



National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

September 16, 2009

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL ARTHRITIS AND MUSCULOSKELETAL
AND SKIN DISEASES ADVISORY COUNCIL**

MINUTES OF THE 69th MEETING

**September 16, 2009
8:30 a.m. to 2:30 p.m.**

I. CALL TO ORDER

The 69th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on September 16, 2009, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting was chaired by Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Attendance

Council members present:

Mr. George Beach
Dr. S. Wright Caughman
Ms. Carmen Cheveres
Dr. Leslie Crofford
Dr. Betty Diamond
Ms. Patricia McCabe Estrada
Ms. Karen Evans
Dr. B. Lee Green
Dr. Kathleen Green
Dr. Linda Griffith
Dr. Joshua Jacobs
Dr. John H. Klippel
Dr. Henry Kronenberg
Ms. Ann Kunkel
Dr. Clifford J. Rosen
Dr. H. Lee Sweeney
Dr. James Weinstein

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Dr. Carl Baker
Dr. Michael Bloom
Dr. Amanda Boyce
Mr. Gahan Breithaupt
Dr. Eric Brown
Dr. Branden Brough
Ms. Justine Buschman
Dr. Robert Carter
Dr. Faye Chen
Mr. Ricardo Cibotti
Ms. Barbara Cohn
Ms. Stephanie Craver
Ms. Wilma Peterman Cross
Dr. Jonelle Drugan
Mr. Patrick Durand
Ms. Sharon Fair
Ms. Barbara Footer
Ms. Valerie Green
Dr. Shanil Haugen
Mr. Andrew Jones
Dr. Daniel Kastner
Dr. Stephen Katz
Ms. Shahnaz Khan
Dr. Gayle Lester
Dr. Helen Lin
Ms. Anita Linde
Dr. Kan Ma
Dr. Marie Mancini
Dr. Kathryn Marron
Dr. Joan McGowan
Ms. Jackie Nelson
Ms. Melinda Nelson
Ms. Anna Nicholson
Dr. Glen Nuckolls
Dr. James Panagis
Dr. Charles Rafferty
Ms. Trish Reynolds
Dr. Louise Rosenbaum
Ms. Karin Rudolph
Dr. Susana Serrate-Sztejn

Dr. William Sharrock
Ms. Theresa Smith
Ms. Allisen Stewart
Ms. Robyn Strachan
Mr. Phil Tonkins
Mr. Hung Tseng
Dr. Bernadette Tyree
Ms. Marcia Vital
Dr. Fei Wang
Dr. Xibin Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Ms. Sara Wilson
Dr. James Witter

Guests

Ms. Jennifer Blacker, IQ Solutions, Inc.
Mr. Michael Bykowski, Consolidated Solutions and Innovations
Dr. Alison Davis, National Institute of General Medical Sciences, NIH
Dr. Howard Dickler, National Heart, Lung, and Blood Institute, NIH
Ms. Tanya Dougans, National Heart, Lung, and Blood Institute, NIH
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Ms. Karen Evans, Lupus Foundation of America
Ms. Amanda Grimm, American Academy of Dermatology
Ms. Patricia Hansberger, Office of the Director, NIH
Dr. John Holden, Center for Scientific Review, NIH
Ms. Kim Holmes, IQ Solutions, Inc.
Ms. Kristin McNamara, Center for Scientific Review, NIH
Ms. Amy Melnick, Arthritis Foundation
Ms. Michelle Rodrigues, SRI International
Dr. Antonio Scarpa, Center for Scientific Review, NIH

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept with no changes the minutes of the 68th Council meeting, held on June 2, 2009.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

February 2, 2010
June 15, 2010

September 28, 2010
February 1, 2011
June 14, 2011
September 27, 2011

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He invited attendees to review the NIAMS ShortTakes online, which include more details on many of the topics covered in his report. He noted that his "Director's Column" urges the Institute to keep the community informed on progress made with funds from the American Recovery and Reinvestment Act (ARRA). Dr. Katz emphasized the Institute's gratitude for the opportunity to participate in ARRA-related activities, which allows NIAMS to help the nation's economy while making significant contributions to scientific research. As ARRA funds are disbursed, NIAMS needs input from Council members and their colleagues on "success stories" highlighting how scientists and institutions are using this money to create or preserve jobs. Council members were encouraged to submit this type of information to NIAMS staff, even if it is anecdotal information.

Dr. Katz acknowledged and thanked four outgoing Council members: Ms. Carmen Cheveres, a patient advocate; Dr. Lee Green, Executive Director of the Office of Institutional Diversity and Research as well as Professor of Health Outcomes and Behavior at the H. Lee Moffitt Cancer and Research Institute; Dr. Joshua Jacobs, an orthopaedic surgeon at Rush University Medical Center; and Ms. Patricia McCabe, a patient advocate. All four have brought important perspectives and made contributions to the Council.

Dr. Katz also congratulated Dr. John O'Shea, Scientific Director and Chief of the Molecular Immunology and Inflammation Branch in the Intramural Research Program of the NIAMS, who will receive the prestigious Lee C. Howley Sr. Prize for Research in Arthritis in November.

Personnel Changes at the NIH/NIAMS

Dr. Katz reported that Dr. Regina Benjamin has been identified as the next U.S. Surgeon General. Dr. Francis Collins, former Director of the National Human Genome Research Institute, has been named as the new NIH Director—Dr. Collins will be invited to the next Council meeting.

With regard to the NIAMS Extramural Program, Dr. Faye Chen has been named a Program Director in the Division of Musculoskeletal Diseases. Dr. Chen previously was in the NIAMS Intramural Research Program's Cartilage Biology and Orthopaedics Branch. The Institute welcomes Dr. Xibin Wang, another new member of the Division of Musculoskeletal Diseases. Dr. Wang also had been working in NIAMS' Cartilage Biology and Orthopaedics Branch. Dr. Ricardo Cibotti has joined the NIAMS as the Director of the Skin Diseases Program in the extramural Division of Skin and Rheumatic Diseases. Dr. Cibotti comes to NIAMS after 6 years at MedImmune in Gaithersburg, MD.

Update on Budget and Congressional Activities

Dr. Katz presented a slide highlighting the status of NIH's fiscal year (FY) 2010 budget and comparing the House bill, the Senate bill, and the President's Budget. On July 24, the House passed H.R. 3293, the FY 2010 appropriations bill that includes the NIH. The bill would provide NIH with \$31.3 billion, which is \$500 million more than the President's request and \$942 million above the comparable amount the NIH received for FY 2009. The bill's allocation for the NIAMS is \$543.6 million, which is an increase of approximately \$19 million, or 3.6 percent, over FY 2009.

The Senate's companion bill was reported from the Committee and is awaiting floor action. This version provides \$30.8 billion for the NIH, which is equivalent to the President's request and \$442 million above the comparable FY 2009 level. The Senate is proposing \$533.8 million for the NIAMS—an increase of approximately \$9 million, or 1.7 percent, over FY 2009.

Once the Senate passes its bill, a Conference Committee, made up of members of both Chambers, will reconcile the differences between the bills. If a final bill is not passed and signed by October 1, the Congress is likely to enact a continuing resolution.

With regard to other Congressional activities, Dr. Katz explained that several bills to reauthorize the Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) programs are at various stages of the legislative process. Currently, the SBIR and STTR programs represent 2.5 percent and 0.3 percent of the NIH's extramural budget, respectively. Some of the bills would increase those amounts to 3.0 and 0.6 percent.

In the area of orthopaedics, Dr. Katz noted that before the Senate adjourned for its August recess, Senator Ben Cardin (D-MD), introduced a companion bill to the House version of Access to America's Orthopaedic Services Act of 2009. The bill, which was referred to the Senate Committee on Health, Education, Labor and Pensions, would require the Department of Health and Human Services to: (1) establish criteria for accounting and reporting the percent of effort expended by researchers funded by NIH or the Agency for Healthcare Research and Quality (AHRQ) on musculoskeletal health; (2) report on the number of new investigators who receive grants for musculoskeletal health research and make recommendations regarding additional resources that NIH or other entities could use to increase the number of new investigators; (3) study the cost-effectiveness of all available methods for measuring bone mass in Medicare beneficiaries; and (4) conduct a third longitudinal study on aging in the United States.

In the House, Representative Bill Pascrell, Jr. (D-NJ), introduced the Knee and Hip Replacement Act of 2009. The bill would require the AHRQ to establish a national knee and hip replacement registry to identify predictors that may lead to poor outcomes in knee and hip replacement surgeries. The Centers for Medicare and Medicaid Services (CMS) would establish policies and procedures to develop and maintain the registry, and would coordinate with AHRQ, NIH, and the Office of the Secretary to avoid duplication of efforts.

With regard to scleroderma, Senator Kirsten Gillibrand (D-NY), introduced a companion bill to the House version of the Scleroderma Research and Awareness Act. Among other provisions, the bill would require: (1) the NIAMS to expand, intensify, and coordinate the activities of the Institute with regarding scleroderma; and (2) inclusion of the status of scleroderma research in the *NIH Biennial Report*.

Highlights of Selected Recent Scientific Advances

- Drs. James Ervasti and Evelyn Ralston have shown that dystrophin (a key protein that is lacking in Duchenne muscular dystrophy patients) directly interacts with microtubules via their constituent tubulin molecules. The NIAMS extramural researchers and intramural scientists collaborated to verify the physical and functional links between dystrophin and microtubules. This work shows that dystrophin contributes to the proper organization of cellular components; furthermore, the defective cellular organization that results when dystrophin is absent may contribute to muscle damage in Duchenne muscular dystrophy (*J Cell Biol.* 2009; 186, 363-9).
- In a multi-institution effort that involves collaborations between NIAMS-supported extramural and intramural scientists as well as Canadian investigators, Drs. Peter Gregersen, Daniel Kastner, and colleagues have done new work that builds on the existing North American Rheumatoid Arthritis Consortium (NARAC). The initial genome-wide association analysis and an independent replication study identified two novel single nucleotide polymorphisms (SNPs) at a gene region with significant association with RA, and confirmed association of two other previously identified loci. The identification of this new risk locus for RA provides new insights into critical pathways that contribute to disease pathogenesis (*Nat Genet.* 2009 Jul; 41(7):820-3. Epub 2009 Jun 7).
- NIAMS-supported extramural researchers joined scientists in the NIAMS intramural program to evaluate the x-rays of nearly 400 patients with ankylosing spondylitis (AS) for more than 20 years (to allow sufficient time for x-ray changes to occur). Data from the work of Drs. Michael Ward and Michael Weisman and colleagues suggest that other markers besides B27 are associated with long-term, severe changes in the spines of patients with AS. Furthermore, while certain non-modifiable clinical characteristics, such as gender, are strongly associated with more severe disease, other factors, such as smoking, can be addressed, which could impact the radiographic consequences of this disease. This information may help newly-diagnosed AS patients to understand the potential clinical course of their illness, and contribute to the development of therapeutic strategies for AS treatment or prevention (*Arthritis Rheum.* 2009 Jul 15;61(7):859-66).

- Council members were provided with an article published in *Nature Biotechnology* that features NIAMS Scientific Director Dr. John O’Shea. The article, which focuses on regulatory T cells and Th17—or T helper 17—cells in autoimmune disease, provides an overview of some of the challenges that immunologists are tackling as they explore the cells that contribute to the immune response. Council members also were provided with an article from *Nature Reviews Rheumatology* on the role of cytokines in the pathogenesis of rheumatoid arthritis, which also includes comments from Dr. O’Shea.
- Using a lupus-prone mouse model, Dr. Dwight Kono and colleagues mutated a gene that interfered with correct functioning of toll-like receptors on endosomes (eTLR). This alteration abolished production of autoantibodies against nucleic acids and reduced disease in the lupus mice, but they retained their ability to mount normal antibody responses to foreign proteins. These studies show that signaling by eTLRs are critical for the production of autoantibodies in lupus, but maybe not for normal immune responses (*Proc Natl Acad Sci USA*. 2009 Jul 21;106(29):12061-6. Epub 2009 Jul 2).
- Dr. Zhou-Feng Chen and colleagues have identified the protein gastrin-releasing peptide receptor, or GRPR, as an itch-specific molecule in the spinal cord in a mouse model. When the GRPR neurons were eliminated in the mice, the mice did not show scratching behavior in response to a number of different itch stimuli, such as the anti-malarial drug, chloroquine, but they were still able to react to pain sensations. Hence, treatments that target GRPR may provide much needed itch relief to patients, while retaining the protective, functional sensation of pain (*Science*, 2009 Aug 6, [Epub ahead of print]).
- Dr. X. Cao and colleagues recently published a *Nature Medicine* paper demonstrating that activated TGF- β 1 is the critical molecule linking bone resorption with bone formation in the vicinity of resorbed bone. The recognition of TGF-beta as a key regulatory molecule linking these phenomena opens the door for new therapeutic strategies, as TGF- β 1 and its associated signals are targeted by existing drugs, such as the ACE-inhibitors commonly prescribed for people who have high blood pressure. The ubiquitous nature and the complex effects of TGF- β 1, however, also emphasize the importance of finding ways to deliver the potential drugs to the appropriate location only (*Nat Med*. 2009 Jul;15(7):757-65. Epub 2009 Jul 5).
- In a recent paper by Dr. Sundeep Khosla, researchers reported an inverse association of serum serotonin levels and multiple measures of bone density and bone mass in a population-based cohort of 275 adult women. This study verifies the association of serotonin with bone mass in women, and indicates that serotonin can serve as a marker for low bone mass. It also suggests that research on the serotonin synthesis/metabolism pathways is needed to develop therapies that selectively target serotonin’s effects on bone without affecting the central nervous system (*Bone Miner Res*. 2009 Jul 13. [Epub ahead of print]).
- Last month, the *New England Journal of Medicine* published two studies—one of which was supported by the NIAMS—that could change the way surgeons think about vertebroplasty as a treatment for people who have vertebral compression fractures. As Council member Dr. James Weinstein illustrated in an accompanying editorial, rates of vertebroplasty vary greatly across geographic areas. Many physicians and patients claim that surgery reduces pain when

other treatments have failed. The latest papers were based on placebo-controlled trials where all patients received anesthesia and witnessed the cement mix being prepared; regardless of whether patients actually received the cement injections, however, they reported faring significantly better after the procedure (*N Engl J Med.* 2009 Aug 6;361(6):569-79 and *N Engl J Med.* 2009 Aug 6;361(6):557-68).

- Dr. Elena Losina and colleagues developed a mathematical model to simulate the various outcomes of end-stage knee osteoarthritis in a Medicare population, and showed that total knee replacement, on average, was considered cost effective at \$18,300 per quality-adjusted year of life. Hospitals with greater case loads of total knee replacements are associated with better outcomes for patients. The latest paper considered the effect of hospital volume, and demonstrated that surgeries at higher-volume hospitals are more cost-effective as well. The model showed that early intervention also is important, as the procedure is most cost-effective when people have the surgery shortly after their arthritis progresses to the extent where knee arthroplasty is warranted (*Arch Intern Med.* 2009 Jun 22;169(12):1113-21; discussion 1121-2).

NIH/NIAMS Activities and Plans for the Future

Dr. Katz reported that at the time of the last Council meeting, the NIH was reflecting on more than 49,000 comments that it received on its draft guidelines for human embryonic stem cell research. The NIH released the new stem cell guidelines on July 6, 2009. Response from the community has been favorable. Highlights include the establishment of standards for the cells that can be used, particularly with regard to informed consent, and a working group of scientists, ethicists, and members of the public who will determine whether those standards have been met. None of the current eligible lines will be grandfathered in automatically.

The Therapeutics for Rare and Neglected Diseases (TRND) initiative is a Congressionally mandated effort to encourage and speed the development of new drugs for rare and neglected diseases. The NIH Office of Rare Diseases Research will oversee the program, and the National Human Genome Research Institute will administer the laboratory operations. The program currently is setting up an oversight process to help it select projects.

With regard to comparative effectiveness research, at the end of June, the Institute of Medicine's Committee on Comparative Effectiveness Research Prioritization (of which Dr. Weinstein is a member), published a report containing 100 topics related to diseases, research methods, and care models that are important to the U.S. population. Many of the priorities address topics of particular interests to NIAMS' communities. These include: osteoarthritis, rheumatoid arthritis, and psoriatic arthritis; psoriasis; acne; chronic wounds; osteoporosis; cervical disk and neck pain; and the elimination of health disparities in musculoskeletal diseases. Dr. Katz noted that the Institute has a history of funding and continues to fund this type of research, citing the Spine Patient Outcomes Research Trial (SPORT), led by Dr. Weinstein's group at Dartmouth, as an example.

The NIH has ongoing efforts to promote research that makes use of large data sets, collected through epidemiologic studies and other research supported by NIAMS and other Institutes and

Centers (ICs). Recently, NIAMS funded applications in response to its Program Announcement for “Genome-Wide Association Analysis of Existing Data Sets for Arthritis and Musculoskeletal and Skin Diseases.”

Dr. Katz noted that later in the day, Council members would hear more about the NIAMS Long-Range Plan, a draft of which was sent to Council members earlier in the month. The plan is being developed as a joint effort between Program Directors in the NIAMS extramural scientific Divisions and the Office of Science Policy and Planning. The NIAMS also received considerable input from the extramural community, including many Council members, which helped shape the Long-Range Plan. One topic that emerged from this ongoing planning process that has been discussed at recent Council meetings is the NIAMS clinical trials portfolio, which Council members received on update on later in the meeting.

Based on discussions at the last Council meeting, NIAMS has taken additional steps to address the structure and review criteria for the T32 awards. A new notice is being prepared for the NIAMS Web site.

The Institute has issued a notice in the *NIH Guide* to articulate the types of research that it considers a priority under R21 funding. The notice specifies that the NIAMS is intentionally focusing the R21 program on: (1) innovative, ground-breaking projects with potential for significant impact; (2) research that involves novel technology or tool development, and has the potential to significantly accelerate research fields; and (3) projects that propose the novel application of methods, technologies, or conceptual approaches from outside biomedical science to a research problem in the NIAMS mission area. Applicants are being strongly encouraged to contact NIAMS Program Directors to see where their applications fit in these areas.

Dr. Katz reminded Council members that in 2007, the NIAMS launched a new program—Building Interdisciplinary Research Teams, or BIRT—to promote collaborations among groups of investigators in disciplines that have not traditionally interacted. The first two solicitations were open to select fields; the third solicitation is open to basic or translational team-science across all of the NIAMS mission areas. Those applications will be presented to Council members this spring.

The White House Office of Science and Technology Policy chose two NIAMS-supported researchers to be among the Presidential Early Career Award for Scientists and Engineers (PECASE) winners for 2008: Dr. Helen H. Lu, from Columbia University in New York, and Dr. Jeremy F. Reiter at the University of California at San Francisco. The PECASE awards are the highest honor bestowed by the U.S. government on scientists and engineers beginning their independent careers. In addition, Dr. Katz reported that the accomplishments of 21 NIAMS staff members were acknowledged at the annual NIH Director’s Award Ceremony in July.

While he was the Acting NIH Director, Dr. Raynard Kington named Dr. Janet Austin (Director of the NIAMS Office of Communication and Public Liaison) to the NIH’s Community Engagement in Research Implementation Working Group. This group will review recommendations on community engagement in research presented by the NIH Director’s Council of Public Representatives, and identify NIH programs and processes that may be

appropriate for their incorporation into training and peer review efforts for NIH. Dr. Austin's office also coordinates the Multicultural Outreach Initiative *Ad Hoc* Group of the NIAMS Advisory Council—this group held its first meeting on the day after the June Council meeting. More information on this group's work will be presented at a future Council meeting.

Council member Ms. Anne Kunkel, an Education Coordinator in the Department of Pediatric Rheumatology at the University of Kansas Medical Center, participated in a recent teleconference that the NIAMS had with the NIAMS Coalition. The Coalition's interests align closely with those of Council members (e.g., the NIH budget, its support of comparative effectiveness research, the new NIH policy on stem cells, etc.). Dr. Katz thanked Ms. Melanie Martinez (NIAMS Public Liaison Officer) and Dr. Branden Brough from the Office of Science Policy and Planning, for coordinating the Institute's Coalition activities.

With regard to NIAMS information dissemination efforts, Dr. Katz noted that NIAMS Clinical Director Dr. Daniel Kastner recently appeared in a story on periodic fever syndrome that appeared on a Chicago television station. The Institute is partnering with CBS Cares and the producers of the Tony-award winning Broadway show *HAIR* on an initiative to raise awareness about osteoporosis. Three public service announcements featuring cast members have been developed. Starting in October, they will be aired on CBS stations throughout the country. Council members viewed one of these announcements. Council members also were provided with a number of information dissemination pieces, including: (1) an excerpt from *Arthritis Today* describing the discovery of the new autoinflammatory disorder deficiency of the interleukin-1 receptor antagonist (DIRA); and (2) an article from the September issue of the *American Journal of Medical Genetics* that highlights this discovery.

Discussion

Council member Dr. James Weinstein, Professor and Chair of the Department of Orthopedics at Dartmouth-Hitchcock Medical Center, noted difficulty in communicating to the public that newer treatments may not necessarily be more effective and may not have been subjected to the proper studies. He asked how scientists can approach this issue in a rational way. Dr. Katz explained that government agencies and employees also face this issue; education is critical to inform the public as well as researchers and health care professionals—it can take many years for practicing physicians to stop using a particular treatment that has been shown to be ineffective.

Dr. Jacobs referenced the Knee and Hip Replacement Act of 2009 and the establishment of a knee and hip replacement registry, noting that the community is pleased that this issue has reached the level of Congressional attention. The United States is one of the few developed countries that does not have a national knee and hip replacement registry. He noted that those registries that have been most successful around the world are run by private entities as opposed to governments. It is unclear where the U.S. registry will reside at this point.

Dr. Clifford Rosen, a member of the Council and Director of Translational Research at Maine Medical Center, agreed with Dr. Weinstein's earlier comments. One of the problems is that there is a great deal of hype regarding new, expensive drugs, and very little information communicated

on potential side effects or adverse events. He suggested that U.S. Food and Drug Administration (FDA) hearings should be more open to health care practitioners (i.e., those who will eventually use the drugs). Better coordination at several different levels is needed; Dr. Rosen suggested that it would be easy to open FDA hearings up to the public via Webcasting. Dr. Katz added that the FDA does not have the support needed to mandate large-scale post-marketing (or so-called Phase 4) surveillance.

Council member Dr. Henry Kronenberg, of the Department of Medicine at Harvard Medical School, referenced a recent revolutionary paper in the bone field, noting that this paper made a convincing argument that what many good scientists thought was completely wrong. This work was not carried out by a large, multi-institution research program, but by a scientist who “had a good idea and didn’t believe what everybody else thought.” Dr. Kronenberg noted that this illustrates the importance of continuing to encourage and support investigator-initiated research.

Dr. John Klippel, President and CEO of the Arthritis Foundation and a member of the Council, noted that he attended a recent meeting of the National Health Council that included a discussion on comparative effectiveness research. He noted that as the results of comparative effectiveness research are disseminated, the real issue becomes how those results are interpreted and used. As these results become public, there are opportunities for the scientific community to demonstrate leadership and provide up-front guidance from a clinical standpoint.

V. CHALLENGES AND OPPORTUNITIES IN PEER REVIEW

Dr. Antonio Scarpa, Director of the Center for Scientific Review (CSR), opened his presentation by thanking Council members for all of the comments and concerns that they have submitted to him. Dr. Scarpa reported that in 2008, the CSR received approximately 77,000 applications, of which 75 percent were reviewed by about 16,000 reviewers at approximately 1,600 review meetings. In 2009, the number of applications has risen dramatically, up to about 112,000, requiring additional reviewers and meetings.

Dr. Scarpa described his office’s efforts to enhance peer review at the NIH. These activities have included: (1) reorganizing the CSR and recruiting staff, (2) improving study section alignment, (3) assigning applications more accurately, (4) shortening the review cycle, (5) advancing additional review platforms, and (6) recruiting the best reviewers.

With regard to advancing additional review platforms, Dr. Scarpa commented that providing additional review platforms helps in recruiting reviewers—for example, electronic modes of review reduce the burdens associated with travel. Approximately 15-20 percent of reviews are now conducted electronically (i.e., through telephone-enhanced discussions, video-enhanced discussions, and asynchronous electronic discussions [AEDs]). Dr. Scarpa noted that out of approximately 1,000 reviewers surveyed, about 80 percent reported being “very satisfied” or “somewhat satisfied” with AEDs.

Dr. Scarpa commented that recruiting the best reviewers is key to CSR’s success. Some of the successful strategies implemented by the CSR to recruit and retain the best reviewers include:

(1) moving one meeting per year to the West coast, (2) using additional review platforms, as noted previously; (3) developing a national registry of volunteer reviewers (the Center now has a searchable database containing 5,000 reviewers); (4) providing tangible rewards for reviewers (e.g., no submission deadlines for chartered members of study sections); and (5) providing flexible times for reviewers.

Approximately 2 years ago, former NIH Director Elias Zerhouni gave the following charge across NIH: “Fund the best science, by the best scientists, with the least administrative burden...” Two advisory committees were formed (one internal to NIH, one external to NIH). The process, which involved all of NIH, began with a diagnostic phase spanning June 2007 through March 2008, followed by design of the implementation plan, which extended through June 2008. In September 2008, phased implementation of selected actions began. Four priority recommendations were generated as a result of this process: (1) engage the best reviewers, (2) improve the quality and transparency of review, (3) ensure balance across scientific fields and career stages, and (4) conduct a continuous review of peer review.

Dr. Scarpa focused on four CSR activities to facilitate the priority recommendations.

- *Review highly transformative research.* A new mechanism has been created through the Office of the Director, the Transformative R01 (or T-R01). This year, the application deadline was January 29, 2009, and the mechanism features an 8-page application. This year, the NIH received 740 submissions and 42 were funded. An editorial board review approach was adopted for this mechanism. This approach features: (1) heavy triage based on innovation and potential science transformation by a small study section of distinguished, broad-science reviewers (i.e., the editors); (2) specific science reviewed by appropriate reviewers (i.e., the editorial board); and (3) final ranking by the editors.
- *Fund early-stage career investigators.* A new investigator has been defined as one who had not previously competed successfully for a significant NIH independent research award. Early-stage investigators are defined as those who are within 10 years of completing their terminal research degree or within 10 years of completing medical residency (or the equivalent). These definitions apply only to R01 applications, and new investigators/early-stage investigators will be clustered together for review.
- *Improve the quality and transparency of peer review.* Dr. Scarpa explained that applications have been shortened and aligned with review criteria. Similarly, summary statements have been shortened, and follow a template for each criteria. The scoring system has been changed as well. With enhanced review criteria, reviewers now assess the likelihood for a project to exert a sustained, powerful influence on the research field(s). There is a new core criteria order, as follows: (1) significance, (2) investigator(s), (3) innovation, (4) approach, and (5) environment. Reviewers have adopted template-based critiques, with the objective of writing evaluative statements while avoiding summarizing the application. Comments are in the form of bullet points, or, if necessary, in the form of short narratives. The scoring system is now based on a 1 (exceptional) to 9 (poor) scale. In addition, based on concern about the variation of scores during different times of the review meeting, the order of review has been recalibrated dynamically by discussing applications in the order of average preliminary

scores from assigned reviewers. Dr. Scarpa also explained that it is now required that reviewers participate in the entire review meeting.

- *Train Chairs and reviewers.* Dr. Scarpa commented that the CSR participates in training activities on an almost weekly basis. CSR and NIH review staff participate in face-to-face training sessions, as do study section Chairs. Reviewers are provided with training materials (e.g., PowerPoint presentations, interactive training, answers to frequently asked questions, mock study section videos, etc.).

Dr. Scarpa then discussed the impact of ARRA on the CSR, reminding Council members that ARRA provided \$10.4 billion for the NIH for 2 years through September 2010. The majority of these funds (\$7.4 billion) have been allocated to ICs and the Common Fund. As a result of ARRA funding, the number of applications received for review by CSR from May 2009 through July 2009 more than doubled—there were approximately 42,000 applications overall, with 18,200 of them being non-ARRA (the majority of the ARRA-related applications, 21,000, were Challenge applications). These applications were successfully reviewed in a 2-month period. Similarly, the number of reviewers used by CSR in June 2009 (about 30,000) was approximately twice the number used in June 2008. Dr. Scarpa noted that for the next 2 years, it is expected that the number of R01 applications will be abnormally high compared with previous years, a major concern that needs to be addressed. He concluded his remarks by acknowledging the hard work and dedication of CSR staff.

Discussion

Dr. Katz opened the discussion by asking if there will be a “pull down” option for applicants to select a study section. Dr. Scarpa confirmed that this is the case, although the final selection must be a study section that is appropriate for the application. Currently, applicants write in their preference; about 90 percent of those requests are honored. In response to another question from Dr. Katz, Dr. Scarpa clarified that there is enough data for each study section to demonstrate the spread of application scores.

Dr. Rosen thanked Dr. Scarpa for his effort and that of CSR staff. He commented that in the research community, there was concern regarding the overlap between submission of ARRA applications and the adoption of the new scoring system. Changes implemented by CSR coincidentally occurred in time to allow the Center to effectively and efficiently manage the number of applications submitted to CSR as a result of ARRA funding opportunities. Dr. Rosen commented that it is clear that not all of those grants could have been handled by the previous system. Dr. Scarpa agreed that the results from enhancing the peer review system at the NIH have been very encouraging. In response to a question from Dr. Rosen, Dr. Scarpa noted that reviewers who are able to work outside of the deadlines do not necessarily have their applications go directly to a special study section. Those applicants are guaranteed a review time of 3 months or less.

Dr. Katz asked about the Council feedback submitted to CSR. Dr. Scarpa indicated that there were many helpful ideas and comments submitted. One relatively common comment was a concern about addressing how A2 applications are managed. Another concern related to the

scoring system. There were also comments related to the amount of space available for reviewers to provide their comments and the switch from a narrative to bullet points. Dr. Scarpa clarified that the study sections are used as an evaluation mechanism, not for mentoring purposes, but there is space for reviewers to include comments related to mentoring. Dr. Katz voiced his support for CSR's changes to the peer review system.

Council member Dr. H. Lee Sweeney, the William Maul Measey Professor and Chair of the Department of Physiology at the University of Pennsylvania School of Medicine, noted that his Department spent a great deal of time at a recent faculty meeting discussing NIH's peer review system. He noted that the reviewers in his Department have been very happy and supportive of CSR's changes to the peer review system. However, the feedback coming back to the applicants has been met with mixed reviews. He noted that in some cases, there are reviewers who still do not know how to properly review a grant application. Dr. Sweeney asked if the study section Chairs have a way of identifying and removing these reviewers. Dr. Scarpa commented that it is possible, but difficult, to remove reviewers from a study section. He also reminded Council members that the reviewers and Chairs are still adapting to the new system of peer review.

Dr. Kronenberg suggested that one of the biggest challenges facing the CSR is changing the behavior of both reviewers and applicants. He also commented that reviewers often spend an inordinate amount of time on the approach section of an application and not enough time considering the project's impact, innovation, and importance (or lack thereof). A concerted effort is needed to change behavior. Dr. Scarpa agreed, adding that use of the shorter application will help in this regard. Council member Dr. Kathleen Green, Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern Medical School, agreed that a shorter application will be helpful, but voiced concern regarding the review of young investigators, particularly in light of the fact that with a shorter application, there is less of an opportunity for them to provide details on their project. She added that young investigators might suffer relatively more than other applicants because they lack an established reputation. Dr. Scarpa indicated that CSR has addressed this issue. "Affirmative action" for new investigators takes place at both the IC and CSR levels. Dr. Scarpa also explained that new investigators, who do not have the experience of established investigators relative to writing a grant application, may have an easier time developing a shorter application. Of the 21,000 Challenge grant applications received by CSR, none of them was accompanied by a complaint based on not having enough space to complete the application.

Council member Dr. Leslie Crofford, Chief of the Division of Rheumatology and Director of the Center for the Advancement of Women's Health at the University of Kentucky congratulated Dr. Scarpa on CSR's revamping of the peer review system at the NIH. She noted that despite the fact that these changes are radically different from what has been done in the past, she has been hearing very positive remarks regarding the new system. She asked about what CSR is doing to address the misalignment that can occur between an application's score and the reviewers' comments. She also voiced concern that the reviews may not provide enough information on the strengths and weaknesses of an application to allow the investigator to make improvements. Dr. Scarpa explained that evaluation of the peer review system is an ongoing process, and the CSR is continuing to collect data.

Dr. Katz thanked Dr. Scarpa for his presentation and comments during discussion, and asked him to update the Council at its September 2011 meeting. He also noted that Dr. Scarpa's presentation would be made available to Council members, who were encouraged to disseminate it within their respective communities.

VI. NIH-NIAMS ARRA FUNDING UPDATE

Dr. Katz began this session by explaining that only some of the ARRA grants have been funded to date. By the next Council meeting, NIAMS staff will provide a full report on what has been funded. He reminded Council members that the ARRA funding goals are to stimulate the economy, create and preserve jobs, and advance biomedical research.

NIAMS Deputy Director Robert Carter described the ARRA initiatives, including:

- *Challenge Grants (RC1s)*. There are 15 challenge topics, identified by NIAMS and all NIH ICs. They focus on specific knowledge gaps, scientific opportunities, new technologies, or research methods (i.e., areas that may advance with a rapid infusion of funds). Funding is set at less than \$500,000 total per year, for a maximum of \$1 million in total costs over 2 years.
- *Grand Opportunities (RC2s)*. This mechanism involves substantial funding for new projects to catapult a field forward and position it for future innovations. RC2s are funded at up to \$500,000 in total costs per year.
- *Core Centers for New Faculty Recruitment Enhancing Research Capacity (P30s)*. This mechanism was established to augment and expand the biomedical research efforts of extramural institutions. Funding is provided to hire, enhance start-up packages, and develop pilot research projects for newly independent investigators.

Dr. Carter also discussed the following series supplements tied to ARRA:

- *ARRA Competitive Revision Supplements*. These supplements are for the significant expansion of new research aims outside the scope of parent awards.
- *ARRA Administrative Supplements*. These supplements are intended for activities associated with increasing the pace of scientific research and/or achieving limited new research objectives, as long as they are within the scope of parent awards.
- *ARRA Administrative Supplements for Students and Science Educators*. These are designed for summer projects within the scope of parent awards, to encourage students to pursue research careers in the health-related sciences, and provide science educators with short-term research experiences at NIH-funded laboratories.

Dr. Carter reviewed the number of ARRA applications received across the NIH. A total of 20,008 RC1s were received, 12 percent were reviewed and scored; 2,587 RC2s were received (54% were reviewed and scored); 561 P30s were received (62% reviewed and scored); and 2,161

competitive revisions were received (85% reviewed and scored). Dr. Carter reported that the NIAMS received between 4 and 7 percent in each of these categories. Success rates will be reported at the next Council meeting.

Dr. Carter explained that there are different “pools” of money from NIH’s \$10.4 billion ARRA allocation. For example, \$7.4 billion is allocated for ICs and the Common Fund, distributed on a percentage-based formula. Dr. Carter reported that NIAMS used its allocation to fund grants through all the initiatives that he had just described. NIAMS used its allocation to fund supplements and RC2 grants. Approximately \$800 million has been allocated to the NIH Office of the Director, including support of projects from IC mission areas (RC1s were funded through the Office of the Director). In addition, there are several initiatives for shared instrumentation, infrastructure, comparative effectiveness research, and other activities. Dr. Carter explained that the funding decisions made for these ARRA-related mechanisms reflected the review criteria. Those criteria include: (1) high impact science, (2) work that can be accomplished within a 2-year timeframe, (3) projects that are not feasible with NIH’s “business-as-usual” grant mechanisms, and (4) the potential to fill a gap or catapult the science in an area to enable future research.

The NIH Office of the Director is emphasizing the potential impact of the research across all ICs as well as the potential to affect a large segment of society. With regard to the ARRA funding process, Dr. Carter explained that initially, the NIH Office of the Director will choose to support some projects. Subsequently, individual ICs make funding decisions for applications in their respective mission areas. RC1, RC2, P30, and supplement awards are anticipated by September 30, 2009. Dr. Carter explained NIAMS administrative supplement requests, noting that a standard operating procedure was created for a consistent review across NIAMS Divisions, with all steps being documented. NIAMS Program Directors are responsible for identifying the most meritorious supplements, which are then reviewed and vetted by the Extramural Program Division Directors, who in turn make funding recommendations to the NIAMS Director and Deputy Director.

Before concluding his presentation, Dr. Carter noted that the NIAMS is soliciting ARRA success stories. Specific information is being sought on jobs retained or created; the enhancement of projects by allowing new efficiencies, new directions, or additional resources; the expansion of research teams through new personnel or collaborations; and immediate and long-term effects. Council members were encouraged to share any ARRA-related success stories and to visit <http://www.niams.nih.gov/recovery/default.asp> for more information.

Discussion

In response to a question by Dr. Rosen, Dr. Katz explained that awards will be made by the NIAMS Acting Grants Management Chief, with the help of his staff. Awards will be announced on September 29 or September 30. A total of \$132 million in ARRA funds is available to the Institute. Of the Challenge grants, about 4 percent came to the NIAMS. Much more detailed information will be available at the next Council meeting. Dr. Katz acknowledged the efforts of Dr. Susana Serrate-Sztejn, Director of the NIAMS Division of Skin and Rheumatic Diseases, in leading NIH’s ARRA development efforts.

Dr. Kronenberg discussed the fact that there were approximately 20,000 applications for the Challenge grants, with only about 200 actually awarded (applicants were aware of the number to be awarded before submitting). He asked how this should be viewed by the research community. Dr. Katz noted that this issue has an added complexity because at many academic centers, investigators were told that they had to submit an application. At the time, the NIH indicated that approximately 200 of these awards would be supported by the Office of the Director (and an additional 600 supported by the ICs), there was no way of knowing that there would be 20,000 applications. Dr. Kronenberg noted that his institution submitted a large number of applications; Dr. Katz indicated that many other institutions also submitted large numbers of Challenge grant applications.

Ms. Kunkel asked where information on ARRA-funded grants will be posted online. Dr. Katz explained that everything funded through ARRA will be posted on a central NIH Web site. Dr. Rosen commented that the NIH could use the large number of Challenge grant applications in a positive way to demonstrate how it responded to the challenges posed by ARRA. Dr. Katz agreed, noting that it demonstrates the enormous research capacity in the United States.

VII. GENETICS AND GENOMICS INITIATIVES

Dr. William Sharrock, Health Science Administrator in the NIAMS Division of Musculoskeletal Diseases, explained that a number of concepts have emerged with the invention of methodology for assessing genetic variation in human populations on a genome-wide basis. He provided the Council with an update on three specific initiatives at the NIAMS.

- *NIAMS: PAR08-123, “Genome-Wide Association Analysis of Existing Data Sets for Arthritis and Musculoskeletal and Skin Diseases.”* This NIAMS Program Announcement has a set-aside and specific review considerations; it is a 3-year effort with three annual competitions (the first round of competition has been completed). This initiative is aimed at supporting the analysis of specific data sets. One of the characteristics of genome-wide association studies and the cataloging of SNPs is that there is a very large and growing database of genotype/phenotype data. It has been the NIH policy to make these data as widely accessible as possible. This initiative is intended to help investigators make good use of these existing data.
- *NIH Genes, Environment, and Health Initiative (GEI): RFA DA-09-003, “Functional Characterization of Genetic Variants and Interactions” and RFA CA-09-003, “Replication and Fine-Mapping Studies.”* The GEI intends to combine what is known about genetics with environmental influences on disease and how the two interact. The NIAMS is most interested in the genetics component of the initiative at this point. The initiative has progressed beyond setting up genotyping centers and the discovery phase of genome-wide associations to RFAs examining the next phases of this work.
- *NIH Roadmap – Epigenomics: RFA RM-08-017, “Epigenomics of Human Health and Disease.”* This NIH Roadmap initiative is examining events at the level of chromosome or

chromatin organization of the genome that have more recently become accessible to genome-wide assessment. The initial set-up phase is mostly complete, and this technology is now being applied to specific disease areas.

Dr. Sharrock noted that the communities that NIAMS supports are taking advantage of these new methodologies, and they have quickly become part of the NIAMS portfolio. These communities have made an impressive showing in competing for NIH-wide funds; this speaks well for NIAMS investigator communities.

Dr. Sharrock then listed recent awards in NIAMS mission areas related to these initiatives. For PAR 08-123, they are: (1) Genetics of Juvenile Idiopathic Arthritis and Subtypes; (2) Meta-analysis of GWAS Data To Identify Novel Rheumatoid Arthritis Risk Loci; (3) Network Approaches to GWA Studies of Rheumatoid Arthritis (RA), Ankylosing Spondylitis, and Psoriasis; and (4) Genome-Wide Study of Pleiotropic Effects on Bone and Muscle.

For RFA DA-09-003, recent awards include: (1) Functional Evaluation of ITGAM SNPs, and (2) FcγRIIb Links CRP Signals With ITGAM Functions: A G x G x G Model of SLE. For RFA CA-09-003, a recent award was: Fine Mapping and Replication of a Genome-Wide Association Scan for SLE in Hispanics.

For RFA RM-08-017, there were two recent awards: (1) Epigenomics of SLE, and (2) Epigenomic Analysis of Facioscapulohumeral Muscular Dystrophy.

Before closing his presentation, Dr. Sharrock emphasized that these are specific initiatives and do not represent the sum of NIAMS' total investment in genome-wide association studies, which would be a much larger discussion.

VIII. LONG-RANGE PLAN: FISCAL YEARS 2010 TO 2014

Anita Linde, Director of the NIAMS Office of Science Policy and Planning, provided Council members with a recap on the development process on NIAMS' Long-Range Plan. The process was undertaken as a way to collectively scan the science the Institute covers (from basic to translational to clinical). The purpose of the Long-Range Plan is to identify needs, opportunities, and challenges to progress; it is not meant to replace the previous plan (which covers FY2006-2009). It is intended to provide a broad scientific outline to propel research progress, continue to support the best investigator-initiated research, and communicate the Institute's perspective.

Ms. Linde emphasized that this Long-Range Plan in no way impinges on the Institute's ability to focus on investigator-initiated research. Areas not covered in the Plan may, in fact, turn out to be priorities for the Institute in the coming years.

The Long-Range Plan has been in development for more than 1 year. In September/October 2008, a request for comments was posted on the NIAMS Web site, and in November/December of that year, roundtable discussions focusing on the Plan were held with outside experts and Institute staff. The Council was updated on progress in February and June of 2009, and the draft

Plan was sent to Council members approximately 1 week before this meeting for their review. Ms. Linde noted that there is a section still under development that focuses on the Institute's information dissemination and outreach efforts—this section will be included in the next version of the Plan.

Dr. Katz asked Council members for their input on the draft Long-Range Plan. Council members, and the rest of the scientific community, are being asked the following overarching questions:

- Are the most promising scientific opportunities in a given field or discipline covered?
- Are the most pressing public health needs in a given field or discipline represented?
- Are approaches for overcoming major challenges and roadblocks adequately reflected?

Dr. Betty Diamond, Chief of the Laboratory of Autoimmune Diseases at the Feinstein Institute of Medical Research and a Council member, noted that the draft Plan discusses investigator-initiated research towards the end of the document. She suggested that this important topic be covered at the beginning, to reassure the community that the NIAMS is not moving away from “small science,” or investigator-initiated science, but rather identifying areas of opportunity. Dr. Katz commented that this was an excellent point, noting that the Institute's commitment to the RPG line has been in the range of 65-67 percent. He emphasized that the Institute is asking the Council to provide feedback on the Plan, either at this meeting or within the next few weeks. He also explained that this Plan was not dictated as something that the NIAMS had to do; it is a statement of the breadth of the Institute's responsibilities and authorities in the areas covered.

In terms of next steps, the Plan will be posted on the NIAMS Web site for public comment in October/November. In November, the Plan will be discussed with NIAMS Coalition representatives, and in February of next year, the final Long-Range Plan will be presented to the Council and posted online. Council members were again encouraged to submit any comments to Ms. Linde.

IX. CLINICAL TRIALS

Dr. Carter provided the Council with an update on the Institute's initiatives in the area of clinical trials. He commented that there is more than one approach to getting research done in the United States, and that although clinical research represents a smaller component of the overall \$30 billion NIH research enterprise compared with translational and basic research, clinical research makes up the bulk of private-sector research (it is estimated that the private sector spends approximately \$60 billion annually on research, mostly done through the pharmaceutical industry).

There are many types of clinical research that are not often carried out by the private sector (e.g., practice-based research), however. The NIAMS, through funding clinical trials, has made a significant investment that has the potential to impact clinical practice. Dr. Carter noted that, in

December 2008, the Institute reviewed its clinical trials portfolio. In April 2009, a scientific retreat session focused on this issue, which was presented to the Council in June. In November and December 2009, roundtable discussions are planned to: (1) focus on the current opportunities for NIAMS-supported clinical trials, and (2) determine how NIAMS can get feedback from the community and identify the opportunities for clinical trials that have the greatest impact.

Dr. Carter noted that all investigators who plan clinical trials will need to first submit an investigator-initiated clinical trial U34 application, which will include milestones. There will be opportunities during the lifetime of the grant to submit for the full proposal to avoid having a gap between the planning grant and the actual study. In addition, all investigator-initiated trials will be done as cooperative agreements, and there will be an R21 mechanism for pilot and feasibility studies for clinical research.

Dr. Carter stated that, from the perspective of maximizing the clinical impact of NIAMS-sponsored clinical trials, that a working group be formed comprised of experts (including Council members) to assist NIAMS in terms of scanning the horizon for the greatest needs and opportunities, and assessing the potential impact of concepts for clinical trials proposed by investigators and the Institute.

Discussion

Dr. Sweeney asked, with the introduction of the U34 mechanism, if that means the Institute has the ability to terminate a grant if the investigator(s) cannot enroll enough subjects or there is some other fundamental reason the trial cannot proceed. Dr. Katz acknowledged that achieving enrollment is a problem with many clinical trials; investigators often are over enthusiastic about the numbers that can be enrolled. The U34 mechanism allows the Institute to have more “say” in what goes on in funded clinical trials.

Dr. Weinstein commented that it is extremely difficult to carry out large clinical trials. He also noted that the comparative effectiveness agenda has many topics that would be relevant and appropriate for clinical trials that fall within NIAMS’ domain. Not every institution is capable of carrying out clinical trials research. The resources expended by many institutions is in many ways frustrating because a number of investigators do not have a complete understanding of the many nuances associated with this type of study. The unintended consequences include not meeting enrollment, consent issues, compliance issues, budget issues, etc. He suggested that there be a competitive process by which certain centers with the appropriate expertise can compete to serve as coordinating centers for these trials. Dr. Katz noted that Dr. Weinstein’s comments echo the Institute’s thinking in terms of the challenges associated with this type of work. NIAMS’ goal is not to serve as an institute for comparative effectiveness. It is a concern for the nation, but NIAMS must remain true to its core values for basic research. The Institute spends a great deal of money on clinical trials and it wants to make sure they are done correctly and will make a difference, there is good consultation with good feedback from the community, and that the consultation is carried out in a transparent manner.

Dr. Diamond reminded Council members that the concept of an institutional pre-review, along the lines of an R21, was discussed at the retreat. She suggested that this topic is still worth considering. She also indicated that she is not in favor of establishing coordinating centers or committees, she would rather see more involvement by experts at the community level participate in a type of prescreen for clinical trials. Dr. Carter noted that the U34 mechanism and the proposed working group could facilitate these types of activities. He also clarified that just because an investigator receives a U34 grant, it does not mean that he or she will receive funding for the full study.

Dr. Kronenberg commented on the need for having an unambiguous definition of the term “clinical trial.”

In response to a question, Dr. Katz explained that approximately 95 percent of NIAMS-sponsored clinical trials have been reviewed within the Institute (using a NIAMS study section), mainly because they involve three or more clinical centers and more than \$500,000 per year. That process will not change. The question of relevance and significance/impact will be considered in this review. Outside experts also are tapped for their input in many instances.

Dr. Crofford characterized the presentation by Dr. Carter as a wonderful initiative and expressed hope that it achieves its intended effect. She expressed some concern about becoming “inbred” with respect to study design, methodology, and innovation. This is a particularly difficult issue when there is a relatively small community of methodologists. She emphasized the need to ensure that there is an understanding that much of what has been done in the past has failed or led to incorrect conclusions because standard methodologies have been applied. Dr. Katz assured the Council that the group that will be put together for consultation will not be involved in the process and the operations of a clinical trial, or the methodology—that is left to review. The group will be looking at the projects to assess questions of importance and impact, not how the study should be done.

In response to a question about the cooperative agreement mechanism, Dr. Joan McGowan, Director of the NIAMS Division of Musculoskeletal Diseases, clarified that cooperative agreements are not contracts and are not directed by the government. The responsibility of the planning grant remains with the Principal Investigators. Cooperative agreements exist because there are resources that the government can bring to the table (e.g., advice from program staff, fiscal resources). Dr. Katz added that in cases where Institute program staff are involved in cooperative agreements, they are never in a position to influence funding.

Dr. Serrate-Sztejn noted that with regard to clinical trials, regardless of the mechanism, trial design remains a significant challenge, particularly in terms of rare diseases. There is a need to engage NIAMS’ communities and explore potential uses of clinical trial designs in the Institute’s portfolio. It is hoped that the issue of trial design will be a topic for the fall roundtable discussions.

Dr. Jacobs acknowledged the importance of these clinical trials-related issues and commended the Institute for addressing them. He asked about the planned working group and asked about its membership. Dr. Carter explained that the working group will include Council members as well

as outside experts. Dr. Rosen agreed with the need to involve outside experts that have the expertise in areas that are not fully represented on the Council.

X. 2011 INITIATIVES

Council members were provided with general descriptions of potential initiatives for 2011. Dr. Katz asked Council members to provide any comments.

Dr. Glen Nuckolls, Health Science Administrator in the NIAMS Division of Musculoskeletal Diseases, was asked to provide additional information on the “Natural History Studies for Rare Rheumatic, Musculoskeletal, and Skin Diseases.” He explained that this is an initiative to support prospective natural history studies for any of the rare diseases within the NIAMS mission area. Data from these studies can help to jump-start research on understudied rare diseases, facilitate the design of more effective clinical trials, and further validate outcome measures or biomarkers. There is a recognized need for these types of natural history studies, yet the Institute receives few applications along these lines. There is a perception among investigators that an application of this type that goes to study section may not be as well received as a hypothesis-driven study. In an effort to help the Institute identify which of these studies would be funded, one of the features that would be built into this initiative would be to ask the applicants to specifically identify “why this study at this time?” and have the reviewers consider the potential for immediate or near-term impact of the data from the natural history study on the design of clinical trials for other hypothesis-driven studies.

Discussion

Dr. Diamond commented that this is a good concept and could be expanded to include those at risk for developing a disease, either identified by genotype or some phenotypic marker. There is good reason to believe that earlier interventions in the disease process are going to be more effective. Identifying the at-risk population would be a major step forward.

Dr. Kronenberg agreed that this is an important concept, not because it will improve the public health of the country disease by disease, but because some of these diseases are at the stage where there are likely to be lessons or wide implications about mechanisms well beyond these specific diseases. Dr. Sweeney agreed on the importance of this initiative and emphasized the need to design outcome measures for trials.

Council member Dr. Linda Griffith, of the Department of Biological and Mechanical Engineering at the Massachusetts Institute of Technology, commented on the concept related to building 3-D tissue models. She suggested that it could be enhanced by explicitly including an immune system component. Many of the challenges faced by the NIAMS relate to trafficking immune system cells into functioning tissues. In the tissue engineering community, the immune system is rarely present when researchers build a system, particularly in *in vitro* model systems.

Dr. Weinstein suggested adding a bullet point to the concept related to the assessment and assistance for clinical studies that includes getting help with enrollment and informed consent,

and understanding those processes. Dr. Katz added that minority enrollment also should be included.

XI. PROMETHEUS UNBOUND: REVITALIZING HUMAN SUBJECTS RESEARCH REVIEW AT THE NIH CLINICAL CENTER

Dr. Kastner explained that the Clinical Center has enormous potential and its use has yielded a large amount of new knowledge for the biomedical research community. However, there has been a perception over the last few years that there are certain impediments to the Clinical Center realizing its full potential. Three years ago, the Intramural Working Group established the Task Force to Streamline Clinical Research. The Task Force developed questionnaires and focus groups to determine investigator-identified obstacles to clinical research at the Clinical Center. The Task Force issued its final report and recommendations in October of 2008. Major barriers to conducting this research included Institutional Review Board (IRB) and ethical issues, adequacy of resources, interactions with industry/technology transfer, and the scientific review/approval process.

At the October 30, 2008, NIH Steering Committee meeting, the Intramural Working Group submitted a proposal to create a Department of Clinical Research to provide protocol support and IRB management for intramural research NIH-wide. The proposal was not accepted based on concerns related to centralization. However, at that meeting, a new group was formed, the Intramural Clinical Research Steering Committee (ICRSC), which Dr. Kastner chairs. The overarching goal of the ICRSC is optimizing clinical and translational research in the intramural research program. The Committee's mission statement is: "The protocol generation and review process should be re-engineered to make it more user friendly, more efficient, and more consistent across the intramural research program while continuing to maintain the highest standards of human subjects protection."

The ICRSC is a cross-section of the clinical research community and intramural research program. It includes two IC Directors, two Scientific Directors, four Clinical Directors, two tenured clinical investigators expert in clinical investigation, one IRB Chair, and a number of *ex officio* members.

In January 2009, the ICRSC submitted a proposal to create protocol service centers (PSCs) to provide support in the preparation and implementation of human subjects protocols. This service center model includes lead and participating ICs linked by a Memorandum of Understanding (MOU) and avoids the potential drawbacks associated with NIH centralization. These PSCs would provide support in the preparation and implementation of human subjects protocols by recruiting a new cadre of individuals, referred to as "protocol navigators." These protocol navigators provide assistance in the preparation of protocols and response to stipulations and expertise in scientific writing, regulatory guidelines, local precedents, etc.

Initially, six thematic PSCs were suggested in the following areas: immunology/infectious diseases, cancer, general medicine, cardiopulmonary, neurosciences, and epidemiology. Some additional thematic PSCs have been proposed (e.g., pediatrics, women's health, genetics). The

ICRSC also proposed the formation of PSC-associated thematic IRBs with trans-NIH oversight; scientific review would remain the domain of the ICs.

Dr. Kastner noted that, in terms of implementation, the National Institute of Allergy and Infectious Diseases has piloted the protocol navigator position and it has resonated well with its intramural community. The National Cancer Institute started recruiting for three protocol navigators and a Project Manager for the Cancer PSC. The NIAMS is contracting navigator services with an experienced protocol writer. Contiguous space for PSCs is planned in the renovation of Building 10.

Dr. Kastner explained the rationale for creating thematic IRBs. These would decrease NIH vulnerabilities by increasing the consistency of review in given subject areas across the intramural research program. By breaking down IC barriers, thematic IRBs also would expand the pool of potential reviewers, offering broader expertise in the areas under review, less chance of having conflicts of interest, and more opportunities for rotations of members. Dr. Kastner also noted that the ICRSC is focusing on developing consistency across the intramural research program with regard to the scientific review of protocols.

Dr. Kastner closed his presentation by making the following summary points:

- The over-riding interest of the ICRSC is to foster clinical research while maintaining the highest standards of human subjects protections.
- Thematic PSCs will provide expanded support for clinical investigators.
- In parallel with the PSCs, but under separate supervision, NIH-wide thematic IRBs will expand the consistency of review across the intramural research program, bring new expertise to the review process, reduce the potential for conflict of interest, and facilitate rotations of members.
- Enhanced scientific review should stimulate better protocol conception and design while reducing burdens on IRBs.

Discussion

Dr. Klippel opened the discussion session by applauding Dr. Kastner for his leadership and emphasizing the need to increase the profile, utilization, and success of the Clinical Center. Dr. Rosen asked if consideration has been given to using an electronic portal to access the navigator and additional resources. Dr. Kastner explained that this is being considered; a number of ICs have various electronic portals and efforts are underway to develop a uniform system across the intramural research program. In response to a question about the identity of the navigators, Dr. Kastner explained that they are mostly senior research nurses at present, and added that this could be an alternative career path for Ph.D. scientists who want to do something other than run a laboratory.

Dr. Kronenberg voiced support for this concept, noting that if successful, it could serve as a model for initiatives well beyond the NIH intramural research program. It also could empower the Clinical Center to increase its service extramurally.

Dr. Diamond asked about benchmarks for success and how the quality of human subjects protection would be measured. Dr. Kastner noted that the time from conception of a protocol to approval and implementation could be one metric. Another could be the number of protocols approved and running. The larger issue is determining how to ensure that this process will create protocols that are safe and that protect human subjects.

XII. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 1,564 applications in closed session requesting **\$1,719,565,935** and recommended 1,564 for **\$1,719,565,935**.

XIII. PORTFOLIO PRESENTATION

This presentation was given during closed session.

XIV. ADJOURNMENT

The 69th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 2:30 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

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

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