

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH  
NATIONAL CENTER FOR COMPLEMENTARY  
AND ALTERNATIVE MEDICINE**

**NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY  
AND ALTERNATIVE MEDICINE  
MINUTES OF THE TWENTY-FOURTH MEETING  
June 8, 2006**

*NACCAM Members Present*

Dr. Carlo Calabrese, Portland, OR  
Dr. Silvia Corvera, Worcester, MA  
Dr. Deborah J. Cotton, West Roxbury, MA  
Dr. Jeanette Ezzo, Baltimore, MD  
Dr. Joan Fox, Cleveland, OH  
Dr. L. David Hillis, Dallas, TX  
Dr. Ted Kaptchuk, Boston, MA  
Dr. Tieraona Low Dog, Tucson, AZ  
Dr. Bala Manyam, Temple, TX  
\*Dr. Lloyd Mayer, New York, NY  
Dr. Joel Pickar, Davenport, IA  
Dr. Bruce Redman, Ann Arbor, MI  
Dr. Danny Shen, Seattle, WA  
Dr. Stefanie N. Vogel, Baltimore, MD  
\*Dr. Cheryl Willman, Albuquerque, NM  
Dr. Elias A. Zerhouni, Bethesda, MD

\*Ad hoc members

*NACCAM Members Absent*

Dr. Gerald Cross, Washington, DC  
COL Richard Niemtzw, Clinton, MD

*NIH Staff Present*

*National Center for Complementary and Alternative Medicine*

Dr. Julia Arnold  
Ms. Adelina Bartels  
Ms. Willer Batten  
Ms. Laura Bergner  
Dr. Josh Berman  
Dr. Dale Birkle  
Mr. Yancy Bodenstein  
Ms. April Bower  
Dr. Sheila Caldwell

Mr. Craig Carlson  
Mr. Steve Casady  
Dr. Margaret Chesney, Deputy Director  
Ms. Alyssa Cotler  
Dr. Laurie Donze  
Ms. Karla Ehrler  
Ms. Linda Engel  
Ms. Valery Gheen  
Dr. Martin Goldrosen, Executive Secretary  
Mr. Kevin Green  
Ms. Anita Greene  
Ms. Mary Gregg  
Ms. Melinda Haskins  
Ms. Camille Hoover  
Dr. Jeanette Hosseini  
Ms. Deborah Jennings  
Dr. Laura Lee Johnson  
Ms. Lekiny Johnson  
Ms. Emmy Jones  
Mr. Roald Keith  
Dr. Partap Khalsa  
Dr. Jack Killen  
Ms. Marguerite Klein  
Ms. Robin Klevins  
Dr. Peter Kozel  
Ms. Catherine Law  
Dr. Qi-Ying Liu  
Dr. Patrick Mansky  
Ms. Loretta McDonald  
Dr. Heather Miller  
Ms. Ilze Mohseni  
Dr. Barbara Moquin  
Dr. Ranganath Muniyappa  
Dr. Richard Nahin  
Dr. Nancy Pearson  
Dr. Carol Pontzer  
Dr. Willie Postell  
Ms. Linda Rich  
Ms. Jeanie Robinson  
Mr. Tim Sannes  
Dr. Martina Schmidt  
Ms. Denise Simmonds-Barnes  
Dr. Barbara Sorkin  
Ms. Andra Standberry  
Ms. Kathleen Stephan  
Dr. Catherine Stoney

Ms. Jennifer Tisch  
Mr. George Tucker  
Ms. Shirley Villone  
Ms. Anem Waheed  
Ms. Dawn Wallerstedt  
Dr. Shan Wong  
Ms. Patricia Yu

*Other NIH Employees*

Ms. Andrea Collins, National Cancer Institute  
Ms. Andrea Deak, National Institute of Mental Health  
Ms. Claire Harris, National Cancer Institute  
Dr. Marni Silverman, National Institute of Mental Health  
Ms. Malaika Staff, National Cancer Institute  
Dr. Susana Serrate-Sztejn, National Institute of Arthritis and Musculoskeletal Disease  
(speaker)  
Dr. Christine Swanson, Office of Dietary Supplements  
Mr. Phil Tonkins, National Cancer Institute  
Dr. Dan Xi, National Cancer Institute

*Members of the Public*

Hannah Bradfal  
Kendra Calhoun  
Christine Choate  
Dr. Daniel Clegg (speaker)  
Michael Dyer  
Adam Haim  
Dr. Aviad Haramati  
Robert Keen  
Dr. John Klippel (speaker)  
Erin Loomis  
Monica Myklebust  
Barabara Patterson  
Georgia Perdue  
Maggie Petterson  
Dr. Mary Ann Richardson  
Dr. Mark Setton  
Stephen Shannon  
Shawn Stout  
Barbara Winterson

## **I. Closed Session**

The first portion of the 24th meeting of the National Advisory Council for Complementary and Alternative Medicine (NACCAM) was closed to the public, in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

A total of 271 applications were assigned to NCCAM. Of these, 224 were reviewed by NCCAM, 47 by the Center for Scientific Review. Applications that were noncompetitive, unscored, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council agreed with staff recommendations on 7 applications and concurred on 152 applications requesting \$27,380,313 in total costs.

## **II. Open Session—Call to Order**

The open session of the NACCAM meeting convened at 1 p.m. Dr. Martin Goldrosen, NACCAM Executive Secretary, called the meeting to order.

Minutes from the Council meeting on February 3, 2006, were unanimously approved, with no votes against and no abstentions. Dr. Goldrosen reminded Council members of the next meeting, scheduled for September 8, 2006.

Dr. Goldrosen also announced a public comment session at the end of the meeting and provided directions for addressing Council.

Dr. Goldrosen introduced Dr. Margaret Chesney, Director of the Division of Extramural Research and Training and Deputy Director of NCCAM.

## **III. Director's Remarks—Update on the State of the Center**

As Acting Chair of Council, Dr. Chesney presented remarks on behalf of Dr. Stephen E. Straus, NCCAM Director. She thanked the retiring Council members for their service: Dr. Deborah J. Cotton, Dr. Jonathan R. Davidson, Dr. Robert E. Fullilove, III, Dr. Alan I. Leshner, Dr. Tieraona Low Dog, and Dr. Larry A. Walker. She welcomed three new Council members: Dr. Silvia Corvera, Dr. Danny D. Shen and Dr. Bruce G. Redman. Dr. Chesney also welcomed two ad hoc Council members: Dr. Lloyd F. Mayer and Dr. Cheryl L. Willman.

Dr. Chesney updated Council on the organizational structure of NCCAM. In implementing its second 5-year plan, NCCAM has instituted several organizational changes to reflect its growth. Two major changes are the creation of the Division of

Extramural Activities (DEA) and the reshaping of the Office of Science Policy and Operations into the Office of Policy, Planning, and Evaluation (OPPE).

DEA coordinates key functions related to extramural programs across the Center. DEA oversees the Office of Scientific Review and the Office of Grants Management and provides support for Council activities. Dr. Goldrosen is DEA's Acting Director; in this role he serves as Executive Secretary of Council.

OPPE is responsible for planning, coordinating, and evaluating the implementation of NCCAM's strategic plan, policies, and scientific programs and initiatives. In addition, the Office prepares reports on NCCAM's research expenditures, directs and coordinates legislative activities, and manages requests that relate to areas such as the Freedom of Information Act. Dr. Heather Miller has been appointed Director of OPPE.

Council discussed how the reorganization within NCCAM will facilitate the Center's operation. Dr. Chesney noted that the relocation of committee management functions to the Division of Extramural Activities brings NCCAM into alignment with other NIH components.

Dr. Chesney announced that on April 19, 2006, Dr. Straus signed a Letter of Intent to establish international research collaboration with three of the principal Chinese government agencies involved in the study of traditional Chinese medicine. The participating organizations are the Ministry of Science and Technology, the China Academy of Chinese Medical Sciences, and the State Administration of Traditional Chinese Medicine. The Letter of Intent aims to advance the international objectives of NCCAM's strategic plan, through:

- Increasing global capacity for traditional medicine research
- Facilitating greater sharing of scientific knowledge and resources among investigators and institutions
- Creating more collaborative opportunities for researchers from the United States and abroad.

Dr. Chesney invited Dr. Jack Killen, Director of NCCAM's Office of International Health Research, to elaborate further on the Letter of Intent with the Chinese government. Dr. Killen emphasized that the goals of the arrangement are to facilitate scientist-to-scientist collaborations and to develop the scientific discipline of research in traditional medicine. Activities will focus on two areas: the study of acupuncture and the development of research methodologies to study the complexities of traditional Chinese medicine.

#### **IV. Address by NIH Director—NIH at the Crossroads: Strategies for the Future**

Dr. Chesney introduced Dr. Elias A. Zerhouni, Director of the National Institutes of Health (NIH). Dr. Zerhouni addressed recent NIH budget challenges and outlined strategies for protecting the core values and mission of NIH in the future.

## NIH Budget Challenges

Dr. Zerhouni explained that the NIH budget is facing a “perfect storm” in 2006, spurred by external forces such as the Federal budget and trade deficits, new defense and homeland security needs, Hurricane Katrina recovery efforts, and the potential for a pandemic flu. Other factors more directly related to the NIH budget include the fluctuations in budget increases, the current focus on physical sciences research, and the 3 to 5 percent inflation rate in the cost of biomedical research. Dr. Zerhouni stressed that NIH has overcome similar challenges in the past.

Dr. Zerhouni discussed the three fundamental drivers of the current budget environment:

- 1. Increased capacity building.** U.S. medical schools have increased their investment in constructing research facilities and in hiring tenure-track faculty. This expanded research capacity is the primary factor driving the drop in grant application success rates, as the demand for funding increased while the budget flattened in 2003.
- 2. Inflation.** Grants have become 40 to 45 percent more expensive to fund because of increases in biomedical research costs and inflation. Since 2003, NIH appropriations have not kept pace with the inflation rate, which resulted in a 7.3 percent loss in purchasing power.
- 3. The budget cycling phenomenon.** A sizeable proportion of the budget for new grants comes from uncommitted funds that become available as grants awarded 4 to 5 years ago end. This phenomenon is expected to improve the supply of grants available in 2007.

## Questions About NIH Funding

Dr. Zerhouni explained that it is important to identify and manage the real budget challenges to avoid making strategic mistakes. He noted common misperceptions about the NIH budget that have led to questions such as:

- **Is NIH overemphasizing applied research?** Funding for basic research is actually somewhat higher than funding for applied research. The proportion of money spent on basic research relative to that spent on applied research has remained steady since 1998, with minor fluctuations in 2003 and 2004 attributable to increases in the biodefense budget.
- **Is NIH shifting toward solicited research with too many RFAs?** In absolute terms, the number of targeted solicited grants has risen, but the overall proportion relative to investigator-initiated unsolicited grants has remained steady. In fiscal year (FY) 1995, 91 percent of NIH grant applications were unsolicited, versus 93 percent in FY 2005.
- **Is the NIH Roadmap shifting major funds away from the grant pool?** Funds for the NIH Roadmap amounted to 0.8 percent of the total budget in FY 2005, 1 percent in FY 2006, and a projected 1.2 percent in FY 2007. The Roadmap was developed to

increase synergy and collaboration across NIH. This is important for NCCAM, which uses Roadmap funds to participate in trans-NIH initiatives. Rather than decreasing the number of investigator-initiated grants, in 2005, for example, the Roadmap provided more than 345 individual awards to 133 institutions in 33 states.

Dr. Zerhouni pointed out that the success rate per application should not be interpreted as correlating to an applicant's chances of being funded. In fact, the success rate per applicant has historically been about 5 percentage points higher than the success rate per application.

### **Adaptive Strategies for the Future**

Dr. Zerhouni discussed strategies that NIH will use to address budget challenges. NIH must protect its core values and new investigators, particularly through awards—such as the Pathway to Independence awards—that provide support to researchers early in their careers. NIH must also manage the supply of and demand for its grants. In addition, NIH must send a unified message about the value of its investments and the need for sustaining the partnerships it has created among scientists across the United States by widely disseminating research results. NCCAM has done this recently for its large clinical trials of acupuncture, glucosamine/chondroitin, and the placebo effect.

It is also important for NIH to promote its vision for the future—transforming medicine from curative to preemptive, thereby making it predictive, personalized, and participatory. Approaches in communicating this vision include describing the return on Americans' investment in NIH. A \$2.50 investment from each American over a 7-year period, for example, has enabled NCCAM to offer a significant payback in information about complementary and alternative medicine.

### **Discussion**

Council asked Dr. Zerhouni how the information he presented could be communicated to colleagues who have misperceptions about the current state of NIH funding. Dr. Zerhouni responded that the slides from his presentation would be available on the NIH Web site. He urged Council members to communicate with other researchers and the public about the real fiscal issues and what NIH is doing to manage them.

Council also asked Dr. Zerhouni for suggestions about how to address the concerns of new investigators, especially as the level of funding for career (K) awards has dropped. Dr. Zerhouni responded that recent NIH efforts to assist new investigators in securing funding include awarding extra points to their grant applications, offering them special review by an advisory council, and allowing them to reapply early for subsequent funding cycles, which shortens feedback and review times and prevents new investigators from having to use soft dollars while waiting to reapply for funding.

## **V. Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)**

Dr. Chesney introduced Dr. Daniel Clegg, principal investigator of the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), which tested the effects of glucosamine and chondroitin sulfate on knee osteoarthritis. The study was cofunded by NCCAM and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Dr. Chesney also announced that the following individuals would be available for questions after Dr. Clegg's presentation: Dr. Susanna Serrate-Sztejn of NIAMS, Ms. Marguerite Klein of NCCAM, and Dr. John Klippel of the Arthritis Foundation.

Dr. Clegg presented an overview of GAIT and highlighted the main findings. He explained that GAIT was initiated in 1999 at the University of Utah School of Medicine and conducted at 16 rheumatology research centers across the United States. The 24-week, randomized, double-blind study compared five treatment groups: glucosamine alone, chondroitin sulfate alone, glucosamine and chondroitin sulfate in combination, celecoxib, and placebo.

Dr. Clegg described several challenges to the product selection process. Issues regarding the quality of the study agents surfaced because glucosamine and chondroitin sulfate are classified as dietary supplements; as a result, no USP methods or reference standards had been established, and no commercial products of pharmaceutical quality were available. Dr. Clegg and his research team, therefore, evaluated and selected suppliers of the raw ingredients (glucosamine hydrochloride and sodium chondroitin sulfate), which they used to formulate their own agents for GAIT.

Dr. Clegg reported that a total of 1,583 participants were randomized and 1,258 completed the study. Participants included in the study had primary osteoarthritis of the knee, based on both clinical and radiological evidence, as well as a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire pain score of 125 to 400 mm. They were stratified into two pain subgroups: mild pain (78 percent) and moderate-to-severe pain (22 percent), using WOMAC baseline pain scores of 125 to 300 mm and 301 to 400 mm, respectively. The primary outcome measure of GAIT was 20 percent or greater improvement in the summed WOMAC pain score at 24 weeks.

The combination of glucosamine and chondroitin sulfate did not provide significant relief from osteoarthritis pain among all participants. However, glucosamine and chondroitin sulfate did provide statistically significant pain relief for the smaller subgroup of participants with moderate-to-severe pain. Dr. Clegg cautioned that the findings for this subgroup should be considered preliminary and need to be confirmed in a study designed for this purpose. Most adverse events were mild and evenly distributed among the five treatment groups.

Interpretation of the findings is limited by factors that include the high placebo response rate and the small sample size of the group with moderate-to-severe pain.



GAIT includes an ancillary substudy to assess whether glucosamine and chondroitin sulfate can reduce or halt the progression of knee osteoarthritis. About one-half of the participants in the primary study were treated for an additional 18 months. The substudy measured joint space width based on knee x-rays taken at baseline and at years 1 and 2. Images are currently being interpreted and safety and efficacy data are being analyzed. The final report is expected in late 2006 or early 2007.

## **Discussion**

Dr. Clegg responded to questions from Council and the public regarding study design, interpretation of the findings, and clinical implications. Highlights of the discussion follow.

When asked about the clinical implications of the GAIT findings for knee osteoarthritis, Dr. Clegg encouraged the use of standard treatments first, such as weight loss, exercise, and pharmaceutical analgesia. Patients who continue to have moderate-to-severe pain may be candidates for using glucosamine and chondroitin sulfate.

Possible explanations for the high placebo response rate were discussed. Dr. Clegg noted that elevated placebo response rates have been reported in other osteoarthritis trials and may relate, in part, to participants' expectations and to the enrollment of participants with relatively mild symptoms.

Council discussed whether including more patients with moderate-to-severe pain would have decreased the placebo effect and led to more significant findings. Dr. Clegg stated that although recruiting more participants with mild pain posed a risk to the study design, enrolling more patients with severe pain posed a risk to recruitment and retention. Because of the placebo arm, patients with severe pain may have been less likely to participate.

When asked about why GAIT was undertaken without more pharmacokinetic research on glucosamine, Dr. Clegg responded that the GAIT team has conducted pharmacokinetic studies in parallel with GAIT and resulting articles are in the publication process.

Council discussed lessons learned about the complexities of dietary supplement research since the inception of GAIT in 1999. Dr. Clegg explained that the widespread use of glucosamine and chondroitin sulfate, as well as multiple clinical reports, provided sufficient indications of relative safety and potential benefit to warrant a phase III trial. He noted that NCCAM is currently funding pharmacokinetic studies on glucosamine and chondroitin sulfate. Dr. Chesney stated that phase III trials are among the research areas subject to a short "pause" in new funding by NCCAM.

Dr. Chesney invited Dr. Klippel to comment. Dr. Klippel stated that manufacturers are promoting the use of glucosamine and chondroitin sulfate to the public based on GAIT results, and consumers who use the supplements generally believe they are effective. He notes that clinicians now look forward to the results of the substudy for more information about potential structural effects of treatment.

## **VI. Public Comment Session**

Dr. Goldrosen opened the floor for public comment. Dr. Mark K. Setton, Associate Professor of World Religions from the University of Bridgeport, addressed Council. Dr. Setton stated that some GAIT investigators had financial relationships with pharmaceutical companies involved in the study. Dr. Setton also commented that the published study report potentially overstates the failures and understates the successes of the results regarding glucosamine and chondroitin sulfate.

Dr. Clegg responded that GAIT investigators had appropriately disclosed their financial relationships. He stated that resources provided by pharmaceutical companies are integral to performing research in the United States, and he expressed confidence in the objectivity of the GAIT investigators.

Dr. Chesney thanked Dr. Setton and Council for their comments and suggested that further discussions about GAIT could be held in the future.

Dr. Goldrosen adjourned the meeting at 3 p.m.

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

Martin Goldrosen, Ph.D. Executive Secretary  
National Advisory Council for Complementary and Alternative Medicine

Margaret A. Chesney, Ph.D.  
Acting Chair  
National Advisory Council for  
Complementary and Alternative  
Medicine