

**Department of Health and Human Services
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Advisory Committee to the Director**

**93rd Meeting
December 1, 2006**

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EXECUTIVE SUMMARY

The 93rd meeting of the Advisory Committee to the Director (ACD) of the National Institutes of Health (NIH) was held on December 1, 2006. NIH Director Elias A. Zerhouni, M.D., introduced three new ACD appointees—Karen A. Holbrook, Ph.D., President, Ohio State University, Mary-Clare King, Ph.D., American Cancer Society Professor, Departments of Medical Genetics and Genome Sciences, University of Washington, and Barbara L. Wolfe, Ph.D., Professor, Departments of Population Health Sciences, Economics, and LaFollette School of Public Affairs, University of Wisconsin Medical School.

John B. Bartrum, Associate Director for Budget in the NIH Office of the Director, reported that the 2007 NIH budget request is flat and the NIH is operating under a continuing resolution. Dr. Zerhouni reported that for 2006, the NIH awarded 12,519 research grants, for an overall success rate of 21.9 percent. Under the continuing resolution, the NIH continues to make new grants in ongoing research areas. Non-competing awards are being issued at 80 percent.

Dr. Zerhouni reported that the NIH has maintained its special focus on the support of new investigators. The NIH's Pathway to Independence Awards eventually will each year support 150 to 200 new postdoctoral fellows for 5 years—2 years of postdoc funding leading to 3 years of R01 funding in a tenure-track position. The first three cycles of the program produced about 900 applications. In the first round, 60 awards were made.

Amy P. Patterson, M.D., Director of the NIH's Office of Biotechnology Activities, in the Office of Science Policy, described the NIH's Clinical Research Policy Analysis and Coordination Program (CRpac), an effort to harmonize policies and regulations across research programs, to foster simplicity, clarity, and efficiency in clinical research policy. Working in collaboration with the NIH Office of Intramural Research, the NIH Office of Extramural Research, the HHS Office for Human Research Protections (OHRP), and the

Food and Drug Administration (FDA), the CRpac is developing tools and resources and building partnerships and models of interaction.

Elizabeth G. Nabel, M.D., Director of the National Heart, Lung, and Blood Institute (NHLBI), presented a proposed NIH policy on data sharing for NIH-supported genome-wide association studies (GWAS). A new database program (already begun) will collect large amounts of genotypic data and bring them together with phenotypic data from large cohort studies. A committee has developed policy in three areas—data management, scientific publishing, and intellectual property. James Ostell, Ph.D., Chief of the Information Engineering Branch of the National Center for Biotechnology Information (NCBI), which handles the database, demonstrated its use. Browsers will be able to search by disease and observe study summaries, substudies, variables, histories, and bibliographies. Registered users will be able to obtain readouts of sets of single nucleotide polymorphisms (SNPs) and their correlations with a disease.

Norka Ruiz Bravo, Ph.D., NIH Deputy Director for Extramural Research, described progress in the development and application of the electronic application system for NIH grants. By the end of 2007, the NIH will require electronic submission through **Grants.gov** for all NIH applications and will complete transition from the PHS 398 application form to the SF424, a form set used by many federal research agencies. Dr. Ruiz Bravo reviewed concerns with the new system, as expressed by investigators, and the ACD members discussed possible changes to the procedures, including concerns about timing and the need for a principal investigator to control an application's final presentation.

Wendy Chaite, J.D., member of the NIH Director's Council of Public Representatives (COPR) and that group's liaison to the ACD, reviewed themes from the recent COPR meeting in November. The COPR members discussed the financial environment of the NIH and NIH researchers and the issue of engaging members of the public in research. Ms. Chaite reviewed some the many contributions of the COPR since its inception 8 years ago, for example, evaluating materials for the plain-language award program and providing input to the NIH Strategic Communications Plan and NIH Public Trust Initiative.

Roger I. Glass, M.D., Ph.D., Director of the Fogarty International Center (FIC), presented a history of the Center, which has sought to address global health challenges through innovative and collaborative programs for research and training and which has supported the NIH mission through global partnerships. The FIC's research represents about 10 percent of the international research activities of the NIH. Fogarty-supported programs can be found in more than 100 countries, with more than 60 U.S. institutions involved in partnerships. Ongoing international programs include the Framework Program, a small-grants initiative begun recently, which brings together persons from U.S. universities to address global health, the President's Emergency Program for AIDS Research (PEPFAR, \$15 billion over 5 years), and the President's Malaria Initiative (PMI, \$1.2 billion over 5 years).

Raynard Kington, M.D., Ph.D., ACD Executive Secretary, reported progress on the effort to create a list of bona fide prescreened awards that NIH scientists and employees may receive. He presented the latest list of vetted awards and asked the ACD members to approve it.

NIH DIRECTOR'S REPORT

The 93rd meeting of the Advisory Committee to the Director (ACD) of the National Institutes of Health (NIH) was held December 1, 2006, on the NIH campus in Bethesda, Maryland, and Webcast globally. The next meeting is scheduled for June 7–8, 2007. NIH Director Elias A. Zerhouni, M.D., welcomed the ACD members and other participants and guests.

Dr. Zerhouni introduced three new ACD appointees—Karen A. Holbrook, Ph.D., President, Ohio State University, Mary-Clare King, Ph.D., American Cancer Society Professor, Departments of Medical Genetics and Genome Sciences, University of Washington, and Barbara L. Wolfe, Ph.D., Professor, Departments of Population Health Sciences, Economics, and LaFollette School of Public Affairs, University of Wisconsin Medical School. He noted that ACD members Catherine D. DeAngelis, M.D., Alexander R. Lerner, C. Martin Harris, M.D., Ralph I. Horwitz, M.D., and Joan Y. Reede, M.D., were unable to attend the meeting.

Dr. Zerhouni thanked, for their service to the Committee and the NIH, five ACD members who were retiring: J. Michael Bishop, M.D., Arthur D. Ullian, Raghavendra R. Vijayanagar, M.D., Phillip L. Williams, and R. Sanders Williams, M.D.

Dr. Zerhouni introduced John B. Bartrum, Associate Director for Budget, in the Office of the Director, who recently joined the NIH, having served in the U.S. Office of Management and Budget (OMB). Mr. Bartrum reported that the 2007 NIH budget request is flat and the NIH is operating under a continuing resolution. The President's budget is \$28.5 billion, the House version is roughly the same, and the Senate version is \$28.7 billion. Under the continuing resolution, the NIH continues to make new grants in ongoing research areas. Non-competing awards are being issued at 80 percent. Mr. Bartrum noted that the budget situation is similar to the situation in the 1983–1984 period.

Dr. Zerhouni presented an overview of the following NIH activities in 2006 related to issues raised by the ACD.

In an article recently published in *Science* (“NIH in the Post-Doubling Era: Realities and Strategies”), Dr. Zerhouni summarized the driving forces currently buffeting the NIH and ways in which the NIH is responding. A great expansion in the number of applications for NIH research grants has developed from the expansion of capacity in the research institutions (especially increases in faculty size). The flat budget and factors such as Hurricane Katrina have added to the tensions.

Nevertheless, for 2006, the NIH awarded 12,519 research grants, for an overall success rate of 21.9 percent. The NIH currently funds about 46,834 research grants within 36,846 research projects. Dr. Zerhouni remarked on the phenomenon in which people sense (incorrectly) a much smaller success rate for NIH grants (as low as 7 percent to 9 percent). In fact, the Institutes and Centers (ICs) have success rates ranging from 14 percent to 29 percent (producing the overall rate of 21.9 percent).

The NIH has responded to the flat budgeting by adjusting the costs of grants. The demand for grants surged at the end of the NIH’s budget-doubling period. In fact, the increase in grant applications during the 2 years following the doubling was larger than the increase in grant applications during the multi-year doubling period. Researchers today state that more than one NIH grant is required to support a laboratory—a result that adds to the increase in applications.

The NIH has continued its focus on supporting new investigators, recognizing that lean fiscal times can cause a decrease in new investigators funded. Between 1,550 and 1,650 new investigators receive NIH first-time grants each year. The numbers were seen to be declining in 2005. In response, the NIH created the Pathway to Independence Award, to provide 150 to 200 awards each year to postdoctoral fellows. Each postdoc receives 2 years of postdoc funding followed by 3 years of independent R01 funding, provided he or she

receives a tenure-track position. The first three cycles of the program produced about 900 applications. In the first round, 60 awards were made.

The Institutes and Centers were asked to determine differential success rates for previously funded investigators and first-time investigators. The results indicated that success for first-time awardees is being preserved. Other trends were observed. The chance of being funded on a first attempt for an application has declined slightly, yet the chances of being funded on second and third attempts (amended applications) have remained steady. This trend reveals a significant degree of wasted effort in developing the initial applications. NIH officials, including IC directors and the Center for Scientific Review (CSR), have begun an effort to address this problem.

Scientists who serve as reviewers have complained of a large bureaucratic effort within the review process. The NIH is responding by making the grant application process fully electronic and by shortening the review cycle. The application, with its 25-page length, tends to overemphasize the details of a project at the expense of qualities such as significance and relevance. In one survey, 74 percent of grantees stated that they were in favor of shorter applications.

In 2006, the NIH continued to ensure that emerging programs and areas of science were supported. The ICs have worked to ensure that scientists with single grants of modest amount are not affected negatively by the lean financial circumstances.

Discussion

The ACD members wondered whether a winnowing effect for applications occurs. That is, do the amended applications represent the better-quality applications? The CSR recently began to track such factors and does not yet have data. Individual ICs have data on the paylines for amended applications that succeed, which might help to answer the question.

Tadataka Yamada, M.D., wondered whether, in light of the excess demand, the NIH should seek to limit the number of scientists. Dr. Zerhouni responded that such ideas are part of larger questions about sustaining national science.

David Botstein, Ph.D., noted that many investigators become discouraged because of what is written in the reviews of their applications and therefore do not submit amended applications. He suggested that applicants be given better advice. Dr. Zerhouni responded that the NIH does, in fact, encourage applicants to reapply. Christine E. Seidman, M.D., encouraged the NIH to reduce the amount of time between an initial submission and ultimate funding. Alan I. Leshner, Ph.D., suggested that the NIH study the reasons why applicants must often apply two or three times before attaining success.

An extended time between funding renewals can be critical to the livelihood of investigators and staffs. A \$250,000 grant likely involves the support of a number of persons, including nonacademics. Dr. Holbrook noted that the merit awards provide an example of the results of a more telescoped process. However, that program has not yet been evaluated.

The falloff in the number of women in science careers is a related problem. Dr. Zerhouni noted that a trans-NIH committee is currently studying ways to support women who interrupt their careers for childbearing by, for example, granting time-of-application extensions for the Pathway to Independence Award. Dr. Seidman added that physician-scientists also face funding difficulties between grants.

Dr. Zerhouni stressed that the most fundamental issue for the nation is the number of scientists. We must maintain the talent pool. There is potentially a large cost in not sustaining science at least at the rate of inflation. Dr. Yamada added that universities continue to construct new buildings, expecting that the science funds will arrive. Dr. Seidman wondered whether the National Academy of Sciences (NAS) should handle the task of determining how much science the United States needs. Related to that would be questions of the need for and value added by scientific research. Annelise E. Barron, Ph.D.,

reminded the committee members of a recent report on the projected increases in scientific investment by countries such as China and Singapore.

Dr. Wolfe raised the idea of new processes. Perhaps a junior investigator should experience one process, with much feedback, whereas a senior investigator should experience a different process—such as working in a continuous way with a single agency contact.

John C. Nelson, M.D., suggested increased transparency. For example, holding town-hall meetings in local communities, at which community members could suggest directions for the NIH.

Dr. Zerhouni asked the ACD members to consider a rebalancing within the science culture, whereby the old model of a professor and two postdocs working together for years is replaced by a professor working with 16 postdocs. What is needed to sustain such a system? What human capital is required?

Dr. Botstein stated that the “percentiling” of fields is problematic. It discourages researchers from pursuing original research and moves them into areas for which grants are more easily obtained. Many percentiles do not cross boundaries. Perhaps, suggested Dr. Zerhouni, the ACD could develop and present in the form of an official letter, a forecast analysis for national research. Dr. Yamada suggested considering new strategies, such as the use of pre-competitive collaboration to create productivity for national science.

Dr. Zerhouni noted that the NIH has begun a number of public-private partnerships through the Foundation for the NIH. These include the development of the Genetic Association Information Network (GAIN), a pre-competitive project for compiling and storing genetic information to be used by researchers, and the Biomarkers Consortium, a program to develop validated biomarkers for use in conducting research.

Dr. Zerhouni noted that the NIH has been addressing the burden of regulations (with an update presented in this meeting) and announced, in October, the first winners of the

Clinical and Translational Science Awards (CTSAs). The CTSAs will create new homes for the intellectual exercise of translating and applying clinical science. The NIH received 35 applications (institutions) for the top awards and 69 applications for planning grants. Many of the participating institutions restructured their programs to offer academic units for translational science. They combined existing resources to support the new CTSA programs. Barbara Alving, M.D., Director of the NIH's National Center for Research Resources (NCRR), reported great excitement among the CTSA awardees and a sense of a broader reach for the program—to institutions that are not awardees.

CLINICAL RESEARCH POLICY ANALYSIS AND COORDINATION PROGRAM: HARMONIZATION OF CLINICAL RESEARCH POLICY

Norka Ruiz Bravo, Ph.D., NIH Deputy Director for Extramural Research, introduced a session on ensuring research protections and harmonizing policies across diverse areas. When institutions accept NIH funding, they agree to comply with a variety of rules and regulations, as described in the *Grants Policy Statement*. The *Statement* currently features 53 requirements that each institution must meet using indirect costs. These costs comprise administrative and facilities costs (e.g., depreciation and use, operations and maintenance). Indirect cost recovery is governed by the OMB through a series of circulars that apply to different types of institutions and discuss issues such as human subjects protections, biosafety, and conflict of interest. Most of NIH's support for research falls under circular A-21, which caps indirect costs at 26 percent.

The growth of regulations contained in the *Grants Policy Statement* and governed by the OMB circulars has been driven in recent times by factors such as the Patriot Act, bioterrorism legislation, select agents legislation, and the Health Insurance Portability and Accountability Act (HIPAA). The NIH has recognized a need to harmonize the regulations across agencies and within the NIH.

In discussion, the ACD members expressed interest in specific allowable indirect costs, such as depreciation and debt service. Dr. Botstein stressed that increases in allowed indirect

costs do not help research as much as do reductions in the regulatory burden. Dr. King noted that layers of bureaucracy differ from site to site and chase investigators out of research that involves people or animals. Opportunity costs are enormous. Dr. Seidman suggested placing limitations on the length of regulatory documents. Nancy E. Adler, Ph.D., suggested applying principles of cognitive psychology to the development and presentation of regulatory materials. Dr. Wolfe noted that many regulations, in seeking to protect vulnerable groups, end up inhibiting research that would help them.

Amy P. Patterson, M.D., Director of the NIH's Office of Biotechnology Activities and the Clinical Research Policy Analysis and Coordination (CRpac) program, in the Office of Science Policy, briefed the ACD on the efforts NIH is making through the CRpac program to foster simplicity, clarity, and efficiency in clinical research policy.

Dr. Patterson described aspects of the evolving research paradigm. Clinical research projects are no longer solely local endeavors of academic medical centers. The research enterprise has expanded in scope and complexity. The requirements for conduct and oversight of clinical research have grown in a fragmented manner, and they continue to respond to features of an older local research enterprise.

The CRpac Program, which is an initiative of the NIH Roadmap for Medical Research, seeks to promote clear, effective, and coordinated policies and regulations for the conduct and oversight of clinical research and to maintain the integrity and enhance the effectiveness of federal and institutional systems of oversight. Its current priorities were identified during the implementation of the NIH Roadmap and are as follows:

- Adverse event reporting.
- Clinical trial data and safety monitoring.
- Applicability of privacy requirements and HIPAA to clinical research.
- Models of IRB review.
- Best practices in informed consent.
- Interpretation of human subjects regulations.

- Science, safety, and ethics in clinical trial design.

CRpac is developing tools and resources and building partnerships and models of interaction. It works closely with other OD offices and the ICs and fosters collaborations with other HHS and Federal agencies and Departments, particularly the regulatory agencies, the HHS Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA).

Regulations apply throughout the stages of clinical research, including clinical trial design, protocol authoring, IRB review, enrollment, specimen collection, monitoring, reporting, and analysis. A Federal Adverse Event Task Force was formed to address disharmonies in Federal requirements for adverse event reporting, which are governed by divergent federal policies that lead to confusion, non-compliance, and increased costs. The Task Force is developing a common lexicon to be used by all agencies, a best-practices blueprint for reporting and analysis, and a core adverse-event report that can be used by all principal investigators (the Basal Adverse Event Report, or BAER).

In developing the BAER, the Task Force identified about 4,000 regulatory data elements being used by the agencies. After further analysis revealed redundancies and overlaps in terms, the group was able to pare down the number of unique elements to about 300. The use of the BAER will enable a more uniform and streamlined approach to adverse event reporting, provide standards, enhance the quality and completeness of the data, and facilitate its further analysis. These improvements in reporting, most importantly, will help enhance the protection of human subjects. Following testing, the BAER system is scheduled for a phased implementation in 2007–2008.

The CRpac is also working on the issue of clinical trial design as it affects science, safety, and the ethics of research. A 2005 meeting organized by CRpac and co-sponsored by several other government agencies examined the design and conduct of randomized controlled trials that employ a “usual care” arm. The conference proceedings, which were published, provided a foundation for the development of a points to consider document to

assist investigators in considering issues related to usual care in the design and conduct of trials.

CRpac also is seeking to optimize the IRB process in light of a shifting research paradigm that now features collaboration, multi-site trials, and a need for alternative IRB structures to provide efficient and consistent reviewing. CRpac collaborated with a number of other agencies in sponsoring a recent conference that explored ideas such as responsibility shared between institutions and review boards, alternative IRBs, liability issues, and economic considerations.

Issues related to informed consent are also a high priority for CRpac and efforts are underway to develop resources to assist investigators in carrying out this fundamental ethical principle of research with human subjects. For example, a guidance on informed consent in human gene transfer research was developed (see <http://www4.od.nih.gov/oba/rac/ic>).

Another CRpac high priority effort is underway to reduce disharmony in policies guiding the use of research specimens and data repositories. CRpac is leading deliberative groups within NIH and across HHS in this area.

Further information about the CRpac program is available at: <http://crpac.od.nih.gov>.

Discussion

Dr. Adler suggested considering different regulatory pathways for observational and epidemiological research. Dr. Seidman cited a need to consider the regulations for biosamples from overseas research. The ACD members suggested that the CRpac include both community members and pharmaceutical industry representatives in its discussions about regulations. Dr. Botstein expressed pessimism about the ability of the CRpac's work to reduce costs to universities, citing the fact that many institutions go beyond regulatory requirements (e.g., in requiring IRB review of research involving anonymized samples (a

category of research that is not considered by OHRP to be human subjects research). Even when further consent is not required, institutions tend to pursue consent to be safe, and this is a burden. Dr. Seidman proposed establishing a fixed expiration date for protocols of 1 year from initiation.

Dr. Nelson asked if there has been an accounting of regulatory costs to clinical research. Dr. Zerhouni remarked that this question has come up repeatedly. One discussion led to a project called the New Research Business Model. Along with the Federal Demonstration Project, the project will pilot new approaches. The NIH's clinical research enterprise needs new legal expertise and advice to differentiate risks and benefits. As an example, new legal thinking was applied to recombinant DNA research 30 years ago. Dr. King suggested that new strategies for disseminating information to the universities would help clarify regulatory requirements. The culture of IRBs needs to change if unnecessary requirements are to be addressed.

Dr. Zerhouni summarized by stating the need to continue the effort toward efficiency, the need to think through how regulatory changes might be made operational at institutions, and the need to challenge current assumptions to promote new legal ideas and frameworks.

GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Elizabeth G. Nabel, M.D., Director of the National Heart, Lung, and Blood Institute (NHLBI), presented a proposed NIH policy for data sharing in NIH-supported genome-wide association studies. A genome-wide association study is defined as:

A study of genetic variation across the human genome that is designed to identify genetic associations with observable traits, such as blood pressure or weight, or the presence or absence of a disease or condition.

The GWAS will generate large amounts of genotypic data, which will be brought together with phenotypic data from large-cohort studies. Related efforts include the GAIN, supported by the National Human Genome Research Institute (NHGRI) and the Foundation for the NIH, and the NHLBI's genome-wide association studies within the Framingham Heart Study. Because of the programs being developed, NIH officers recognized a need to act prospectively to provide leadership in developing policies for data sharing. The greatest public benefit will be achieved by making the data sets available to researchers throughout the country. The researchers can then engage in hypothesis-driven or discovery science.

In April, the NIH formed a committee to develop a data-sharing policy, based on the following rationale:

- The NIH is the steward of the American public's investment in global health.
- Information that is not shared represents a lost opportunity to improve the health of the public.
- The NIH has been encouraging wide sharing of information for several years.

The committee developed policy in three areas—data management, scientific publishing, and intellectual property. The NIH has funded large prospective cohort studies that have produced vast amounts of phenotypic data, which now can be married to new genotypic studies. The NIH will ask investigators to make genotypic and phenotypic information available to a central repository managed by the National Center for Biotechnology Information (NCBI). The investigators will also submit protocols, questionnaires, variables, and other materials of their research.

Local IRB approval will be obtained prior to the submission of information to the repository. The investigators will be asked to provide an institutional statement ensuring that the data are in accordance with any applicable laws and regulations. Any limitations on use of the submitted data must be requested at the time of submission/application. The Office of Human Research Protection has provided guidance that the central repository itself will not be engaging in human subjects research.

Identifiers are removed and arbitrary codes for participants are applied by the investigators before the data is submitted to the repository. The repository will not have access to the key or to the codes. The NIH will develop standing committees (perhaps within the ICs) to oversee the process of allowing access to the data in the repository. An investigator wishing to access and use data will submit an application to a data access committee, describing the research project for which the data will be used. If the application is approved, the investigator will sign an agreement ensuring proper use (publication timing, confidentiality, local policies and procedures, etc.). The investigator will submit annual progress reports.

The OHRP has determined that secondary research using the data will not be considered human subjects research and use of the data sets will not require IRB approval. Investigators will be responsible for complying with policies such as HIPAA regulations and local institutional review.

In a proposed model for publishing, a clock is set when submitted data becomes public in the repository. The data will be available to all persons immediately, but for 9 months, only the investigators who submitted the data will be allowed to submit abstracts and manuscripts for publication. All future publications using the data will be required to acknowledge the primary investigators and funding organizations. NCBI may compute associations for some studies as appropriate, and make them available with the controlled data download.

Dr. Nabel provided a timeline. The development program currently is in a public consultation phase. A town hall meeting to obtain public comment will take place on December 14. The final policy will be developed during January and February 2007. The policy will be released in March-April 2007. Information is available at the NIH Web site.

James Ostell, Ph.D., Chief of the Information Engineering Branch, NCBI, presented screen shots and demonstrated use of the NCBI database being developed. It is named dbGaP, for database genotype and phenotype. Dr. Ostell explained that a number of sources (GAIN,

Framingham) have been depositing information in the database, including control sets from outside organizations.

The database has two faces—a readily accessed area, for general browsing and exploring clinical studies, and a controlled access area for downloading data sets. Browsers will be able to search by disease and observe study summaries, substudies, variables, histories, and bibliographies. The database will offer documents, such as questionnaires, for each study. Attributes within studies will be given accession numbers, allowing them to be cited in a controlled way. Dr. Ostell gave an example of the readout of a set of single nucleotide polymorphisms (SNPs), showing, by color, those most highly correlated to a disease. Clicking on a color brings up a list of only the most highly correlated SNPs. Clicking on an SNP brings up a list of base pairs.

Although phenotypes and genotypes can be measured in different ways (e.g., different population stratifications) by the source studies, experts have determined that the information, as collected, will be comparable.

Discussion

Dr. Botstein suggested a slightly different scenario in which, when the primary investigators publish quickly (e.g., in 1 month), the 9-month publishing ban for others is suspended. The ACD members wondered how the NCBI will accomplish the computing of associations for the data. Francis Collins, M.D., Ph.D., Director of the NHGRI, explained that this process has yet to be determined and will include input from the investigators. The ACD members expressed concern about a possible lag time if the NCBI has difficulty determining the associations—this could affect the investigators' ability to publish in a timely fashion. Dr. Botstein encouraged the committee to consider eliminating the 9-month moratorium on publishing by other researchers. Dr. Nabel stated that the NIH is planning for a data-cleaning period of only 4 to 6 weeks.

Dr. King emphasized that use of the control data sets will be very valuable. It will be important to include some information about the control sets (e.g., age at exam, sex, ancestry). The program will include representative minority populations in the data. Dr. Collins noted that the Genes and Environment Initiative, in particular, will have a focus on health disparities.

Dr. Seidman encouraged the NIH to make the policies for the GWAS identical to the policies for the GAIN. Dr. Collins stated that such is the intention.

Dr. Leshner asked about the cost of the project. Dr. Ostell responded that many of the processes are automatic and productivity should increase as some manual processes speed up. Dr. Zerhouni added that a trans-NIH NCBI Resource Board has been created to model the long-term resource requirements for the system. Dr. Botstein proposed that the NCBI Web site present the data in such a way that the initial information and computations are distinguishable from later computations. Dr. King stressed a need to provide ancestry for the data and to ensure their value as control data. Dr. Wolfe proposed creating a uniform set of questions to be used generally by researchers to address variables.

ELECTRONIC RESEARCH ADMINISTRATION

Dr. Ruiz Bravo described progress in the development and application of the electronic submission system for NIH grants. By the end of 2007, the NIH will require electronic submission through **Grants.gov** for all NIH applications and will complete transition from the PHS 398 application form to the SF424, a form set used by many federal research agencies. The transition to an all-electronic system is part of a broad mandate from the OMB.

The new process requires the downloading of an application package, preparation of the application, submission to Grants.gov, and checking of the submission in the eRA Commons site. The PI prepares the application and forwards it to an authorized organization

representative (AOR) at the institution, who submits it to Grants.gov after which both the PI and AOR have the opportunity to view their application in the Commons site.

Applications must be submitted to Grants.gov by 5:00 p.m. (applicant's local time) on the receipt deadline date. Errors and warnings must be addressed within 5 business days. Dr. Ruiz Bravo presented a timeline showing grant mechanisms that have already shifted to the electronic process and those that will shift during the next 10 months, completing the process. More than 18,000 electronic applications have been received so far. Thousands of investigators, administrators, and NIH staff members have been trained. Thousands of PIs and institutions have registered in the eRA Commons. The quality of the applications received has been improving (fewer errors) and text of system messages have also been improved. The NIH expects to receive between 4,500 and 5,000 unique electronic application submissions in the 2 weeks surrounding February 5, 2007.

The NIH has been working with the Federal Demonstration Partnership and outside organizations to facilitate the program. The electronic receipt deadline for R01s was moved from October 2006 to February 2007 at the request of the applicant community. Parent announcements were developed for investigator-initiated, unsolicited research.

The research community has expressed concerns, including the following:

- System problems might result in late applications.
- Error checking performed in two stages could keep an application from being accepted.
- Mac system users will be unable to submit applications in the software provided.
- Help desks will be unable to handle the volume of calls.
- Applicants might be unable to print or view assembled applications before submission.
- The NIH might require too many attachments for the research plan.
- There might be problems using the software form.

NIH has addressed many of these concerns. The NIH has established procedures (through the eRA help desk) to ensure that applicants who experience system problems are not penalized for lateness. If Grants.gov has downtime near a receipt date, the deadline will be extended. Mac system users will be able to submit applications using new Pure Edge software released in December, Citrix servers, PC emulation software, and commercial service providers. The NIH plans to shift to the Adobe forms being developed by Grants.gov, which are platform independent, in the near future (during 2007).

The inability to print or view the submitted application is a limitation of the Grants.gov form-viewer software. Therefore, the NIH allows the AOR to view the application in the Commons after submission. During a 2-day window, the applicant can reject the version and submit a corrected application. Dr. Ruiz Bravo noted that the request for multiple attachments for the research plan serves to provide bookmarks for reviewers and to allow systems to check for required information.

The applicant community has provided some positive feedback, noting that the resolution of the electronic images is better than that of the scanned paper applications and that the automated headers, footers, pagination, and tables of contents are helpful. Many institutions have expressed an appreciation for having Grants.gov as a single point of submission to all federal agencies.

During the past year, the NIH has performed significant outreach to announce the shift to an all-electronic system, featuring E-mail announcements, press releases, electronic subscriber-based communications, and presentations at meetings. It has included eSubmission looking-ahead notices on summary statements and NIH extramural staff signature lines. Information is available at the eSubmission Web site: <http://era.nih.gov/electronicreceipt/index.htm>.

The NIH has advertised the R01 transition with guide notices, press releases, newsletter articles, presentations and booths at scientific and administrative meetings and E-mail distribution. Applicants can also learn about the electronic submission requirement through funding opportunity announcements (FOAs), the application guide, NIH Web site pages,

and summary statements. Dr. Ruiz Bravo announced training events in December and regional seminars in Utah and North Carolina in April. The NIH Web site offers a variety of training resources.

Discussion

The ACD members expressed concern about the time constraints of the new electronic process and the inability of the PI to control the submission. Near a receipt deadline, the AOR at an institution potentially will experience a bottleneck. There likely will be a large error rate for naïve users. As a result, applicants could be penalized. In particular, the PIs will lose control of exactly when the application is submitted to the NIH. Dr. Botstein proposed creating a system whereby a backup copy of an application, in PDF form, is submitted simultaneously to a repository, and its date of submission established.

Megan Columbus, the NIH Program Manager for Electronic Submission of Grant Applications, described the process once the AOR submits an application to Grants.gov. When Grants.gov receives the application from the AOR, the Grants.gov sends an e-mail within minutes stating that the application has been received. Grants.gov then can take from several minutes to two days to process the application, which triggers another message to the AOR that the application has been validated, another that the application is ready for agency retrieval, and yet another that the agency has retrieved the application. Once NIH retrieves the application, messages are sent to both the PI and the AOR informing them of the status of the application.

The ACD members expressed concern about the earlier processes. They cited a need for the PI and AOR to confer and resolve problems before the official submission. Dr. Barron stated that a PI would prefer to be the person able to have the final look at an application before hitting the “send” button. Also, noted Dr. King, the PI needs to know that the formatting of the application will not be altered in the process.

Dr. Seidman cited a need for better communication with the institutions, advising them about the potential time needed to assemble an application. In particular, those that use a Mac system may experience great complexity.

Dr. Ruiz Bravo summarized the ACD's concerns:

- Creating PDF files from a Mac system.
- Advising institutions on the length of time that applications will require.
- Clarifying that the time stamp of Grants.gov is the date of receipt.

Dr. Zerhouni proposed creating a user's group of ACD members who are very concerned. Drs. Barron, Botstein, King, and Seidman volunteered to serve. Dr. Ruiz Bravo stated that she will follow up with them regarding plans to resolve these potential problems.

Dr. Adler again raised the issue of waste associated with the large number of applications that are unsuccessful on the first attempt. Dr. King responded with a suggestion that the science be reviewed alone first, then, for those projects found to be in a competitive range, the Grants.gov process be used with a full application. The ACD members discussed pros and cons of this proposal. Dr. Zerhouni noted that such ideas are being discussed by the Peer Review Advisory Committee.

Dr. Seidman proposed that the next ACD meeting feature a presentation and discussion of the peer review process.

NIH DIRECTOR'S COUNCIL OF PUBLIC REPRESENTATIVES LIAISON REPORT

Wendy Chaite, J.D., a member of the NIH Director's Council of Public Representatives (COPR) and the COPR Liaison to the ACD, reviewed themes from the recent COPR meeting in November. She noted that the COPR discussions and recommendations

incorporate COPR's sensitivity to the fiscal environment the research community and the NIH is currently facing.

The mission of COPR is to bring matters of public interest to the attention of the NIH leadership and as NIH ambassadors, to disseminate NIH information amongst public constituents. COPR members have made many contributions since the inception of the Council eight years ago, including among other things, evaluating materials for the NIH Plain Language Award Program; and providing input for the NIH Strategic Communications Plan and NIH Public Trust Initiative. Most recently, at the urging of COPR, Dr. Zerhouni added a fourth "P" representing "Participatory" to NIH's 4P's messaging campaign for defining medical research for the future.

The November COPR meeting featured presentations by experts regarding the important issue of engaging members of the public, where appropriate, throughout the research continuum. The COPR members requested information on current NIH-funded research that involves public participation and/or community engagement to determine the state of the science. In addition, COPR discussed the need for NIH and others within the research enterprise (academia, etc.) to develop and implement strategies to improve the competencies of researchers to work with the public. For example, it was suggested that the NIH, with COPR input, develop tools for researchers to use that could help them in engaging the public in the research process. Other ideas include NIH creating an awards program and fostering the development of evidence-based science regarding the value of public participation (i.e., the science of public participation). COPR noted that in appropriate circumstances, public participation in the NIH grant process, especially initial phases such as concept design may be of particular value. Greater public trust and awareness could potentially translate to greater recognition and support of research as a higher national priority.

Ms. Chaite encouraged the ACD members to take part in the next COPR work session and public meeting to be held April 19-20, 2007. Ms. Chaite described the wide range of professions and experiences represented on the COPR and noted that current funding mechanisms do not sufficiently promote community participation. The recent effort to

potentially allow voluntary health organizations to support meritorious research applications that are unfunded by the NIH is one avenue that could foster increased community involvement. Dr. Ruiz Bravo reported that a working group is exploring the concept and is currently in discussion with the NIH Foundation staff regarding potential implementation strategies.

The ACD members can nominate persons to serve on the COPR; December 15 is the deadline for submitting applications. In response to a suggestion to increase media representation on COPR and other advisory councils, Raynard Kington, M.D., Ph.D., ACD Executive Secretary, noted recent and ongoing outreach efforts by the NIH to improve media presentation of scientific issues, and efforts to include public members, such as media representatives, on advisory boards.

Discussion

Dr. Barron, the ACD Liaison to COPR, stated that she has been struck by the dynamics of COPR. She commented that to a certain degree, the fate of the NIH rests in part on the public's perception of its value and responsiveness. COPR can help scientists to better understand ways to improve that perception. Dr. Barron too encouraged the ACD members to become involved in the work of COPR.

Dr. Alan Leshner expressed an appreciation for the COPR's efforts to involve the public and to change the dialogue between science and the public, as opposed to simply educating the public about science.

For the record, Ms. Chaite asked that the issue of human protection rights be considered in relation to the newly created Genome-Wide Association Studies (GWAS), which was presented to the ACD by Dr. Elizabeth Nabel who leads that GWAS initiative.

INSTITUTE DIRECTOR'S REPORT: FOGARTY INTERNATIONAL CENTER

Roger I. Glass, M.D., Ph.D., Director of the Fogarty International Center (FIC), presented the following mission for the Center: To address global health challenges through innovative and collaborative programs for research and training and to support and advance the NIH mission through global partnerships. The Institute is named after Congressman John E. Fogarty. The FIC seeks to:

- Train the next generation of medical researchers (U.S. and foreign) in foreign health.
- Build centers of research excellence abroad through collaborations and partnerships.
- Rebuild international relations through health.
- Reduce health disparities and inequalities.
- Increase America's involvement in global health.
- Provide scientific leadership in issues of global health.

The Fogarty Center budget consumes about one-quarter of 1 percent of the NIH budget. Its research represents about 10 percent of the international research activities of the NIH. Fogarty-supported programs are found in more than 100 countries, with more than 60 U.S. institutions involved in partnerships.

The FIC has supported the AIDS International Training and Research Program (AITRP) since 1988, and today, many of the leaders of AIDS research programs in Africa began their work with AITRP. The FIC's Framework Program, a small-grant initiative begun recently, brings together persons from U.S. universities to address global health. The Fogarty-Ellison Scholars are medical students/fellows who are sent in pairs to medical centers in the developing world and who return with great experience and energy.

The Disease Control Priorities Project is a new collaboration of the FIC, the World Bank, the World Health Organization, the Bill and Melinda Gates Foundation, and the Population Reference Bureau. Its goal is to assess priorities and determine whether the world can tackle its most challenging health problems. A review by the project revealed an increasing lifespan throughout the world. It developed a list of "best buys" for health that includes preventing neonatal mortality, ensuring healthier mothers and children, promoting good

nutrition, reducing deaths from cardiovascular disease, and stopping the AIDS pandemic. Dr. Glass has been meeting with the other NIH directors to discuss ways in which the ICs can better invest in global health.

One legacy of President Bush's administration likely will be its massive investment in a few key health programs. These include the President's Emergency Program for AIDS Research (PEPFAR, \$15 billion over 5 years) and the President's Malaria Initiative (PMI, \$1.2 billion over 5 years). In addition, the administration has put resources into planning for a possible global avian flu epidemic. The FIC can help these programs evaluate impact and make the best use of funds. The NIH is involved in collaborative research agreements with India and has partnerships in Iran, Syria, Israel, and Yemen.

In the future, many of the people staffing large global health programs overseas will come from FIC programs. Potential partners for the FIC include U.S. government agencies, the private sector, foundations, universities and medical research groups, international health organizations, developing world medical research councils, and the ICs at the NIH. Finally, the FIC has been bringing experts to the NIH campus to make presentations about global health—for example, Barry R. Bloom, Ph.D., Dean of the Harvard School of Public Health.

There are many cases of the health of Americans benefiting from advances through collaborative international research. Dr. Glass stated that political concern, new economic understanding, broader funding, scientific advances, and global consciousness are acting in concert to enable improvements in the health of underserved populations. We need to seize this opportunity and build on the momentum.

Discussion

Dr. Leshner encouraged the FIC to develop priorities, perform capacity building, and develop an overarching strategy that can help to focus energies. Dr. Glass stated that the FIC is developing a new strategic plan. It is continuing to meet with leaders in global health to identify directions and strategies.

Dr. Nelson suggested that the FIC consider working with the World Medical Association. Dr. Seidman encouraged the FIC to foster international research that benefits all, including Americans (and including cost benefits). By focusing in that way, the FIC will receive strong engagement from the U.S. community.

Dr. Botstein encouraged the FIC to support research on new genes that cause specific diseases. Such research, using consanguineous families, is often best performed in global settings. Dr. Adler urged the FIC to partner with work in the United States on health disparities, to allow international work to inform domestic work.

WORK GROUP REPORT ON OUTSIDE AWARDS FOR NIH EMPLOYEES

Dr. Kington reported on progress in the effort to create a list of bona fide prescreened awards that NIH scientists and employees may receive. Each award was vetted by NIH staff attorneys and at least one member of the ACD.

Dr. Kington presented the latest list of vetted awards (incorporated in the meeting binder) and asked the ACD members to approve it. The ACD members moved, seconded, and approved the list of prescreened awards. Dr. Kington stated that he would obtain the votes of the ACD members who were absent from the meeting.

FINAL DISCUSSION

Dr. Nelson reminded the group of the proposal to calculate the financial cost of the research regulatory burden. He proposed creation of a working group to study the topic and perform the calculations. Dr. Ruiz Bravo welcomed the participation of the ACD in ongoing efforts of the Office of Extramural Research to perform such calculations. She volunteered to make available to the ACD a summary of recent reports on regulatory costs. Dr. Botstein suggested that the calculations include the costs of IRBs, AORs, and other activities.

Dr. Barron noted that this was Ms. Chaite's final ACD meeting, her term with the COPR having expired. Drs. Barron and Zerhouni thanked Ms. Chaite for her service to the committees.

ADJOURNMENT

Dr. Zerhouni reminded ACD members that the topic of peer review will be on the agenda of the next meeting. He thanked them for their input and adjourned the meeting.

SUMMARY AND CONCLUSIONS

The Advisory Committee to the Director of the National Institutes of Health convened on December 1, 2006, to receive updates on the FY 2007 NIH budget and appropriations process, to learn about ongoing efforts to harmonize clinical research policies, to learn about the new database program for genome-wide association studies and progress in the development of a fully electronic grant application process, to receive a report on the recent meeting of the Director's Council of Public Representatives, to hear about the activities of the Fogarty International Center, and to vote on the most recent list of bona fide prescreened awards that NIH scientists and staff members may receive, as compiled by the ACD's Work Group on Outside Awards for NIH Employees.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

Raynard S. Kington, M.D., Ph.D.
Executive Secretary, Advisory Committee to the Director
Deputy Director, NIH

Elias A. Zerhouni, M.D.
Chairman, Advisory Committee to the Director
Director, NIH

LIST OF ABBREVIATIONS AND ACRONYMS

ACD	Advisory Committee to the Director
AITRP	AIDS International Training and Research Program
AOR	Authorized Organization Representative
COPR	Council of Public Representatives
CRpac	Clinical Research Policy Analysis and Coordination Program
CSR	Center for Scientific Review
CTSA	Clinical and Translational Science Award
FDA	Food and Drug Administration
FIC	Fogarty International Center
FOA	Funding Opportunity Announcement
FY	fiscal year
GAIN	Genetic Association Information Network
GWAS	Genome-wide association studies
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICs	(NIH) Institutes and Centers
IRB	Institutional Review Board
NAS	National Academy of Sciences
NCBI	National Center for Biotechnology Information
NCRR	National Center for Research Resources
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NSF	National Science Foundation
OHRP	Office for Human Research Protections
OMB	Office of Management and Budget
PEPFAR	President's Emergency Program for AIDS Research
PI	principal investigator
SNP	single nucleotide polymorphism