National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

June 14, 2005

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

MINUTES OF THE 56th MEETING

June 14, 2005
8:30 a.m. to 4:00 p.m.

I. CALL TO ORDER

The 56th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on June 14, 2005, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting began at 8:30 a.m.

Attendance

Council members present

Dr. Graciela S. Alarcon
Dr. Gena R. Carter
Dr. Brian L. Kotzin
Dr. Martin J. Kushmerick
Dr. Cato T. Laurencin
Dr. Richard T. Moxley
Dr. Robert J. Oglesby (Ex Officio)
Dr. Jack E. Parr
Dr. Lawrence G. Raisz
Dr. Francesco B. Ramirez
Ms. Mary Elizabeth Replogle
Dr. Randy N. Rosier
Dr. Raymond Scalettar
Dr. John R. Stanley
Dr. Steven L. Teitelbaum
Ms. Sharon F. Terry
Dr. Jouni J. Uitto

Council members not present

Dr. Bevra H. Hahn
Ms. Victoria B. Kalabokes

Staff and Guests

The following National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) staff and guests attended:

Staff

Dr. Janet Austin
Ms. Susan Bettendorf
Mr. Gahan Breithaupt
Dr. Eric Brown
Ms. Kelli Carrington
Ms. Anne Connors
Mr. Frank Cromwell
Ms. Jennifer Curry
Mr. Ray Fleming
Dr. Elizabeth Gretz
Dr. Steven J. Hausman
Ms. Jane Hymiller
Mr. Oluwasegun Ijiyemi
Ms. Bonnie Jackson
Dr. Stephen I. Katz
Dr. Cheryl A. Kitt
Ms. Tara Knox
Dr. Gayle Lester
Dr. Richard Lymn
Dr. Joan A. McGowan
Mr. Robert Miranda-Acevedo
Dr. Barbara Mittleman
Dr. Alan N. Moshell
Ms. Melinda Nelson
Dr. James Panagis
Ms. Wilma Peterman
Dr. Paul Plotz
Ms. Karin Rudolph
Dr. Susana A. Serrate-Sztein
Dr. William Sharrock
Ms. Helen Simon
Ms. Sheila Simmons
Dr. Madeline Turkeltaub
Dr. Bernadette Tyree
Dr. Yan Wang
Ms. Eileen D. Webster-Cissel

Guests

Ms. Roberta Biegel
Ms. Adrienne Oleck
Dr. Eileen Resnick
Dr. Antonio Scarpa

Other NIAMS staff members and guests also were present. Dr. Stephen Katz, Director of the NIAMS, chaired the meeting.

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 55th Council meeting, held on February 8, 2005.

III. FUTURE COUNCIL DATES

Future Council meetings are tentatively planned on the following dates:

September 13, 2005
January 17, 2006
May 23, 2006
September 26, 2006
February 27, 2007
June 12, 2007
September 27, 2007

Dr. Katz noted that the NIAMS is in the process of revising these future Council meeting dates to schedule the meetings on Tuesdays when possible. Council members will be provided with an updated list of meeting dates when they are finalized.

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz informed Council members that newly appointed Council member Dr. Bevra Hahn, who is a Professor of Medicine, Chief of the Division of Rheumatology, and Vice Chair for Faculty Affairs in the Department of Medicine at the University of California, Los Angeles School of Medicine, was unable to attend this Council meeting. Dr. Katz also welcomed Dr. Lawrence Raisz, Director of the University of Connecticut Center for Osteoporosis, who was attending his first meeting as a member of the Council.

NIAMShorttakes

The NIAMShorttakes, prepared by Mr. Ray Fleming, focuses on the NIAMS' new Centers of Research Translation. The Shorttakes also provides a detailed

review of recent research advances and other updates; Dr. Katz encouraged Council members to read the Shorttakes, which is available online.

Personnel Changes

Dr. Yan Wang, who has been serving as the Acting Director of the Review Branch in the NIAMS Extramural Program, has been named as the new Director of that Branch. Ms. Sheila Simmons and Ms. Bonnie Jackson have joined the NIAMS as Senior Grants Management Specialists in the Institute's Extramural Program. Dr. Richard Lymn, Chief of the Muscle Biology Branch, has announced his retirement, and Dr. Charisee Lamar has left her post as a Program Director for the NIAMS Multidisciplinary Centers and Diversity Programs and has moved to the National Institute of Child Health and Human Development.

Dr. Antonio Scarpa has been named as the new Director of the National Institutes of Health (NIH) Center for Scientific Review (CSR). Dr. David Schwartz has been named as the Director of the National Institute of Environmental Health Sciences. Dr. Jim Battey has announced that he will remain as Director of the National Institute on Deafness and Other Communication Disorders.

Update on Budget and Congressional Activity

The President's Budget has been released, and the NIH received a total increase $145.7 million, or 0.5 percent, for fiscal year 2006. The NIAMS' increase is $1.9 million, or 0.4 percent, for a total budget of $513 million for fiscal year 2006. The NIAMS is expected to maintain the success rate at the level of past years (approximately 20%). To make this possible, most mechanisms are being held at last year's levels—there will be no inflationary increases for direct recurring costs in noncompeting continuation research project grants. The NIAMS and the NIH are developing long-term strategies for managing budgets and ensuring support for the highest scientific priorities.

The House and Senate Appropriations Subcommittees held hearings on March 9 and April 6, respectively, and although Dr. Katz did not provide any verbal testimony, his written testimony is included on the NIAMS Web Site. There also has been some discussion about NIH reauthorization. The last reauthorization occurred in 1993; no current legislation has been presented by the Congress in this regard.

Recent NIH Activities

On May 20, an NIH Director's budget retreat was held. One clear need discussed at the retreat was addressing the recommendations found in the National Research Council's recent report entitled "Bridges to Independence: Fostering the Independence of New Investigators in Biomedical Research." Participants at the retreat also discussed potential cost-saving measures in terms of facilities

management, the Intramural Research Program, and the finances and dynamics of the NIH Roadmap process.

As part of the Roadmap Initiative, the NIH recently launched an effort to develop clinical and translational research sciences as a discipline; this trans-NIH effort will be led by the National Center for Research Resources (NCRR). The NCRR is working to obtain community feedback on this initiative, which will create a home for clinical and translational research in academic health centers. It is hoped that within the next 6-8 years, clinical and translational sciences will have an academic home with a committed faculty, a clear academic pathway, and a degree-granting curriculum, with a strong level of mentoring for young scientists. Currently, young faculty members entering clinical and translational sciences take on a difficult and high-risk venture—this initiative is intended to address some of these challenges.

At the next Council meeting, Dr. Deborah Ader, Health Scientist Administrator in the NIAMS Rheumatic Diseases Branch, may present on a Roadmap initiative known as the Patient-Reported Outcomes Measurement Information System, or PROMIS. Dr. Ader is leading this effort on behalf of the NIAMS. PROMIS is aimed at developing computer-adaptive testing to many of the difficult-to-discern symptoms associated with chronic diseases (e.g., pain, fatigue) and developing metrics that can be used across areas of interest to NIH Institutes.

Highlights of Recent Scientific Advances

- The June 10, 2005, issue of *Science* includes a review of a 2-day meeting on bone quality entitled "Bone Quality Filled Holes in Fracture Risk" authored by Eric Stokstad. The meeting included discussions with industry on common areas of interest.

- Dr. Anne Bowcock of Washington University in St. Louis presented her work on a NIAMS-funded study at a special lecture at a recent Society for Investigative Dermatology (SID) meeting. The study examines the role of genes in psoriasis and views psoriasis as a complex inherited disease. Dr. Bowcock and colleagues utilized data from a DNA repository and studied the presence of modifier genes beyond the CW6 locus, which is known to differentiate those with early onset psoriasis from those with late onset disease.

- In another psoriasis study, Dr. Brian Nickoloff and a team of researchers at the University Hospital of Zurich in Switzerland, the University of Zurich, and Loyola University Medical Center in Chicago developed an animal model to investigate the molecular basis of psoriasis and demonstrated how the proliferation of T cells is key to the formation of psoriatic lesions. Additionally, the researchers highlighted the importance of tumor necrosis factor as a molecular mediator for the development of these psoriatic lesions.

- Dr. Robert Klein at the Oregon Health and Science University and colleagues identified the gene Alox15 while working with two strains of mice that have different bone densities. It was known that Alox15 was important in the lypoxygenase pathway with regard to metabolism of certain fatty acids, but until Dr. Klein's findings, it was not known to be important for bone. Once its complete function is known, this gene will be a target for therapeutic intervention.

- Dr. Jeffrey Katz and other researchers at the NIAMS clinical research center at Brigham and Women's Hospital described the rates of primary and revision total knee replacement (TKR) in U.S. individuals older than 65 using Medicare claims and information on TKR in 2000. The primary knee replacement rate was lower in African Americans than in whites, as well as in those qualifying for Medicaid supplementation than in those with higher incomes. Furthermore, African Americans had higher rates of mortality, readmission, and wound infection after primary knee replacements than did whites. In addition, patients who qualified for Medicaid supplementation had very high complication rates, particularly after primary knee replacement. Although overall rates of postoperative complications during the 90 days following TKR are low, these data underscore the health disparity challenges facing this country.

- A recent *Journal of the American Medical Association* paper by Dr. Steve Cummings and colleagues at the California Pacific Medical Center focused on bone mineral density and the risk of incident nonspinal fractures, specifically whether bone mineral density predicts fracture risks as effectively in African American women as it does in white women. Decreased total hip and femoral neck bone mineral density was associated with increased risk of fracture in both older African American women and white women, but this relationship is largely explained by other risk factors in African American women. African American women had a lower fracture risk than white women at every level of bone mineral density. This study suggests that rate-specific normative databases may be appropriate in terms of these predictions. The study was funded by the NIAMS and the National Institute on Aging.

- In a recent advance in cartilage and osteoarthritis basic research, Dr. David Rhee and colleagues at Case Western Reserve University studied the function of the secreted glycoprotein lubricin. The researchers developed lubricin knockout mice and examined joint failure over time. Results indicated that lubricin has multiple functions including the protection of articular cartilage and the inhibition of synovial cell overgrowth.

- In the current *Proceedings of the National Academy of Sciences*, Dr. Chris Evans at Brigham and Women's Hospital and colleagues at the University of Pittsburgh have shown that gene transfer may be a potential therapy for rheumatoid arthritis. Researchers examined the safety and feasibility of using

IL-1Ra gene transfer in postmenopausal women with advanced rheumatoid arthritis. Promising outcomes suggest that further investigation in this area is warranted.

- A recent study conducted by investigators at the University of Rochester on the use of rituximab to treat lupus indicates that the drug may be useful in reducing symptoms with minimal side effects. Rituximab is an anti-B cell antibody that is approved by the U.S. Food and Drug Administration (FDA) for use in lymphoma. Additional studies are needed to better understand its effectiveness and safety and to better determine its role in lupus treatment.

- Dr. John Harley of the University of Oklahoma and coworkers are continuing to study the Epstein-Barr virus (EBV) as a possible causative factor in the early development of lupus in susceptible patients. In a related effort, Dr. Judith James of the Oklahoma Medical Research Foundation is examining serum supplies from a U.S. Department of Defense bank to track the development of antibodies against EBV infection in lupus.

Highlights of Recent and Upcoming Activities

A few months ago, the NIAMS gave permission for its brochure entitled "Childhood Sports Injuries and Their Prevention: A Guide for Parents with Ideas for Kids" to be reprinted and included in the *Kraft Baseball Guide*. The brochure targets parents and coaches and includes health and nutrition information as well as product information for children. Kraft printed 130,000 copies of the *Guide* which were distributed through Kraft displays located in each of the 240 Giant Eagle grocery stores.

The Institute's Strategic Plan for fiscal years 2005-2009 is currently under development. As part of this plan, the NIAMS is developing strategies to address issues that cut across its extramural programs. The strategic plan will be presented at a future Council meeting.

V. INITIAL THOUGHT AND DISCUSSION ON IMPROVING THE EFFECTIVENESS OF NIH PEER REVIEW

Dr. Antonio Scarpa, the new Director of the NIH CSR, provided Council members with his vision on how to improve the NIH peer review process. CSR receives, processes, and assigns all applications submitted to the NIH, which totaled approximately 75,000 in the last year. In addition, CSR conducts primary scientific reviews of about 55,000 applications each year, drawing from a pool of approximately 14,000 reviewers. Serving as a portal between outside investigators and the NIH, CSR's mission is to provide the NIH with fair, independent, expert, and timely review of grants so that the NIH can fund the most promising research. In deliberating on potential changes to CSR procedures,

Dr. Scarpa has obtained input from Institute/Center Directors, NIH administrators, professional societies, clinical research leaders, and international experts.

The system has been somewhat unresponsive to some of the rapid changes that have occurred in society, medical schools, and the way research is conducted. There is a lack of protected time for clinical research and what may be an unsustainable reliance on faculty salary related to grants. In addition, there has been a major shift in the way science is conducted through large groups, facilities, and programs. CSR needs to adapt to these changes. One of Dr. Scarpa's first priorities is shortening the review process (i.e., decreasing the time investigators must wait between application submission and receipt of comments and priority scores). Every scientist, Chair, Dean, Institute Director, and even Congress is concerned about the length of time it takes for reviews. Another priority is fostering a culture that is more favorable to applications that are high risk, innovative, and have a greater potential payoff. As stewards of the system, CSR cannot afford to ignore the most innovative research. CSR must also address the concern that clinical research is not properly evaluated. The biggest challenge in this regard is recruiting and retaining the best reviewers.

CSR will form two committees that will be horizontally integrated and includes individuals from Institutes, Centers, and outside experts. One of the committees will be composed of "engineers" who will examine the current system, identify the components that work well, and attempt to fix those that are less effective. The second committee will include innovative thinkers who will address whether the current system only needs to be adjusted, or whether an entirely new and different system should be adopted.

Dr. Scarpa outlined activities that CSR plans to implement in the near term:

- Decrease the review process by 40 days. If investigators can receive their critiques 3-4 weeks before the next application deadline, this potentially could save an entire review cycle (about 4 months).

- Create and pilot an electronic review system that includes a form of electronic "chat" so that reviewers would not have to travel to Bethesda to participate in a review.

- More effectively manage paper volume. At present, appendices for applications (which are comprised mostly of published papers and reprints) consume more than 120 acres of forest per year.

- Create and utilize a 1-page template for information that will be distributed to each applicant and reviewer that explains how application-related information can be changed.

Dr. Scarpa emphasized CSR's commitment to improving the system in an expeditious manner, noting that science (and the places where science is conducted) is changing, and CSR cannot fulfill its mission if it does not adapt to the changes that have occurred and that will continue to occur.

NIAMS Council member Dr. John Stanley, Milton B. Hartzell Professor and Chair of the Department of Dermatology at the University of Pennsylvania School of Medicine, emphasized the importance of recruiting and retaining reviewers who have the appropriate knowledge. An incentive of some type may be necessary to help retain senior reviewers. Finding ways to simplify the application process (e.g., by decreasing the application length so that applicants are forced to submit focused applications) would make the process much easier for both the reviewers and the applicants. Dr. Scarpa noted that retaining reviewers with appropriate expertise is even more critical in clinical research, where for example, it can be extremely difficult to identify a cardiovascular surgeon who is willing and able to commit to traveling and attending a 2-day review meeting. If individuals can participate in these meetings electronically from their homes or offices, it might help solve the problem. Dr. Scarpa commented that CSR also is working to shorten the application form.

In response to a question from Dr. Yan Wang, Chief of the Review Branch at NIAMS, Dr. Scarpa explained how the CSR plans to cut 40 days from the review process, primarily through streamlining the procedures for receiving and assigning grant applications and sending them out. CSR is committed to reducing the time by this 40-day period within the next year for all applicants. NIAMS Council member Dr. Brian Kotzin, Vice President and Head of the Inflammation Therapeutic Area at Amgen, Inc., noted that if the speed of the review is increased, it may decrease the need for all of the supplemental material that is submitted because there would be less of a gap between application submission and the review. He also commented that incorporating a higher level of consistency into the review process would be a significant improvement. He asked whether Dr. Scarpa thought that the recent study section reorganization was effective. Dr. Scarpa replied that broadening the study sections was a good idea, but the reorganization is only one step to improving the review process. Dr. Scarpa also noted other improvements to the system such as shortening the review period and recruiting/retaining the best reviewers.

NIAMS Council member Dr. Cato Laurencin, University Professor and Lillian T. Pratt Distinguished Professor at the University of Virginia, described the peer review system at the National Science Foundation (NSF), where all applications are submitted, reviewed, and scored electronically. At NSF review meetings, application scores are placed on a grid so that the more meritorious applications can be identified quickly and easily. In some cases, the NSF also sends individual reviews to the reviewers before the review meeting, so that they can get a sense of the applications' strengths and weaknesses from the primary and secondary reviewers before the meeting. This approach significantly cuts down on the time

needed for discussion during the review meeting. Dr. Laurencin asked whether the NIH has considered this type of approach, particularly in terms of utilizing an electronic review system. Dr. Steven Hausman, NIAMS Deputy Director, noted that the NIH is taking steps in this direction. Currently, paper applications dating back to 2002 are in the process of being scanned, and all reviewers now receive CD-ROMs containing the applications instead of boxes of paper applications. The NIH eventually plans to implement a completely electronic process, and a number of experiments with electronic-assisted review are underway. Dr. Scarpa noted that the NSF system works well, and could serve as a model for some of the efforts at CSR. Dr. Wang explained that Internet-assisted review has potential for advancing rapid scientific review, particularly through a feature that makes the review-related materials available online so that reviewers can access the materials from their homes or offices. NIAMS Council member Dr. Jouni Uitto, Professor and Chair of the Department of Dermatology and Cutaneous Biology at Jefferson Medical College, asked about the review turnaround time at the NSF. Dr. Laurencin responded that applicants typically are given their scores a few weeks following the review meeting.

Dr. Uitto commented that many study section reviewers are new investigators who lack a "big picture" perspective. The CSR should consider addressing this issue. Dr. Cheryl Kitt, Director of the NIAMS Extramural Program, noted that one possibility may be instituting flexible terms on study sections, particularly for senior investigators and reviewers who will have grants up for competitive renewal during their term. Dr. Scarpa added that utilizing electronic means to avoid having reviewers traveling to Bethesda frequently for review meetings also may help retain senior reviewers.

Dr. Martin Kushmerick, Professor in the Department of Radiology at the University of Washington and a member of the NIAMS Advisory Council, described the need to promote a culture that is favorable to innovation in the review process. At present, including new ideas in proposals often is detrimental, particularly for new investigators. Dr. Steven Teitelbaum, a Professor at Washington University School of Medicine, described the issue of conflict of interest on study sections, which can present a number of problems (e.g., pressuring senior members of a group to not participate in a study section because their presence would exclude certain other members of that group from having their grants reviewed by that study section). Dr. Scarpa noted that having a large number of well-qualified reviewers is the best way to address these conflict-related problems.

Dr. Francesco Ramirez, Chief Scientific Officer at the Hospital for Special Surgery in New York and a member of the NIAMS Advisory Council, asked about the timing of the changes described by Dr. Scarpa. Dr. Scarpa explained that some of the changes will be implemented quickly. For example, as soon as CSR has been reassured that it is legal to utilize Internet "chats" in the review

process, CSR will act immediately. CSR also hopes to have shortened the review cycle by 40 days for at least half of the applications by February 1, 2006.

VI. BURDEN OF MUSCLE DISEASES MEETING REPORT

Dr. Richard Moxley, Professor in the Department of Neurology and Director of the Neuromuscular Disease Center at the University of Rochester and a member of the NIAMS Advisory Council, recently co-chaired a meeting on the burden of muscle diseases with Dr. Richard Lymn, Director of the NIAMS Muscle Biology Branch. The meeting included clinicians and researchers in the field of muscular dystrophy; patients and advocacy group representatives; health care economists; epidemiologists; and representatives from the NIAMS, the Centers for Disease Control and Prevention, the Agency for Healthcare Quality and Research, and the Health Resources and Services Administration. Virtually all attendees participated in large group discussions that were held during the workshop, and many have indicated an ongoing interest in pursuing collaborative research projects related to topics that were covered.

Congress became aware of a lack of information regarding the economic burden of various muscle diseases and injuries. The Senate Appropriations Committee asked the NIAMS and other Public Health Service components to sponsor a workshop to address this concern.

The meeting's planning committee decided to focus on the most common muscular dystrophies because they have clear clinical definitions and present a major challenge in terms of care for patients, family members, and providers. Six overlapping goals were developed: (1) identify the limitations in the ability to assess burden of disease, (2) identify measurements to evaluate the effects of an actual intervention, (3) determine the general components of the burden for specific types of muscle conditions, (4) identify the components of the burden of chronic muscle disease, (5) determine the most useful methods to measure burden, and (6) identify current sources of data that are available to measure the burden. Participants were asked to offer comments during the large group discussions that complement the remarks made by the speakers in advance of attending the meeting, so each participant had an idea of topics that they were going to be asked to discuss, even if they were not formally presenting.

The first topic discussed at the meeting focused on the uses and challenges associated with burden of disease data. Several uses of burden of disease data were covered, and the challenges associated with collecting these data were described (e.g., the absence of a central authority to set priorities for collection, cost of data collection, time required of caregivers and patients to complete surveys, and the need to strike a balance between using detailed disease-specific data and broader burden measurements that are more comparable between different disease categories). Parents of children with muscular dystrophy discussed the importance of defining burden more broadly to include the impact

of disease on patients, families, and caregivers. Financial burdens in addition to medical bills, such as lost parent and patient income, also were discussed. There is a need to capture intangible burdens besides mortality and disability (e.g., anxiety patients and their families face when obtaining a diagnosis, emotional impact on parents and siblings, and isolation experienced by patients).

The second topic covered instruments to measure the health and psychosocial burden. The pros and cons of various quality of life measurement surveys were highlighted. The issue of study bias was raised and illustrated by the fact that patients and families who are coping well are more likely to participate in studies. Quality of life surveys are difficult to validate, and there are concerns that these surveys may not measure what is truly important to the person with the disease. Parent or caregiver proxy reports often rate the affected individual's quality of life lower than does the individual. Additionally, patient self reports often fail to provide a full picture of the disease impact and do not adequately assess the burden on the care providers or other family members.

The third topic, quality of life instruments, included information on preference-based summary measures of health. The most widely used measures are quality-adjusted life years (a summary of longevity and health-related quality of life) and disability-adjusted life years (a time-based population summary of years lost to premature death and years lived in disability). Although population-based preferences are useful in setting health policy, patient-based preferences are more helpful in guiding clinical treatment. In assessing the muscular dystrophies, which are characterized by great personal burden but a low prevalence, it is crucial that patient burden be adequately measured. No single measure is suitable for evaluating all aspects of burden, and various methods of refining generic measures were proposed.

The fourth topic addressed key aspects of the burden of muscular dystrophy and similar conditions. Although population-based data sets are useful for capturing all of the people in a region who have a condition rather than merely using those who utilize clinics and hospitals, the value of any such data based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes is limited because the different types of muscular dystrophy do not have separate ICD-9 codes. In terms of cost measures for chronic myopathies, there was a focus on the necessity of extracting and assessing cost information from multiple data sets when studying low-incidence diseases such as muscular dystrophy. Most of the available data sets are large administrative data sets that generally lack descriptive detail, limit usefulness due to the generic ICD-9 codes, and do not capture indirect costs (e.g., the cost of lost wages to caregivers). Various approaches to developing a comprehensive cost picture were discussed.

During the closing general session, key needs for future work on the burden of muscle diseases and other progressive mobility disorders were discussed. Panel moderators provided summaries of the opportunities, challenges, and

recommendations that emerged from the discussions. Three critical recommendations emerged: (1) utilizing a data review and measurement instrument development process that can be replicated by other government agencies and research groups studying different diseases, (2) modifying available data collection instruments wherever possible to obtain data quickly, and (3) locating funding sources for data mining and instrument development. Meeting participants also suggested that several working groups be convened to review and develop measurement instruments for quality of life and to explore burden of disease survey methodology with guidance from health economists.

Dr. Katz thanked Drs. Moxley and Lymn for serving as meeting Co-Chairs. One major challenge appears to be developing some common metrics and gathering the data or identifying existing data. Dr. Stanley voiced concern that policymakers may inadvertently be taking a simplistic view when looking at the burden of various diseases with common metrics to determine where resources should be allocated. This approach can be detrimental to the study and treatment of less common diseases. There are many examples of how the study of rare diseases has led to many important advances in more common diseases (e.g., the study of pseudohermaphrodites resulted in important information about benign prostatic hypertrophy), and it is critical that policymakers get this message. Dr. Katz agreed, emphasizing that the study of rare diseases has yielded a large amount of valuable information about medicine in general. He added that it is difficult, if not impossible, to develop metrics for certain aspects of the burden of disease (e.g., measuring the burden in a family that knows a child will die before reaching the age of 20).

Dr. Moxley noted that the FDA is asking researchers submitting applications to marry their endpoint measures with something that is of value to the patient. It may be helpful to ask patients for help in crafting messages that tie fundamental measurements reflective of the disease process to patient-identified priorities. There are many terminology barriers researchers will have to address in this regard (e.g., the difference between patients feeling “fatigued” versus feeling “weak”). Dr. Raymond Scalettar, Clinical Professor of Medicine at George Washington University and a member of the NIAMS Advisory Council, asked if the meeting included a discussion of social service or insurance recommendations. Dr. Moxley replied that there was limited comment on social services. One Canadian participant discussed her experience with patients who have myotonic dystrophy and the critical role that having a strong base of social service outreach has played, particularly in terms of genetic counseling. There were no recommendations related to insurance that resulted from the meeting; however, Dr. Moxley has been in contact with health economists who attended the meeting and who may begin to examine existing data sources for information to begin addressing these types of issues.

VII. REVIEW/DISCUSSION OF THE NIAMS EXTRAMURAL PROGRAM SCIENTIFIC RETREAT

The NIAMS Extramural Program Scientific Retreat was held at Wye River in April and attended by NIAMS staff and invited extramural researchers. Two main topics of discussion were: (1) a review of NIAMS scientific programs, and (2) a discussion of issues related to the budgetary restriction NIAMS faces now and in the future.

During a discussion on osteoarthritis, it was noted that some pharmaceutical companies now view osteoarthritis as a biomechanical disease that should be approached biomechanically, rather than considering the disorder as a target for drug design and development. The NIAMS leads NIH's research effort in the area of osteoarthritis through three programs: (1) a basic biology program focusing largely on cartilage biology, (2) a clinical program, and (3) the Osteoarthritis Initiative, which primarily focuses on epidemiology and imaging. Participants discussed whether the R01 is the best tool for conducting research in this area and whether larger mechanisms should be considered. Risk factors that were covered included ethnic, racial, and gender issues as well as nonskeletal-confined issues (e.g., obesity, hypertension, diabetes, etc.). One approach to expanding osteoarthritis research and broadening investment in this area may be to partner with other Institutes that focus on these nonskeletal-confined disorders.

During a discussion of regenerative medicine (also known as reparative medicine), which involves replacing damaged tissues through tissue engineering, tissue remodeling, and biomechanical means, it was noted that this area has a lot of potential but few clinical successes at present. Use of stem cell biology, which is a major component of this effort, is controversial and carries with it some risks (e.g., there is a concern that some technologies have gone to the clinic prematurely, and that concern applies to stem cell technologies). It is important to avoid repeating mistakes made in other areas (e.g., gene therapy). Additionally, more basic research is needed to ensure that the biology and control of these approaches are well understood.

Other topics related to scientific programs discussed during the retreat included the clinical aspects of musculoskeletal tissue regeneration from the surgeon's point of view, cutaneous regenerative medicine, and the growth and regeneration of skeletal muscle in diseases. There also was discussion of whether a workshop on regenerative medicine should be convened. Regenerative medicine eventually will be used by biologists in a number of fields, and moving the science forward in this area should be a trans-NIH effort. The NIAMS could sponsor a workshop on this topic, but it should include a number of other NIH Institutes.

The latter part of the retreat involved a session on the difficult choices facing the NIAMS in light of the budget situation (i.e., what the Institute can and cannot live without). Dr. Katz led a discussion of issues that are important to NIH-funded

researchers, including percentiles, success rates, downward negotiations, and the payline. It is critical that the payline not drop to a point at which new investigators are discouraged from applying for grants. Retreat participants discussed whether the R01 should continue to be the major mechanism used by the NIAMS. Maintaining the payline and the impacts that larger programs (e.g., Research Program Projects (P01s), Centers of Research Translation, Requests for Applications (RFAs), Program Announcements (PAs, etc.) have on the payline were discussed. Utilization of other mechanisms, such as small grants (R03s), was discussed. Time also was spent on how best to resolve reconciling the needs of the NIH Roadmap with the NIAMS mission.

Participants discussed limiting the amount of money that an investigator can/should receive or the number of grants that can be awarded to an investigator. Overall however, there was a general sense that grants should be awarded based on merit and not limited by the number of grants a particular investigator has been awarded. Additional discussions focused on the advantages and disadvantages of training grants, P01s, R01s, and NIH Exploratory/Developmental Research grants (R21s).

Dr. Raisz asked about the differences between T32 and F32 awards, particularly as they relate to the timing of award decisions. Dr. Teitelbaum replied that this issue was not discussed at the retreat. However, Dr. Katz noted that the Institute is investigating this in some detail. The timing of the announcement of T32 awards has been moved up, and the NIAMS is examining whether this mechanism is providing results that are aligned with its intended purpose. Dr. Katz also explained that he has been working with representatives from American Academy of Orthopedic Surgeons (AAOS), American Society for Bone and Mineral Research, and the Society for Investigative Dermatology (SID) to identify senior scientists to participate in reviews of grants that do not go through the CSR review process (e.g., T32s, P01s).

VIII. DISCUSSION OF NIAMS PROGRAM PROJECTS

Dr. Katz reminded Council members that program project grants, or P01s, have served the NIAMS well, but difficult decisions face the Institute in the near future because of budgetary constraints. P01s may be one of many areas facing possible change, particularly because of the significant effects P01s have on the payline. Dr. Katz has communicated with a number of organizations such as the SID and AAOS that clearly identified preserving the payline as a top priority. Other suggestions from these organizations include having grants last for no less than 4 years on average and having downward negotiations not exceed 10 percent.

Dr. William Sharrock, Health Scientist Administrator in the NIAMS Musculoskeletal Diseases Branch, explained that the payline is a percentile that comes from the pool of R01s reviewed by CSR. Every dollar that goes into one of the special mechanisms that the NIAMS uses (e.g., training grants, P01s,

RFAs, Centers) is a dollar that is not supporting the research reflected in the percentile payline. Although the Institute's appropriation increase is a significant factor in determining whether the NIAMS has a good payline, the money set aside as a percentage of the competing dollars available in a given fiscal year also is a large a factor in how much money is available to support the R01s from the percentiled CSR competition.

Dollars allocated for P01s are not spent according to the percentile payline. P01s are large, multicomponent mechanisms that have a very specific purpose and are reviewed by special committees convened by the Institute. P01s are intended to provide scientific progress in a way that is not possible through the award of a series of individual R01 grants. P01s are designed to incorporate collaboration, interaction, and synergy that distinguish this mechanism from others. It is difficult to determine whether the P01 mechanism has produced science that would not have been achieved through individual R01s, and the Institute is attempting to determine whether the P01 mechanism is working as it was intended. Dr. Sharrock and others at the NIAMS examined the management of P01s from the point at which they are accepted for review to the point at which a decision is made on whether to fund a given application. P01s have a significant impact on the budget—in 2003, almost 14 percent of the dollars available for competing grants were dedicated to P01s. Dr. Sharrock reminded Council members that the more money allocated to pools of competing awards that are not part of the percentiled CSR reviewed pool (e.g., P01s), the less money there is available for that pool of awards.

The budgetary impact of P01 grants is a function of the number of P01 applications the Institute accepts for review, the size of their budget requests, and the success rate. For fiscal years 2002, 2003, and 2004, P01 applications had a 51 percent success rate. Continuing P01 grants had a 64 percent success rate during those years. Although the P01s represent a fairly small number of applications, they have a significant budgetary impact because they tend to have direct cost totals approaching $1 million. By way of comparison, the R01 success rate has been much lower during this 3-year period, at 20 percent (16% for new applications, 39% for continuing R01s). As opposed to R01s, which are reviewed by CSR standing study sections, individual P01s are reviewed in isolation by *ad hoc* committees convened by the NIAMS Review Branch. No percentile is assigned to P01s, they receive a priority score that is given without looking at the other P01s that are on the table for that fiscal year. In general, the principal investigators (PIs) for P01s are prominent, accomplished, experienced scientists, which is not the case for many R01s (although continuing, or Type 2, R01s are ongoing projects that often are led by experienced, accomplished PIs). Not all P01s are accepted for review—the NIAMS communicates with investigators before they submit their applications, and the Institute can discourage or even refuse applications.

Dr. Sharrock presented a comparison of the review results between 16 R01s and corresponding component projects within P01s (NIH guidelines allow for submitting parallel R01s with a P01, and in these cases, the R01s and P01 component projects were the same) that were submitted to the NIAMS within the last four Council rounds. Thirty priority score points was arbitrarily selected as the boundary for whether an R01 scored significantly better or worse than its corresponding P01 component project. Of this group of 16, 9 P01 component projects scored significantly higher than their corresponding R01s, 4 scored significantly lower, and there was no significant difference in 3 cases. Dr. Sharrock concluded that in this limited sample, it appears that there is an advantage to being reviewed as part of a P01 as opposed to an individual R01, and this likely plays into the higher success rate associated with P01s. Because the payline could be improved by the NIAMS making fewer P01 awards, consideration needs to be given to ensuring whatever P01s are supported are consistent with the intent of the mechanism. It also would be appropriate for the Institute to consider its administrative process, particularly in terms of how P01s are reviewed and scored, and how funding decisions are made.

Dr. Sharrock and colleagues contacted representatives from other Institutes that have made policy adjustments with regard to P01s to determine how they are administratively managed at these Institutes. The National Cancer Institute (NCI) and National Heart, Lung, and Blood Institute (NHLBI) have instituted an elaborate two-stage review process for P01s in which a technical committee first reviews the component projects and scores them. Then, a parent committee reviews these scores and compares all of the P01s to determine how well they fit the criteria for a program project grant. This second-level review is intended to maintain a measure of consistency and impose a uniform standard on the scoring of P01s. Several Institutes, including the NCI and NHLBI, set aside funds for P01s at the beginning of the year to control the impact on the budget. Other Institutes, such as the National Institute of Mental Health and National Institute of Dental and Craniofacial Research do not accept unsolicited P01s. They only accept them in response to a specific solicitation identifying an area of science where it has been judged that the P01 mechanism could make a particularly large contribution.

Dr. Sharrock concluded his remarks by commenting that it might be advantageous for the NIAMS to consider how it is using this mechanism and the possible payline-related benefits associated with potentially restricting this investment. He presented three options: (1) institute a cap on funds that would be available in a given year for this mechanism, (2) restrict the number of applications that the Institute handles by implementing a selection process, and (3) examine the peer review process and possibly make changes to ensure consistency and uniformity.

Dr. Katz noted that the P01s funded by the NIAMS have been awarded to outstanding investigators, and the bar has been set extremely high in terms of the quality and interconnectedness of these awards. Dr. Teitelbaum noted that P01s

cannot be adequately reviewed in the same way that R01s are reviewed, primarily because the PIs for P01s typically are distinguished investigators who are well known on a personal and professional level throughout the scientific community. It is critical to review the P01 review process, but it is may not be possible to adjust the peer review process for these awards to achieve the same stringency and degree of fairness under which R01s are reviewed. Dr. Katz added that the NIAMS senior leadership takes the scores into account when making award decisions related to P01s, but there also are many other factors that are considered during the process.

Ms. Sharon Terry, Executive Director of PXE International, asked if the individual components of a P01 tend to be scored higher than individual corresponding R01s because the P01 components are examined in relation to one another and with the support of the other components. Dr. Sharrock explained that the "synergistic" effect of the P01 components generally is factored in after the individual components have been scored. It is common for a P01's overall score to be better than the arithmetic average of its components; this generally is seen as reflecting the synergy and interdependence of the program.

Dr. Kushmerick asked if the individuals who review P01 applications are drawn from the same pool of reviewers as the R01s. Dr. Sharrock noted that those asked to sit on P01*ad hoc* review committees often have served on CSR study sections and generally are experienced reviewers. Dr. Kushmerick added that P01 grants not only contain a measure of synergy, but also may contain more innovation than typical R01s, and they typically are reviewed by more senior investigators. These factors could help account for the fact that the P01s have a higher success rate than R01s. Dr. Sharrock suggested that the NIAMS try to determine what it is that P01s do more effectively than R01s and ensure that when money is taken from the R01 pool and used to fund P01s, that these awards reflect this.

Dr. Kotzin emphasized that the R01 payline is critical. A more stringent process for P01s to succeed may be needed. He asked what the implications would be on the R01 payline if the P01 success rate was dropped to 20 percent. Dr. Sharrock replied that it would take some time to reach a new steady state because the previously awarded P01s have continuing years. The total amount for P01s (both competing and noncompeting awards) is approximately $35 million each year. If these funds were moved to percentiled R01s, it would move the payline by about 10 percentile points. However, because of the continuing commitment to ongoing P01s, the effect would not be large and it would not be immediate. Additionally, some of the components of P01s that would not be funded under this scenario would be submitted as individual R01s, some which would compete successfully. This scenario could enlarge the R01 pool considerably.

Dr. Raisz commented that P01s in general are very well reviewed; their higher success rate may be due to the fact that they represent significant efforts on the part of a large number of experts, and P01s generally have been refined

extensively before they go forward for review. A review of existing P01s would help to determine whether the synergies and infrastructures created by this mechanism are unique enough and set it apart enough from the R01 mechanism. Dr. Sharrock noted that the NIAMS has not attempted to assess whether P01s deliver a type or quality of science that is clearly superior to the science generated by R01s. One approach could involve examining the publication output from P01s and considering whether those papers include multiple authorship reflecting collaboration among members of the award, although this type of effort would be very labor intensive. Dr. Raisz suggested that the NIAMS consider reviewing P01s that were awarded 5-10 years ago to assess their outcomes.

Dr. Ramirez, who has a P01 award and is writing the competitive renewal for an R01, discussed the perceived laxity of the review process and high success rate associated with the P01 mechanism. He explained that the P01 is the only vehicle for large investigator-initiated projects. The only other similar mechanism that uses a non-R01 review process is the RFA. He suggested that it might be more appropriate to compare P01s with RFAs instead of R01s. To ensure that the P01 mechanism is generating the results that the Institute is looking for, the NIAMS should closely examine the review process and length of these awards. In addition, the Institute could consider maintaining a fixed number of P01s and limiting them to short-term projects (e.g., 8 years). Another suggestion included using the P01 mechanism to help publicize the Institute's activities, in the same way that RFAs give the public an idea of NIAMS programmatic activity.

Dr. Katz emphasized that for a P01 to be accepted and approved by the Institute, it must be critical to the NIAMS mission. He also noted that the success rate for RFAs is much lower than the rates for any other mechanisms, and there is little flexibility to adjust the amount of money dedicated to RFAs (only 4% of the NIAMS budget in 2005 is allocated for RFAs).

Dr. Uitto, who holds the longest lasting P01 funded by the NIAMS (18 years), described the success of his project and emphasized that the P01 is an effective vehicle for addressing specific diseases using a multifaceted, multidisciplinary, cross-cutting approach. It might not be appropriate to compare the individual components of P01s to R01s within the context of an R01 review, primarily because the collaboration and synergy associated with the P01 components are not taken into consideration in this scenario. Dr. Stanley asked whether P01s are funded according to their score. Dr. Katz explained that the NIAMS Program Director attends the P01 review, and the in-depth summary review statement is reviewed carefully by the Program Director, Branch Chief, and Drs. Kitt and Katz before a decision is made on whether to fund a specific P01. There have been years in which the NIAMS funded P01s that had lower scores than other P01s—the score is only one factor that enters into the decisionmaking process. Dr. Stanley noted that submitting P01s as individual R01s would provide some basis of comparison between the two mechanisms. Dr. Kitt responded that P01s have

components of synergy and integration that set them apart from R01s, and these components are factored into the funding decision.

Dr. Stanley commented that the NIAMS should seek to determine whether the results of P01s could be accomplished through the R01 mechanism. Although it is possible to track a PI's accomplishments based on their publications, the amount of support that the PIs receive to reach these accomplishments rarely, if ever, is considered. It also is extremely difficult to evaluate the accomplishments of P01s, particularly in terms of the resources put into these awards, because the mechanism is unique and there are no other vehicles to compare it with. Ms. Terry asked if the NIAMS could consider advertising an "investigator-initiated science" payline that would include the success rates for both R01s and P01s. She also asked if there is an entry route to P01s for new investigators. Dr. Katz replied that this is a fairly controversial area. Some experts believe that new investigators are very well served by applying for P01s; other experts feel that it is not an effective way to bring in new investigators.

Dr. Parr commented on the need to ensure that P01 awardees are conducting the research that they proposed to carry out in their application. Dr. Katz assured him that the NIAMS tracks the PIs' progress and confirms that they are working in manner that is consistent with their application. Dr. Sharrock noted that the same work carried out by PIs with P01 awards is not being done with component R01s, so it is difficult to tell whether the P01 mechanism is yielding results that would not otherwise occur through the use of R01s.

Dr. Laurencin described an NIH mechanism that may represent a compromise of sorts between the P01 and R01 mechanisms, known as glue grants. Investigators submit R01s that are scored, and if found to be meritorious, funded. Groups of investigators then can submit a grant that brings them together for collaborative work. Glue grants are funded up to $300,000 per year for 4-5 years. This mechanism includes the R01 review and funding process while giving investigators the opportunity to carry out synergistic work in a way that is similar to the P01. Dr. Katz noted that this mechanism is similar to the NIAMS' core grants. Dr. Uitto added that every 5 years, P01s undergo a renewal competing process that includes a comprehensive review of the grant.

Dr. Ramirez noted that the NIAMS has an opportunity to make the P01 a valuable, distinct vehicle for good science. If four separate investigators are working very closely together in the spirit of a P01 but submit R01 applications, they will not be as competitive as other individual R01s applications, because independence is considered as a metric of success. This element of cooperation and synergy will not exist without the P01 vehicle.

IX. NIAMS MIDDLE SCHOOL CURRICULUM

Dr. Barbara Mittleman, Chief of the Scientific Interchange Section in the NIAMS Intramural Research Program's Office of Science and Technology, described a curriculum supplement for seventh and eighth graders entitled "Looking Good, Feeling Good: From the Inside Out." The NIH Office of Science Education (OSE) solicited proposals from the various Institutes and Centers to develop curriculum supplements for students in kindergarten through high school. The NIH views these activities as important and hopes that they contribute to convincing young people to consider careers in science. The NIAMS proposed a curriculum for seventh and eighth grade science classes that focuses on muscles, skin, and bones. OSE accepted NIAMS' proposal and funded two-thirds of it; the NIAMS funded the remaining third. Several companies that write textbooks and curricula responded to a Request for Proposals (RFP), and an award was made to Biological Sciences Curriculum Studies (BSCS), a major producer of life science textbooks in the United States. BSCS helped design the curriculum using their Five E Model, which aims to: (1) engage the students in the process, (2) allow them to explore it in an active way, (3) explain the material, (4) elaborate in other areas, and (5) evaluate by integrating and extending what the students have learned. The curriculum also includes components of the National Science Education standards, which relate to scientific method, how scientists think about conducting science, and the methodological approaches to carrying out science-based work. The curriculum was designed to cover about 1 week of classroom time, replace an existing module covering the same topics, be engaging and memorable, and be appropriate for use in schools all across the country.

A process advisory committee within the NIAMS was formed, and a committee of outside experts was created to provide content advice (e.g., prioritizing potential topics to be included in the curriculum). A writing committee also was formed that included content experts and teachers. Basic core concepts were selected, and diverse field test schools were identified (e.g., public schools; private schools; schools in urban and rural areas; schools with predominantly African American populations, white populations, Native American populations, etc.). Teachers from the field test schools were trained on using the curriculum and scheduled time in their classrooms to teach it. Dr. Mittleman conducted a site visit and although her presence may have affected the teacher and/or the students, her overall impression was that the students enjoyed the material. Each student and teacher from the field test sites was asked to complete evaluation forms to determine whether any adjustments to the curriculum were needed.

Once finalized, the curriculum took slightly more than 1 week to teach in the classroom. Dr. Mittleman described the lessons contained in the curriculum, which included the following:

- Learning that muscles, skin, and bones are living organisms.

- Determining what it is that makes bones strong.

- Investigating how a series of muscle contractions produces the movements needed to kick a ball.

- Learning that the body is an integrated system.

- Using quantitative research and data from animal studies to determine how muscles develop, and relating this information to students' own physical activities.

- Discussing sun exposure and vitamin D, as well as the interrelated nature of skin, bones, and muscles.

- Having the students make presentations on what they learned, with an emphasis on the fact that choices they make and the actions they take have implications in terms of the science and in terms of their health.

The curriculum is available for free to any teacher who registers on the OSE Web site. Web-based activities associated with the curriculum have paper analogs so that schools without Internet access can still fully utilize the curriculum. The curriculum is meant to be used in its entirety, but it is likely that teachers will pick and choose particular lessons and activities to teach their students. It is expected that the curriculum will get very wide exposure; it is anticipated that 20,000-30,000 copies will be distributed. Unfortunately, there is no way to measure how use of the curriculum compares with the number of requests for it, but OSE is developing an evaluation program to address these types of issues.

Dr. Teitelbaum asked whether students introduced to this curriculum have a better sense of what it is like to be a scientist. Dr. Mittleman replied that this was one of the goals, but conveying this to students is difficult. The curriculum appears to be successful in infusing science throughout the classroom—students read research papers, collect data, and are challenged to use the scientific method in the same way as scientists. However, the degree to which the curriculum accomplishes these goals is unclear. Dr. Katz asked whether or not the curriculum is being used. Dr. Mittleman explained that there are data showing that the curriculum has been ordered and sent to teachers, but there are no data on the frequency or degree to which the curriculum is being used.

X. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 652 applications in closed session requesting $149,226,348 and recommended for $148,166,420.

XI. ADJOURNMENT

The 56th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 4:00 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.

_____	_____
Cheryl A. Kitt, Ph.D. Executive Secretary, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council	Stephen I. Katz, M.D., Ph.D. Chairman, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council
Director, Extramural Program National Institute of Arthritis and Musculoskeletal and Skin Diseases	Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases