

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

**NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY
AND INTEGRATIVE HEALTH
MINUTES OF THE FIFTY-EIGHTH MEETING**

February 5, 2016

NACCIH Members Present

Dr. Martin Blaser, New York, NY
Dr. David Borsook, Waltham, MA
Dr. Alice Clark, University, MS
Dr. Stephen Ezeji-Okoye, Palo Alto, CA
Dr. Tracy Gaudet, Washington, DC
Dr. Steven George, Gainesville, FL²
Dr. Christine Goertz, Davenport, IA
Dr. Patricia Herman, Santa Monica, CA²
Dr. Steven Hersch, Charleston, MA
Dr. Susmita Kashikar-Zuck, Cincinnati, OH²
Dr. Janice Kiecolt-Glaser, Columbus, OH
Dr. David Kingston, Blacksburg, VA^{1, 2}
Dr. Helene Langevin, Boston, MA
Dr. Deborah Powell, Minneapolis, MN
Dr. Cynthia Price, Seattle, WA²
Dr. Eric Schoomaker, Bethesda, MD
Dr. Reed Tuckson, Sandy Springs, GA
Dr. Chenchen Wang, Boston, MA

¹Telephone

²Ad-hoc

NACCIH Members Not Present

Dr. Craig Brater, Indianapolis, IN
Dr. Richard Niemtzow, Alexandria, VA

NIH Staff Present

Dan Xi, NCI, NIH

Members of the Public

Ing Aharonovich
Iris Aharonovich

Berna Dill
Kim Jenner
Casandre Maiselle
Breanne Vannostrand

I. Closed Session

The first portion of the fifty-eighth meeting of the National Advisory Council for Complementary and Integrative Health (NACCIH) 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 130 applications were assigned to NACCIH. Of these, 56 were reviewed by NACCIH, 74 by Center for Scientific Review. Applications that were noncompetitive, not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council agreed with staff recommendations on 70 applications, requesting \$20,352,744 in total costs.

II. Open Session—Call to Order

The open session convened at 10:10 a.m. Dr. Martin Goldrosen, NACCIH Executive Secretary, called the meeting to order. The minutes of the October 2015 NACCIH meeting were approved unanimously.

III. NACCIH Director's Report

NACCIH Director Dr. Josephine Briggs welcomed the four new Council members: Drs. Steven George, Patricia Herman, Susmita Kashikar-Zuck, and Cynthia Price.

National Institutes of Health (NIH) funding for fiscal year (FY) 2016 is \$2 billion higher than the previous year. NACCIH's appropriation for FY 2016 is almost \$6 million higher than FY 2015, bringing the budget back to pre-sequester levels for the first time since FY 2010.

The largest portion of NACCIH's funding (60.7 percent in FY 2015) goes to research project grants. Because these projects are usually funded for 4 or 5 years, the amount of money available for competing (new) grant awards in any one year is much less than the amount spent on noncompeting (continuing) grants. The success rate of applications for NACCIH research project grants varies between 9 and 14 percent; this low rate reflects NACCIH's limited budget and the large number of applications. The overall mean success rate for NIH as a whole is 18 percent. NACCIH's training and career development grants primarily use the T and K mechanisms rather than the F mechanism.

Recent stories in major news media have featured NACCIH-funded research, particularly Dr. Christina Smolke's research on the synthesis of opioids, which offers the possibility of teasing apart the structure of the opioid entity to maximize the effect on pain with fewer side effects. Dr. Beth Bock's research on yoga for smoking cessation and Dr. Ted Kaptchuk's work on the ethics of placebos have also been covered by major media.

Discussion. In response to questions about the payline and flexibility in funding from year to year, Dr. Briggs explained that small Institutes and Centers (ICs) like NACCIH cannot have rigid paylines because

a single large grant can have a substantial impact on the overall budget. NCCIH creates flexibility by setting aside a certain amount of funding for each Council round and, occasionally, by choosing to fund a project late in one fiscal year rather than early in the next.

Dr. Reed Tuckson expressed concern about the low success rate of grant applications and asked what other options are available for funding complementary health research. Dr. Briggs replied that the U.S. Government is the largest source of funding for complementary health research; the United States invests more in complementary health research than any other country does. Most projects are not of interest to the private sector, although a few foundations such as The Bernard Osher Foundation are possible funders, and some employers and insurers are becoming interested in certain topics such as pain management. NCCIH is not the only IC that funds complementary health research. The National Cancer Institute also has sizeable investments, and NCCIH has partnered with other ICs and other agencies such as the Department of Veterans Affairs on some projects. Dr. Christine Goertz added that the Patient-Centered Outcomes Research Institute is interested in funding projects in complementary and integrative health.

IV. Perturbing the Early Life Microbiome and Its Consequences

Dr. Martin Blaser presented research findings on ways in which the microbiome, particularly the microbiome present in early life, may affect lifelong health, including conditions such as obesity.

The microbes that live in and on the human body are ancient and niche-specific, and many are persistent, living in an individual for long periods of time. Microbial cells and genes in the human body outnumber human cells and genes. The human microbiome evolved along with its hosts, and a dynamic equilibrium exists between them. Perturbing this ancient relationship may have profound consequences.

Infants are born with a microbiome quite different from that of adults. They develop their adult microbiome during the first 3 years of life—a period when immunity, metabolism, and cognition are also developing. Many of the organisms in a child’s microbiome come from the mother; they are transmitted during passage through the birth canal, breastfeeding, skin-to-skin contact, and (in animals and some traditional human cultures) pregestation of food. In modern times, the diversity of microorganisms transferred from mother to child has diminished because of factors such as bathing, formula feeding, cesarean sections, and the use of antibiotics. It is hypothesized that the diversity of the human microbiome is decreasing successively from generation to generation in high-technology societies. Both human studies and evidence from animal models support this concept.

The increasing use of antibiotics may be related to recent increases in obesity, and this relationship may be mediated by the microbiota. Farmers learned 70 years ago that feeding low doses of antibiotics to livestock promotes their growth and increases feed efficiency (the amount of meat produced from a given amount of animal feed). The earlier in life antibiotics are started, the greater the effects are on growth and body composition. Studies in mice have shown that exposure to antibiotics early in life, even for short periods of time, has lasting effects on growth and body mass. Short periods of exposure to antibiotics can perturb the microbiota at least temporarily. Transfer of the perturbed microbiota into germ-free mice changes the animals’ growth pattern and body mass, suggesting a role for the microbiota in antibiotics’ long-term effects. Limited human data also suggest that individuals who were exposed to antibiotics in the first 6 months of life have increased adiposity later.

Further research is needed to better understand the consequences of antibiotic use and other factors that affect the microbiota in humans. With such understanding, it may be possible to develop remedial measures—science-based probiotics and prebiotics—to correct disturbances in the microbiome in the hope of minimizing long-term consequences.

Discussion. In response to questions, Dr. Blaser said that the consequences of the presence of antibiotics in the food supply and the environment are unknown, and this is of greatest concern in countries where antibiotic use is very high, such as China. Data currently available in the United States do not make it possible to correlate an individual’s microbiome with past antibiotic exposure, but such studies might be possible in Scandinavian countries that have full records of antibiotic use. Future research may enable the development of a microbiome that treats obesity, although the window of time for reversal of obesity may be limited to early life. The substantial variations in antibiotic use among countries and among individual medical practices suggest opportunities for education. Obesity is not the only clinical condition that has been associated with antibiotic use. Research from Finland suggests that both children’s exposure to antibiotics and their mothers’ exposure to antibiotics during or shortly before pregnancy are linked to milk allergy. The microbiome test kits currently available can only satisfy people’s curiosity; the science is not sufficiently advanced for these kits to produce medically useful knowledge.

V. Concept Clearance: Contribution of Sleep Disturbances to Chronic Pain Initiative

Dr. Robin Boineau, medical officer in the Office of Clinical and Regulatory Affairs, presented a proposed concept on the contribution of sleep disturbances to chronic pain. Chronic pain is a major public health issue in the United States because of its high prevalence and its relationship to high levels of opiate use. Research suggests that a bidirectional relationship may exist between sleep and pain. It is well established that pain disturbs sleep, and a smaller amount of research indicates that sleep deprivation or disruption may increase sensitivity and vulnerability to pain.

In May 2014, NCCIH played a lead role in sponsoring a comprehensive workshop on the contribution of sleep disturbances to chronic pain. The workshop identified many gaps in knowledge on this topic and methodological questions that need to be resolved. For example, what pain systems are affected by disturbed sleep? What are the mediators and modifiers of the effects of sleep on pain? What are the most appropriate outcome measures? What research paradigms best reflect clinical situations, and what populations are most appropriate for study? These and other questions about the sleep-pain relationship need to be addressed in future research.

The purpose of the proposed initiative is to advance NCCIH’s interests in studying the contribution of sleep disturbances to chronic pain and to determine whether alleviating sleep disturbances reduces or prevents the development of chronic pain. The proposed plan involves developing funding opportunities in three stages:

1. Adding supplemental funds to ongoing research grants to allow investigators to add sleep variables to pain studies or vice versa
2. Partnering with other ICs to support mechanistic research on sleep and pain

3. Supporting clinical research to develop and refine interventions to improve sleep and reduce pain or, when preliminary data are adequate, to support clinical trials to evaluate the efficacy or effectiveness of complementary and integrative approaches.

This multiple-step approach would have the benefits of communicating NCCIH's interest in pursuing research in this area to the scientific community, allowing a rapid initiation of a portfolio in this area, and providing an opportunity to build momentum and collect preliminary data on the sleep-pain relationship.

Discussion. Dr. Kashikar-Zuck strongly supported the concept. She noted that her work with adolescents with chronic pain illustrates the importance of adequate sleep. Dr. Tracy Gaudet also expressed strong support, with the hope that studies on integrative approaches to alleviate sleep disturbances will eventually be included in the portfolio. Dr. Goertz asked whether supplements had to be tied to applications within NCCIH's portfolio. Dr. Briggs replied that this is not essential; studies funded by other ICs could also qualify. Dr. George said that a broader approach to discovery might be more appropriate than narrowly defined mechanistic research in the early stages of investigation in this area. Dr. Eric Schoomaker commented that the Defense & Veterans Pain Rating Scale asks about sleep, with the assumption that pain worsens sleep. However, it now appears that causality may operate in both directions. Dr. Briggs commented that NCCIH's initial funding would be devoted to investigations of correlation rather than causation, but that it is important to consider the directions of possible causal relationships. Dr. Chenchen Wang said that a large body of data indicates that mind and body interventions may improve sleep as well as reduce pain.

A motion to approve the concept was made, seconded, and passed unanimously.

VI. Council Operating Procedures

Dr. Goldrosen reviewed Council operating procedures, including processes for NCCIH reports to Council, secondary review of grant applications, concepts for research initiatives, and appeals.

Council unanimously passed a motion approving the operating procedures as presented.

VII. NCCIH Support for Clinical Investigations

Dr. Catherine Meyers, Director of the Office of Clinical and Regulatory Affairs, discussed some of the resources NCCIH has developed for clinical research oversight. Seventy-five percent of NCCIH's grants involve human subject research, and oversight of this type of research is a high priority. Dr. Meyers's office is responsible for developing NCCIH's approaches to the oversight of human subject research and providing expertise in this area.

The Clinical Research Toolbox, launched in 2012, is a major resource for NCCIH-funded investigators. This Web-based collection of templates, forms, guidelines, checklists, and other materials supports clinical researchers during the startup phase of a project, as well as during clinical research and on-site monitoring.

The on-site monitoring program, launched in 2012, is a distinctive feature of clinical research oversight at NCCIH. The Center carries out on-site monitoring of complex clinical trials and those conducted under Investigational New Drug applications. The monitors have established a good relationship with

investigators, and the program has become an educational tool to assist NCCIH-funded investigators in conducting their research.

Usage data for the Clinical Research Toolbox, gathered through Google Analytics, indicate that in comparison to general Web site visitors, those who visit the toolbox look at more pages and spend more time on the site. Those who visit multiple pages in the toolbox often download materials, and many return to the toolbox repeatedly.

The toolbox is being used as a resource in academic curricula and has generated interest at institutions around the world, although 90 percent of users are from the United States. NCCIH staff review and update the toolbox regularly.

Discussion. Dr. Briggs explained that NCCIH seeks to be a leader in clinical research quality, including prompt reporting of clinical trial results. Other ICs have used some of NCCIH's clinical research resources as models.

In response to a question from Dr. Schoomaker about standardization of research protocols, Dr. Briggs explained that standard-setting for some aspects of clinical research, such as outcome measures, is often desirable. In fact, NCCIH recently led an effort to standardize characterization of patients and outcomes in back pain research. It is more difficult, however, to determine when standardization of interventions such as mindfulness or massage would be appropriate.

Dr. Kashikar-Zuck inquired about ways to increase access to de-identified data from clinical trials. Dr. Briggs explained that NIH has a policy that any grant over half a million dollars must have a data sharing plan, but this is not the same as actual implementation of data sharing. NIH is very aware of the need to optimize resources to share data effectively. NCCIH has provided the coordinating centers of some of its large completed trials, such as the Ginkgo Evaluation of Memory (GEM) Study, with resources for sharing data.

Dr. David Borsook asked about the 25 percent of NCCIH-funded research that does not involve human subjects. Dr. Briggs explained that most of it is research on natural products.

VIII. Council Working Group Report on Clinician-Scientist Workforce Development

In October 2015, Dr. Briggs requested that Council convene a working group on workforce development, with a focus on identifying needs and gaps in the training and career development of clinician-scientists. Dr. Helene Langevin served as chair of the group, and Dr. Partap Khalsa, Deputy Director of the Division of Extramural Research, was the designated Federal official.

Dr. Langevin presented a summary of the group's findings, which are described in greater detail in a written report to Council. The working group concluded that the primary driver in decisions on this topic should be anticipated research needs in the field of complementary and integrative health in 5 to 10 years. Clinician-scientists are valuable to the research enterprise and have varied career paths. NCCIH should continue to support these different career paths, addressing specific roadblocks in each path. As part of this effort, innovative approaches should be developed to support research training for clinicians with complementary and integrative health degrees.

Some current NCCIH training and career development programs have been more successful than others. Successful programs should be leveraged, and less successful programs should be carefully examined and enhanced where possible. The working group also recommended that NCCIH develop programs to support the host environments at all types of institutions involved in research training in complementary and integrative health; make efforts to raise the visibility of complementary and integrative health in the research and clinical community; and tie NCCIH's training and career development initiatives to the Center's priority areas for research funding, while remaining open to potential support of new areas as appropriate.

Discussion. In response to a question from Dr. Janice Kiecolt-Glaser, Dr. Briggs explained that there are no firm NIH-wide plans for major changes in training grants, but that questions have been raised about whether the T or F grant mechanisms are the most successful. Dr. Khalsa added that NCCIH is tracking whether certain pathways are more successful than others, but with the Center's small size, it is difficult to reach definitive conclusions.

Dr. Schoomaker recommended that workforce development be aligned with NCCIH's Strategic Plan, recognizing that the ultimate goal is the advancement of science, rather than workforce development per se. Dr. George noted that clinician-scientists may move back and forth between the clinical and research worlds and may need support during these transitions. Dr. Goertz pointed out that a wide range of researchers can be considered clinician-scientists, including true clinicians who are also involved in research, as well as individuals with clinical training who have devoted their careers exclusively to science. She also noted the importance of providing appropriate incentives so that clinician-scientists are recognized as high-value members of a research team. Dr. Price explained that special challenges face complementary health clinicians who go to mainstream institutions for research training. Faculty at these institutions may need support so that they, in turn, can provide appropriate support for their students. Dr. Tuckson urged that efforts to enhance the training of clinician-scientists should be linked to NIH-wide efforts to improve diversity in the biomedical workforce.

IX. NCCIH Strategic Plan Update

Dr. Karin Lohman, Director of the Office of Policy, Planning, and Evaluation, reviewed the development process of NCCIH's 2016 Strategic Plan. Initial planning began in February 2015, but the process was put on hold for several months while the NIH-wide Strategic Plan was finalized. The NCCIH Strategic Framework was developed by NCCIH staff and reviewed by Council in October and November 2015. NCCIH staff developed a preliminary discussion draft of the plan during December 2015 and January 2016. That draft has now been distributed to Council for input. After Council members' comments are incorporated into the draft, the plan will be made available for public comment in February and March, finalized in April and May, and presented to Council in final form in June.

The NCCIH Strategic Framework has three scientific objectives:

1. Advance fundamental science and methods development
2. Improve care for hard-to-manage symptoms
3. Foster health promotion and disease prevention.

These objectives are closely aligned with the scientific objectives of the NIH-wide strategic plan.

The NCCIH framework also includes two additional objectives—enhancing the research workforce and disseminating evidence-based information—and eight high-priority research topics. For each high-priority topic, the draft plan outlines its importance, what success looks like, the high-priority objectives within the topic, and research areas within the topic that are of low priority.

Discussion. Dr. Briggs explained that the high-priority topics are envisioned as parts of a living document that can evolve. As time goes on, they may be replaced by other topics, or new topics may be added. She also pointed out that strategic planning at NIH differs from strategic planning in some other organizations because many parts of the health care system are not under NIH's control. NIH has a strong interest in translation but little ability to direct the implementation of research findings.

Council members offered the following ideas for the next draft of the Strategic Plan:

- Dr. Schoomaker advised giving priority to topics that would help achieve the three main scientific objectives. He recommended that process-based objectives, such as workforce enhancement and dissemination of information, be placed in a subordinate position.
- Dr. Blaser recommended broadening the probiotics high-priority topic to include additional aspects of probiotics besides their impact on the gut-brain axis. As the importance of probiotics in medicine increases, it would make sense for one IC to develop broad in-house expertise in this area, and NCCIH may be the most appropriate IC to do this.
- In the draft plan, one of the strategies within the objective on advancing fundamental science is “Advance understanding of the neurobiological mechanisms through which mind and body approaches affect health, resiliency, and wellbeing.” Dr. Langevin advised NCCIH to reexamine this wording because neural mechanisms are not the only mechanisms of action of mind and body approaches; body-based effects also play important roles.
- Dr. Herman urged NCCIH to include more explicit discussion of the integration of complementary approaches into health care in the text of the Strategic Plan.
- Dr. Tuckson recommended carefully considering the methodology and criteria for evaluation of real-world programs, such as the community- and employer-based wellness programs mentioned in one of the strategies for the third objective.
- Dr. Goertz expressed concern about classifying “Research on complementary approaches for which the mechanism of action cannot be ascertained” as low priority under the pain management topic. If interpreted strictly, this classification could make studies on manual and manipulative therapies ineligible for funding.
- Dr. Steven Hersch recommended increasing the emphasis on targets—such as ameliorating pain or improving sleep—and decreasing the emphasis on methods. He observed that the current draft of the Strategic Plan seems to focus less on health endpoints than on how you get there.
- Risk-benefit ratios and patient-centered care were mentioned repeatedly during discussion of the Strategic Plan, and it was suggested that more emphasis should be given to these issues in the next draft.

Dr. Briggs told Council members that all of these ideas—as well as any others they may wish to submit in writing or by talking with NCCIH staff—would be taken into consideration in the preparation of the next draft of the Strategic Plan.

X. The Precision Medicine Initiative® Cohort Program: An Update

Dr. Briggs presented an update on the Precision Medicine Initiative (PMI) Cohort Program, for which she has been serving as interim director for the past 6 months. The Cohort Program is part of a larger initiative announced by President Obama in his 2015 State of the Union address. The mission of the initiative as a whole is to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments.

The PMI Cohort Program will include one million or more volunteers, who broadly reflect the diversity of the United States. The cohort will be longitudinal, with continuing interactions with participants and recontact for secondary studies. Participants will be recruited in two ways: Anyone can sign up as a direct volunteer, and additional participants will be recruited through health care provider organizations. Participants will be treated as partners in all phases of the Cohort Program. They will be involved in study design and oversight, and they will have access to data about themselves. Data will be obtained through questionnaires, a baseline health examination, electronic health records, and analyses of biospecimens (blood samples). The program also expects to make use of mobile health (mHealth) data collected through smartphones and wearable sensor devices. Genetics will play a role in the study, but many other determinants of health will also be investigated.

The PMI Cohort Program will be larger than any current NIH-supported cohort study. However, studies similar to the PMI are under way in other countries. For example, in the United Kingdom, the UK Biobank study, which is similar in many ways to the PMI Cohort Program, has recruited half a million participants.

Funding opportunity announcements for several important components of the PMI Cohort Program have been issued, and partnerships with federally qualified health centers are being developed to ensure that low-income Americans are well represented in the cohort. Enrollment of direct volunteers in a pilot study will begin in March 2016, and general recruitment is expected to begin in the summer of 2016.

Discussion. In response to questions, Dr. Briggs explained that the PMI Cohort Program will have a single biobank with a single backup facility, and that legacy biospecimens will not be used. Therefore, duplication of biospecimens is unlikely to be a problem. No decision has yet been made about whether to include fecal specimens in the biobank. The size of the cohort was mandated by the White House, and it gives impressive power for the investigation of common diseases. However, some research questions will be addressed in subgroups of the cohort rather than the cohort as a whole. Children will not be included in initial enrollment, but the study expects to pilot a process by which family members of a primary enrollee can become engaged in the study; these family members may include children and older adults. Enrollment of older adults is a concern because there is evidence that willingness to participate is lower in this age group than among younger people. The use of innovative communication methods will play a key role in engaging study participants.

XI. Public Comment and Adjournment

Ms. Kim Jenner and Ms. Iris Aharonovich of the Reflexology Association of America briefly described reflexology and explained that their organization hopes to increase awareness of this technique in the United States. They inquired about the possibility of adding a link to their organization's resources to the NCCIH Web site.

The meeting was adjourned at 3:30 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 Integrative
Health

Josephine Briggs, M.D.
Chairperson
National Advisory Council for
Complementary and Integrative
Health