuring that the public has ongoing access to new and more effective health care products and procedures resulting from advances in medical research. Provisions of the Bayh-Dole Act (35 U.S.C. 200 et seq.) and the Federal Technology Transfer Act (15 U.S.C. 1501 et seq.) are intended to stimulate the commercialization of federally funded inventions by ensuring the transfer of federally funded technology to the private sector entity best suited to conduct the further research and development needed for potential commercialization and public health benefit. HHS has designated NIH as the lead agency for biomedical technology transfer and intellectual property (IP) policy matters affecting public health. The NIH Office of Technology Transfer (OTT) evaluates, protects, markets, licenses, monitors, and manages the wide range of intramural NIH and FDA discoveries and inventions; works with NIH's Office of Financial Management to manage the NIH Royalties Program; and takes the lead in developing technology transfer policies for NIH's intramural and extramural research programs.

Technology transfer policies, as they apply to extramural research, are administered by NIH OER and include principles, guidelines, and regulations related to invention reporting and intellectual property policy matters. NIH extramural policies are designed to enhance access to publications resulting from NIH-funded research (see *NIH Public Access Policy* below in this chapter); ensure appropriate sharing of data, tools, and research resources; and promote the transfer of technology (in the form of licenses and patents). All recipients of Federal grants or contracts must report details of inventions and patents that have been made through such awards. NIH OER administers the web-based Interagency "Edison" (iEdison) electronic reporting system through which inventions supported by more than 20 Federal research agencies can be reported through a single interface; approximately 500 grantee or contractor organizations are registered and using the system.

For the intramural research program, OTT reviews invention disclosures reported by the ICs and FDA; works with ICs/FDA to assess commercial and patent potential; oversees patent prosecution; negotiates licenses for commercial use in research and development; monitors licensing agreements with companies to ensure development compliance and royalty payment obligations; and administers the collection and distribution of royalties. Over the past decades, NIH has executed thousands of license agreements. In calendar year 2009, licensees reported nearly $6 billion in sales of products covered by NIH licenses (see Table 2).

Table 2: Intramural Technology Transfer this Biennial

Activity	FY 2008	FY 2009
New U.S. patent applications filed	176	156
Patents Issued	88	110
Licenses Executed	259	215
Royalties Earned	$ 97,200,000	$91,200,000

NIH technology transfer activities include marketing and outreach to companies, coordinating inter- and intra-agency activities, and facilitating access to patented technology for NIH intramural and extramural research programs. The NIH Pipeline to Partnerships (P2P) searchable database, developed with the NIH Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs, encourages the development of technologies licensed from OTT or being developed by NIH SBIR/STTR awardees. P2P has expanded to include unique technologies from 158 companies as of November 2009. OTT also has launched the electronic Product Showcase to display technologies from NIH intramural research that were licensed to companies for commercial development and now are on the market. These products are used every day to detect, treat, or prevent disease or assist researchers as tools to explore ways to develop newer and more effective health care products and procedures. As of November 2009, there were 225 products in the Showcase database with new ones added regularly.

The National Library of Medicine

Through NLM, NIH provides the world's largest medical library, including electronic information services that deliver trillions of bytes of data to millions of users every day. The library collects materials in all areas of biomedicine and health care and plays a pivotal role in translating biomedical and behavioral research into practice. NLM collections stand at more than 12 million items—books, journals, technical reports, manuscripts, microfilms, photographs, and other forms of medical information. To maintain the currency of its collection, the library acquires publications from a wide variety of sources. Each year NLM reviews and processes approximately 25,000 monographic items for possible addition to the NLM collections, and acquires and licenses more than 22,000 print and electronic serial titles. Housed within the library is one of the world's finest medical history collections of old and rare medical works.

Far more than a physical facility, NLM also is responsible for PubMed®/MEDLINE®, a database freely accessible on the Internet and that has more than 19 million journal article references and abstracts going back to 1948. The database draws on 5,300 of the world's leading biomedical journals published in the United States and more than 80 other countries. Links from PubMed references to full text articles in PubMed Central, NLM's digital archive of journal articles, or on publisher websites are now available for more than half of the 19 million references—and more than 86 percent of those published after 1999. MedlinePlus, a companion Web information service, is a goldmine of authoritative, up-to-date health information from all NIH components, other Federal agencies, and authoritative private organizations. It

includes information about prescription and over-the-counter drugs, an illustrated medical encyclopedia, interactive patient tutorials, and the latest health news for health professionals and consumers alike, and gives easy access to medical journal articles. In FY 2008, high-quality consumer health information in more than 40 languages (beyond English and Spanish) was added to MedlinePlus to address the growing need for understandable information for non-English-speaking patients treated in hospitals and clinics across the United States. More than three billion searches of NLM online information resources are done each year by health professionals, scientists, librarians, and the public. (See also the sections on *Disease Registries, Databases, and Biomedical Information Systems* and on *Health Communication and Information Campaigns and Clearinghouses* in Chapter 3).

To manage its collection and maximize accessibility, NLM employs sophisticated cataloging and indexing schemes that in and of themselves are important tools for the Nation's network of medical libraries. These activities include maintaining and developing the online NLM Classification, a scheme for the shelf arrangement of medical literature in libraries, and MeSH®, the library's controlled vocabulary thesaurus. MeSH® consists of descriptors in a hierarchical structure that permit searching at various levels of specificity. The MeSH® thesaurus is used for indexing articles for PubMed/MEDLINE.

The library virtually stands at the center of biomedical research—receiving, storing, disseminating, and connecting published research results, including articles deposited in response to the NIH Public Access Policy (see section below), with research data from laboratories and research centers around the world. NLM also supports, develops, and disseminates standard medical terminologies in the Unified Medical Language System. As the HHS coordinating body for clinical terminologies, NLM plays a leadership role in developing U.S. and international health data standards, including those related to electronic health records and the expansion of standards to cover genetic tests.

Public Access Policy

The NIH Public Access Policy ensures that the published peer-reviewed results of NIH-funded research are accessible to the public. In April 2008, the NIH mandatory Public Access Policy regarding peer-reviewed publications took effect. This policy replaced a voluntary practice that had been in place since May 2005. In accordance with the Consolidated Appropriations Act of 2008[24] and the Omnibus Appropriations Act of 2009,[25] the NIH Public Access Policy now requires the submission of peer-reviewed papers resulting from NIH-funded research to PubMed Central (PMC), a free, full-text, digital archive of biomedical, behavioral, and life sciences journal literature. These papers are made publicly available on PMC within 12 months of the official publication date. PMC and its international sites in the United Kingdom and Canada also support the public access policies of other U.S. and international funders of biomedical research.

The NIH Public Access Policy is off to a promising start, and NIH has made considerable progress toward full compliance. During the voluntary period (May 5, 2005, to December 31, 2007), NIH was able to collect only 19 percent of the target estimate of 80,000 papers per year arising from NIH funds. Based on publication data for July 2008 to June 2009, it is estimated that NIH now funds approximately 88,000 papers a year. Even with the higher target, NIH has received more than 60 percent of the papers published between July 2008 and October 2009.[26] These papers either are already available in PubMed Central or will be at the expiration of the typical 12-month embargo. This positive beginning to the requirement is due in large part to cooperation from NIH awardees and publishers. Since the policy became a requirement, the percentage of final published papers deposited directly by publishers has increased from 12 to 26 percent, and manuscripts submitted by authors have increased from 7 to 36 percent.

Through the Public Access Policy, NIH has been able to make tens of thousands of papers publicly available on PMC, which contains more than 1.9 million papers overall, most from publishers who have

been participating in PMC since 2000. These papers are heavily accessed. On an average weekday, some 360,000 users retrieve more than 700,000 papers. These users include patients, doctors, educators, and scientists at universities and small businesses. Access to NIH-supported papers on PMC increases the likelihood that all of these groups will use the NIH investment in research to improve public health.

[24] Division G, Title II, Section 218 of Pub. L. No. 110-161.
[25] Division F Section 217 of Pub. L. No. 111-8.
[26] The period from January 2008 to June 2008 is not reported, as papers published during these months were likely accepted for publication after the law creating the policy change was passed, but before the policy requirement took effect, and their rates are therefore possible to attribute to either policy condition.

Ensuring Responsible Research

NIH recognizes that with public support for research comes an obligation to ensure that research is conducted in a responsible manner to promote the integrity of NIH-supported biomedical and behavioral research and research training, to protect the health and safety of the public, and to conserve public funds. Responsible conduct of research features many interrelated attributes—including objectivity, honesty, accuracy, efficiency, safety, and ethical behavior. NIH addresses these issues through an array of policies, programs, and activities.

Ethical Conduct

Ethical Conduct for NIH Employees

The fundamental Federal principles of ethical conduct hold that conscientious performance of duty is placed above private gain, that employees shall not have financial interests that conflict with that duty, and that employees will avoid any actions creating the appearance that they are violating the law or the standards of ethical conduct. It is the responsibility of every NIH employee to abide by the statutes and regulations, including the supplemental standards of ethical conduct for HHS employees, and the implementation policies and procedures of NIH. Significant ethics training resources at NIH help employees meet that responsibility. The Ethics in Government Act (5 U.S.C. Appendix) requires each agency to provide an initial ethics orientation to new employees. NIH provides a Web-based training system to meet that obligation, as well as the annual ethics training for all other NIH staff. It is significant to note that, since 2004, NIH has made annual ethics training mandatory for all employees, a standard that far exceeds the government-wide requirement.

The NIH Ethics Program consists of a central NIH Ethics Office located organizationally within the NIH OD and an ethics office in each IC, managed by a Deputy Ethics Counselor and an Ethics Coordinator. NIH ethics staff members are readily available to answer questions and provide ethics and conflict-of-interest counsel, as needed, and the NIH Ethics Office provides extensive information and resources on its website. Attorneys from the HHS Office of the General Counsel, Ethics Division, maintain an office at NIH to provide legal advice and assist IC ethics counselors and coordinators as needed. For the ethics staff, there are semi-monthly meetings and extensive NIH Ethics Office-sponsored training in selected topics throughout the year. Training opportunities from the Office of Government Ethics also are made

available to NIH ethics staff and are-well attended.

Financial Conflict of Interest in Extramural Research

Proper stewardship of Federal funds includes ensuring objectivity of results by protecting federally funded research from compromise by financial conflicts of interest (COIs). Public Health Service (PHS) and HHS regulations (42 CFR 50, Subpart F, and 42 CFR 94), promote objectivity in NIH-funded research by providing standards to ensure that the design, conduct, and reporting of research under NIH-funded awards is not biased by any financial COI. The regulations are applicable to institutions that apply for PHS[27] funding for research and, through implementation of the regulations by these institutions, to each investigator participating in the research. Each institution receiving NIH research funds is required to have written guidelines on the avoidance of COI (i.e., financial interests, gifts, gratuities and favors, nepotism, and other areas such as political participation and bribery) and on the management, reduction, and elimination of identified conflicts. Institutions are required to report identified investigator financial COIs to the Grants Management Officer at the funding IC.

The regulations that govern objectivity in research were established in 1995. In the intervening years, the pace of translation of discoveries into interventions has accelerated significantly. Also, the U.S. biomedical research enterprise has grown in size and complexity. Awareness of the increasing complexity of biomedical research and the increased interaction between the government and the private sector in meeting common public health goals led to the question of whether changes to the regulations are needed. NIH recognizes that improvements can be made to its system of oversight, as well as to recipient organizations' management of the financial COI process, but also believes that the complex and controversial issues surrounding financial COI warrant a carefully considered, open dialogue with all affected parties. For these reasons, NIH, on behalf of HHS and PHS, developed an Advanced Notice of Proposed Rulemaking (ANPRM) to begin a dialogue about broadening the regulations to address institutional COI and to gain public input on all aspects of potential regulation in this area.

The comment period for the ANPRM closed on July 7, 2009. NIH is analyzing the comments received, as well as other related information, to determine how best to move forward in potentially changing the current regulations. If regulatory change is deemed appropriate, a Notice of Proposed Rulemaking would allow for further public comment on any draft regulation. If warranted, the goal would be to have new regulations announced with initial implementation by fall 2010.

NIH also has established conflict of interest, confidentiality and nondisclosure rules for reviewers of grant applications and research and development contract proposals. The rules require reviewers to identify and certify real or apparent COI both pre- and post-meeting. Employment, financial benefit, personal relationships, professional relationships, or other interests may be a basis for COI, and any one condition may serve to disqualify a reviewer from participating in the review of an application or proposal.

[27] The PHS comprises all HHS Agency Divisions (of which NIH is 1 of 11) and the Commissioned Corps.

Conflicts of Interest in Clinical Research

COI can be especially problematic in clinical research. For that reason, there is guidance in addition to the policies and regulations noted above. The OHRP guidance, "Financial Relationships and Interests in Research Involving Human Subjects," covers extramural research and the NIH "Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH" ensures both the

integrity of research and the safety of subjects in the intramural program.

Research Integrity

NIH recognizes that public support for research comes with an obligation to promote integrity in the conduct of that research. Honesty, accuracy, efficiency, and objectivity are important values that characterize what is meant by integrity in research. As defined by regulation,[28] *research misconduct* means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results; it does not include honest error or differences of opinion. Allegations of research misconduct in biomedical and behavioral research or research training supported by NIH tend to be unique rather than routine events at most institutions. However, a research misconduct allegation has the potential for high impact on public health or clinical treatment, the individuals involved, the institution where the alleged misconduct took place, and public trust. (See also, *Ethical Conduct*, above).

OER manages allegations of potential research misconduct that are reported to any member of the NIH extramural staff, and also provides annual training to the IC Research Integrity Officers (RIOs) and extramural staff, through online tutorials and training symposia. Within each IC, a senior official is designated as the IC RIO. Extramural staff is instructed to report immediately any allegation of potential research misconduct to the IC RIO, who then forwards the allegation to one of the Extramural Research Integrity Liaison Officers or the Agency Extramural Research Integrity Officer in OER. A preliminary review of the allegation is conducted then to verify information and assess whether the allegation may be appropriate for an inquiry. On rare occasions, NIH may request an inquiry, but by regulation, the HHS Office of Research Integrity is authorized to request institutions to perform inquiries and investigations related to allegations of potential research misconduct. If a finding of research misconduct is found, the offender may incur administrative actions, including but not limited to: replacement as Principal Investigator on the award; requirement to clarify, correct, or withdraw related publications; suspension or termination of any PHS grant, contract, or cooperative agreement; ban from serving in any advisory capacity to PHS; and suspension or debarment, i.e., exclusion from eligibility for Federal grants, contracts, and cooperative agreements.

The same standards of research integrity and comparable procedures for investigating allegations of scientific misconduct apply to NIH intramural research program. For intramural research staff, the "Guidelines for the Conduct of Research" set forth the general principles governing the conduct of good science. The guidelines cover the responsibilities of research staff in the collection and recording of data, publication practices, authorship determination, mentoring, peer review, confidentiality of information, collaborations, and financial conflicts of interest. NIH employees are required to report suspected or apparent misconduct in science to the Agency Intramural Research Integrity Officer (AIRIO) or Deputy Director for Intramural Research. The AIRIO decides whether the allegation warrants an inquiry to determine whether there is enough evidence behind an allegation or apparent instance of scientific misconduct to warrant moving to the next level of response—an investigation. If the formal investigation determines that misconduct has occurred, NIH sanctions could include removal from a particular project, special monitoring of work, suspension without pay, or termination of employment. The NIH AIRLO decides whether to accept the investigation report, makes a finding of misconduct, and imposes the recommended NIH sanctions. The final step in the process is a review by the HHS Office of Research Integrity, which then makes recommendations on possible PHS sanctions that could include debarment from serving on NIH study sections or receiving NIH grants. The *Intramural Research Program Sourcebook* contains all Policies and Procedures for Investigating Scientific Misconduct.

[28] 42 CFR Parts 50 and 93. Available at: http://ori.dhhs.gov/documents/42_cfr_parts_50_and_93_2005.pdf.

Human Subjects Protections in Research

The HHS Office for Human Research Protections (OHRP) implements the Federal regulations governing the protection of human subjects (45 CFR 46) for all HHS agencies, including NIH. OHRP is responsible for (1) negotiating assurances with each institution that conducts HHS-sponsored human subjects research, (2) registering local Institutional Review Boards (IRBs), which assess risk, benefit, and many other matters with respect to proposed and ongoing studies involving human subjects, (3) issuing policy and guidance that clarifies the regulations, (4) providing educational materials and programs for investigators and IRBs, and (5) overseeing compliance. Because of the clinical research conducted in the NIH intramural program, NIH itself has an assurance with OHRP. (See also, *Ethical Conduct*, above for information on OHRP guidance concerning COI in human subject research).

The Office of Extramural Programs (OEP) in the NIH OER conducts activities to ensure the compliance of NIH grantees with HHS regulations and NIH policies regarding the protection of human subjects in extramural research. OEP staff assess the proposed resolution of human subjects concerns identified during peer review of extramural research applications prior to funding, and respond to requests to change human subjects designations of ongoing NIH extramural research projects. OEP also provides training to NIH extramural staff and the extramural scientific community regarding NIH policies on human subject protection and develops and implements policies to ensure that participants in NIH-funded extramural research projects are adequately protected. OER maintains a grants policy website dedicated to research involving human subjects. This comprehensive site provides, in one place, HHS and NIH requirements and resources for the extramural community involved in human subjects research in its roles as applicants/grantees, offerors/contractors, peer reviewers, and institutional officials.

As noted above, because of the clinical research conducted in the NIH intramural program, NIH itself has an OHRP-approved Federal-Wide Assurance (FWA) of compliance with the HHS regulations for the protection of human subjects. The Office of Human Subjects Research (OHSR) in the NIH OIR—functioning under the assurance and in cooperation with the ICs—implements the policies and procedures of the NIH Human Research Protection Program. With the responsibility to protect the rights and safeguard the welfare of human subjects who participate in intramural NIH research studies, OHSR establishes and maintains the 11 NIH IRBs that are linked to the FWA, provides training for researchers and IRB members, and manages the Human Subjects Research Advisory Committee. In turn, the 11 NIH IRBs are responsible for the prospective and continuing review of NIH intramural research that involves human subjects. The Human Subjects Research Advisory Committee advises the DDIR on policies and procedures regarding the conduct of human subjects research. The importance of this advisory role is underscored by the fact that, under the FWA, the DDIR is the institutional official responsible for human subject investigations at NIH. An additional body, the NIH Intramural Clinical Research Steering Committee, also serves as a forum for trans-NIH governance and policy development in the area of human subjects research. The Committee coordinates efforts and ensures clear communications about goals, progress, and future directions. Within the NIH Clinical Center, the site of most NIH intramural human subjects research, the Department of Bioethics provides a center for research, training, and service related to bioethical issues, and is available as a source of advice to the NIH IRBs.

NIH also is working to enhance the safety, efficiency, and effectiveness of the clinical research enterprise by promoting greater consistency in the rules and policies governing the conduct and oversight of clinical research. In addition to the regulations administered by OHRP, clinical investigators are subject to FDA regulations. Moreover, differences in the HHS and FDA regulations can be compounded through policy interpretation. In addition, policies and practices of the NIH ICs can lead to other complications for clinical investigators supported by NIH. Recognizing that the inconsistencies in the oversight system can hamper the efficiency and effectiveness of the clinical research system, NIH created the Clinical Research Policy Analysis and Coordination (CRpac) Program to promote greater consistency in human subject protection policies and requirements. Launched as an NIH Roadmap initiative, CRpac aims to advance the

development of clear, effective, and coordinated rules for clinical research to achieve maximally effective human subject protections. For example, CRpac has led major efforts to improve understanding and compliance with adverse event reporting requirements and standardize the reporting of adverse event data,[29] and to develop draft guidelines for human specimen and data collections funded by NIH. (See also the section on *Clinical and Translational Research* in Chapter 3.)

[29] An adverse event is an unfavorable medical occurrence associated with the subject's participation in research.

Animal Care and Use in Research

The Office of Laboratory Animal Welfare (OLAW) in the NIH OER oversees the use of animals in NIH-supported biomedical and behavioral research conducted by extramural institutions. OLAW provides guidance and interpretation of the *PHS Policy on Humane Care and Use of Laboratory Animals*; monitors compliance with the policy; evaluates all allegations or indications of noncompliance with Federal animal welfare requirements; and supports educational programs that further the humane care and use of research animal subjects. As a condition of receiving PHS support for research involving laboratory animals, institutions must provide a written Animal Welfare Assurance (Assurance) to OLAW describing in detail the means they will use to comply with the PHS policy and Federal statutes and regulations relating to animals, and committing the institution and its personnel to full compliance. OLAW negotiates and approves these assurances as required by Pub. L. No. 99-158, HHS acquisition regulations, and the PHS policy, and holds institutional officials, Institutional Animal Care and Use Committees (IACUC), researchers, and other agents of the institution accountable for ensuring conformance with the institution's Assurance.

OLAW maintains a comprehensive website with links to relevant laws, policies, and guidance; an online tutorial; and a variety of other training materials and resources regarding laboratory animal welfare. In 2008, two online seminar series were launched to focus educational outreach to institutional officials at grantee institutions and to IACUC members. The webinar format enabled invited speakers to communicate timely, relevant information through an interactive forum with constituents at worksites across the Nation, at no expense to the viewers. The feedback on the seminars has been extremely positive, and the process has been fine-tuned to enhance the experience and extend the number of attendees to more than 300 institutions.

A workgroup led by OER developed a new comprehensive Animals in Research website in 2008. The website provides information for the general public about the benefits of medical research with animals, alternatives to animal research, advances in animal research, and animal health and welfare. For researchers and institutions, the website provides information about emergency preparedness and crisis communication, up-to-the-minute policy and guidance, grants resources, funding opportunities, and training and education, as well as answers to frequently asked questions.

The Office of Animal Care and Use (OACU) in the NIH OIR administers the intramural program of animal care and use. OACU develops guidelines and policies for the responsible care of laboratory animals and the proper operation of NIH animal facilities, and offers a variety of training courses and health and safety information for personnel who work with animals. Each NIH component that uses animals in research has an Animal Care and Use Committee, which reviews and approves (or disapproves) requests to use animals in research, and has a senior veterinarian who directs its animal care and use program. An Animal Research Advisory Committee meets monthly to discuss trans-NIH topics and provide advice to the NIH DDIR, who is the NIH Institutional Official accountable for animal care and use. All components of the intramural NIH animal care and use program are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Bioethics Research, Training, and Translation

NIH has a long history of engagement with bioethics—the study of ethical issues and controversies resulting from advances in biology and medicine. NIH was a pioneer in the development of independent ethical review of clinical research studies. In 1996, NIH established the Department of Bioethics within the NIH Clinical Center to conduct conceptual, empirical, and policy-related research into bioethical issues; offer training and educational programs in bioethics; and provide ethics consultation to clinicians, patients, and families. In the 1990s, NIH began a dedicated investment in the study of the ethical, legal, and social implications of genome research through a novel set-aside, as part of the Human Genome Project. And, in the last two decades, NIH has supported many additional bioethics research and training projects, ranging from short-term courses in research ethics regarding minority participation in AIDS research to studies addressing the ethical, social, and legal issues of human microbiome research. Nonetheless, advances in science and medicine have been accelerating at a rapid pace and, more than ever, NIH needs the foresight and vision to understand the ethical and societal implications of discoveries in biomedical, behavioral, and technological research and the knowledge arising from these advances. In the last 3 years, there also have been calls for NIH to make a greater and wider commitment to addressing the ethical, legal, and social issues—such as, privacy, safety, commercialization, and COI—raised by the research it supports—including biotechnology, tissue engineering, nanomedicine, and synthetic biology. NIH's commitment to the support of bioethics helps maintain and enhance public trust and confidence as NIH explores new frontiers in science.

Integrating bioethics across the entire NIH research portfolio is a long-range agency goal that requires mid- and long-term planning and strategies. As a first step, a trans-NIH task force was formed in early 2009 to develop a research agenda for FY 2010 and FY 2011 and to develop a long-range plan. Additional support for bioethics research was provided through the FY 2009 ARRA Challenge Grant initiative. Support also has been requested in FY 2010 through NIH's regular appropriations process.

The long-range plan will identify research and training gaps and opportunities and formulate a strategy for addressing them over the next 5 to 10 years. It also will include consideration of the optimal administrative approach for sustained support for, coordination of, and accountability for NIH bioethics efforts. Finally, the long-range plan will include the design of an evaluation to assess the value and impact of the investments. Altogether, the plan will provide a framework that will enhance the integration of ethical inquiry and practice into the conduct of research across the entire spectrum, from the most basic projects to the most applied; help maintain the academic discipline of bioethics and expand bioethics investigators and scholars; and develop curricula and ethics training programs. The goal is to facilitate the early identification and deliberation of complex bioethical issues and generate knowledge needed for responsible conduct of science that takes into account its broader societal impact.

Promoting Responsible Research through Policy Development

NIH has a vested interest in promoting research at the cutting edge of science and technology—for example, gene transfer, infectious agents, stem cells, nanomedicine—research that has potential benefits but often unknown risks for which little or no guidance exits. For example, the protection and enhancement of public health, agriculture, and the food supply is a national priority and has led to increased Federal funding for research on infectious agents, especially those that pose a severe threat to human, plant, and animal health. At the same time, concerns have been voiced by the public, scientific community, Administration, and Congress regarding biosafety and biosecurity in research laboratories that work with the most dangerous pathogens and toxins. Concerns also have been raised about the risks that certain information from life sciences research could be misused to threaten public health and other aspects of national security. NIH has a responsibility to anticipate the evolution of issues such as these,

and to provide leadership and support for efforts at the NIH, HHS, and national levels that are designed to promote research, assure safety, address ethical concerns, and enhance public understanding and trust, through the development of sound public policies.

Much of the leadership and support regarding new and evolving policies about responsible conduct of research is vested in the NIH Office of Science Policy (OSP). Within OSP, the Office of Science Policy Analysis (OSPA) coordinates NIH responsibility for the interpretation, development, and implementation of policies regarding human embryonic stem cells. In addition, OSPA coordinates action on nanotechnology policy issues. This includes providing management and analytic support for the Trans-NIH Nanotechnology Task Force. The Office of Biotechnology Activities (OBA), also within OSP, monitors scientific research and progress in the areas of recombinant DNA,[30] genetics technologies, and dual-use research[31] to anticipate future developments, including potential safety, ethical, legal, and social concerns. OBA also manages the CRpac program, discussed above, which promotes greater consistency in human subject protection policies and requirements.

[30] Recombinant DNA is DNA created by combining genetic material from different sources to create a new genetic sequence.
[31] Dual-use research is defined as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security.

Stem Cell Research

NIH is responsible for the interpretation and implementation of legislation, Executive Orders, and Administration policies relating to stem cell research. OSPA advises NIH, Congress, the scientific community, and the public on current stem cell policies and specific research activities allowable under current policies and regulations. The office plays an integral role in developing guidelines for research involving human pluripotent cells of all types.

On March 9, 2009, President Barack Obama issued Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*. The Executive Order states that the Secretary of HHS, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.

The NIH Guidelines for Human Stem Cell Research were published on July 7, 2009, and are available at http://stemcells.nih.gov/policy/2009guidelines.htm. The Guidelines implement the Executive Order as it pertains to extramural NIH-funded stem cell research, establish policy and procedures under which the NIH will fund such research, and help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. In addition, on July 30, 2009, the President directed all Federal departments and agencies that support and conduct stem cell research to adopt the Guidelines. For hESCs derived from embryos donated in the United States on or after the effective date of the Guidelines (July 7, 2009), specific provisions regarding the embryo donation and informed consent process apply and are detailed in Section II of the Guidelines.

On September 21, 2009, NIH Director Francis S. Collins announced that NIH is accepting requests for human embryonic stem cell lines to be approved for use in NIH-funded research. Dr. Collins also announced the members of a new working group of the Advisory Committee to the Director (ACD)—the Working Group for Human Embryonic Stem Cell Eligibility Review. After considering the analysis done by the Working Group, the ACD makes recommendations to the NIH Director regarding the eligibility of particular human embryonic stem cell lines for use in NIH-funded research. hESCs that meet Section IIA

requirements are considered through NIH administrative review.

The NIH Director makes the final decisions regarding the eligibility of all hESCs. Those lines deemed eligible are listed on the NIH Human Embryonic Stem Cell Registry. Once a human embryonic stem cell line is listed on the Registry, there is no need for further submissions requesting review of that particular line. The first hESCs were listed on the Registry on December 2, 2009.

Recombinant DNA, Genetic Technologies, and Dual Use Research

OBA manages a range of activities related to responsible use of recombinant DNA, genetic technologies, and dual use research including:

- Administration of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines*), which address the safe and ethical use of basic and clinical research involving recombinant DNA molecules at institutions that receive any NIH funding for recombinant DNA research;
- Management and analytical support for the NIH Recombinant DNA Advisory Committee (RAC);
- Operation of the NIH Genetic Modification Clinical Research Information System (GeMCRIS), an electronic resource for information and adverse event reporting on gene transfer trials, which also is used by FDA;
- Outreach and education to stakeholder communities regarding biosafety and biosecurity; and
- Management and analytic support for the National Science Advisory Board for Biosecurity (NSABB).

The RAC reviews all proposals for human, gene transfer, and clinical research (often referred to as “gene therapy”) at institutions receiving NIH funds for recombinant DNA research. RAC review occurs before biosafety review at the institution where the research will be conducted, enabling RAC review to inform local review. As a Federal advisory committee, RAC issues recommendations to the NIH Director. RAC proceedings and reports are posted to the RAC website to enhance their accessibility to the scientific and lay publics. As new issues are identified, the RAC helps NIH develop safety symposia and policy conferences to engage the scientific and public communities in thoughtful dialogue regarding emerging issues and concerns.

The RAC has been a vital national forum promoting critically important scientific progress in a transparent, responsible, and safe manner and enhancing public trust in the science. For example, in March 2009, NIH published in the *Federal Register* a proposal for comment to expand the scope of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines*) to include nucleic acid molecules that are synthesized rather than being made by recombinant techniques. The proposal represents the first major expansion to the document’s scope since it was first written more than 30 years ago. This action was in response to a recommendation made in the December 2006 report of NSABB, *Addressing the Biosecurity Concerns Related to the Synthesis of Select Agents*. NSABB recommended to the HHS Secretary that the language and implementation of current biosafety guidelines be examined to ensure that such guidelines and regulation provide adequate guidance for working with synthetically derived nucleic acids. NIH was tasked with conducting the assessment. OBA also consulted with the RAC, which noted that the biosafety risks are related more to the product being produced than the technique being used, and recommended expanding the scope of the *NIH Guidelines* to specifically cover synthetic nucleic acids. The public comments generally have been supportive of the proposal. NIH also held a public consultation about the proposed changes in a day-long meeting in June 2009. A revised version of the proposal was reviewed by the RAC at its quarterly meeting in December 2009. A *Federal Register* notice requesting comment on a revised proposal was published on April 22, 2010. OBA anticipates a final proposal will be published by the end of 2010.

SACGHS provides policy advice to the Secretary, HHS, on the broad array of complex medical, ethical,

legal, and social issues raised by the development and use of genetic technologies. SACGHS is charged with undertaking the development of a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. In April 2008, SACGHS submitted its report on the *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*. The report is the culmination of extensive fact finding, analysis, expert consultation, outreach to the public, and deliberation by the committee, and highlights gaps in the oversight system for genetic testing and provides recommendations to maximize the benefits of genetic testing and minimize harms.

OBA also is a focal point for the development of policies addressing biosafety and biosecurity. This includes the development of policy regarding dual use research (life sciences research that yields information or technologies with the potential to be misused to threaten public health or endanger other aspects of national security). NIH was a key participant in the HHS Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight, which was established in FY 2008 in response to concerns about the risks associated with the proliferation of high- and maximum-containment laboratories in the United States. The Task Force reviewed the current systems of biosafety oversight and made recommendations to improve biosafety and biocontainment oversight at U.S. laboratories. NIH also participated in the Working Group on Strengthening Laboratory Biosecurity in the United States, established in January 2009, by Executive Order 13486, *Strengthening Laboratory and Biosecurity in the United States*. The Working Group is charged with reviewing and evaluating laboratory operations regarding the use, handling, storage, or transport of biological Select Agents and toxins.[32] The Working Group developed a report, which included recommendations for new legislation, regulations, guidance, and practices for enhancing laboratory security and reliability of personnel at all Federal and nonfederal facilities working with biological Select Agents and toxins. NIH also has developed new, comprehensive biosafety recommendations for work with potentially pandemic flu viruses[33] that have the ability to infect humans. The guidance was developed to ensure that important research on pandemic influenza is carried out using biosafety containment and practices that will protect laboratory workers and the public.

NSABB, managed by OBA, is a Federal advisory committee established to advise the Federal Government on ways to minimize dual use biological research risks and inform the development of Federal and institutional oversight guidelines. In response to heightened security concerns surrounding the potential misuse of dangerous pathogens within research settings, NSABB was charged with recommending strategies for enhancing the reliability of personnel who have access to Select Agents and toxins. The challenge was to identify policies aimed at mitigating the risk of misuse of Select Agents by individuals who have legitimate access to them as part of their jobs, without unduly hindering the pace of life sciences research. The NSABB issued its findings and recommendations in May 2009, and they are being considered at various levels of the Federal Government, along with those of the Executive Order Working Group and other groups that have focused attention on these important issues.

[32] Select Agents are biological agents and toxins that have the potential to pose a severe threat to public, animal or plant health, or to animal or plant products. The possession, use, and transfer of Select Agents and toxins are regulated by HHS and the U.S. Department of Agriculture.
[33] Examples include 1918 H1N1, human H2N2 that circulated in 1957-68, and strains of HPAI H5N1.