National Institutes of Health
NIH...Turning Discovery Into Health

DIRECTOR'S COUNC

April 6–7, 2000 Meeting Minutes

3rd Meeting of the Director's Council of Public Representatives
Thursday-Friday, April 6-7, 2000

(COPR) by describing recent activities of COPR members, including their participation in the Government Performance and Results Act (GPRA); the participation of five COPR members in the June NIH budget retreat; reviews of several Institute directors who have served at NIH for terms exceeding five years; and the participation of several members as part of an Advisory Committee to the Director working group that is reviewing gene transfer clinical studies. Dr. Kirschstein also presented an update of several key issues affecting NIH, including the development of draft guidelines for overseeing the use of human embryonic stem cells in research and a review of early budget negotiations before congressional appropriations committees.

Dr. Steven E. Hyman, Director of the National Institute of Mental Health (NIMH), described a growing awareness among administration officials and global leaders of the important impact of mental illness on public health and on the economy, particularly in developing countries. NIMH has developed a new series of effectiveness trials in which a variety of treatments may be tested in relevant settings. He said that concerns about recent increases in the use of Ritalin and other psychoactive drugs to treat preschool children have helped lead Surgeon General David Satcher to convene a conference that will review available data on such use of medications in young children, and consider the design of additional preschool population studies. Dr. Hyman also answered questions concerning a recent report from the National Alliance for the Mentally Ill (NAMI). Dr. Hyman expressed concern over the inaccurate characterization of congressional instructions to NIMH. While the five disorders of greatest concern to NAMI are at the core of the NIMH mission, the Congress and the American people have many additional concerns within the NIMH mission, such as childhood mental diso

that evaluate clinical research proposals. He said that this new approach within the study sections is working very well and has added an important component to improve the public health impact of these studies.

Dr. Hyman said that a recent report published in the *Journal of the American Medical Association* indicates a substantial increase in the use of several psychotropic drugs to treat preschool children. This increase is not uniform across the population, but instead tends to be very specific to certain segments. For example, Ritalin treatment has increased sharply among upper-middle-class Caucasian boys. Although this drug is safe and effective for treating well-characterized cases of attention deficit disorder, its use for other less well-characterized behavioral disorders may not be indicated. To address such questions, Surgeon General David Satcher plans to convene a conference that will review available data on Ritalin use and discuss the design of additional preschool population studies. Dr. Hyman said that, because such studies raised perplexing ethical issues, it would be important to involve educators as well as representatives of the general public. Focusing on the needs of children is an essential component of these deliberations.

Dr. Hyman said that a recent report from the National Alliance for the Mentally Ill (NAMI) was highly critical of the NIMH research portfolio, alleging that the Institute's research portfolio neglects the five key mental illnesses that Congress has mandated it to study. For example, the report implies that NIMH redirected funds from research on schizophrenia to support research on AIDS-related mental illnesses, and it also recommends that NIMH not perform basic scientific research but focus only on specific diseases. Dr. Hyman said that the report is inaccurate on several counts, and that many members of the NAMI board of trustees had expressed to him disagreement with its conclusions. He also said that Congress requires NIMH to study mental illnesses beyond the five disorders that NAMI highlighted. Dr. Hyman pointed out that, in fact, the suggestions and encouragement from Congress was actually larger in areas other than the five areas of particular concern to NAMI. Some of these other areas included youth violence, eating disorders, and Alzheimer's disease. He also reminded the group that in reference to the report's implications about redirected funds to AIDS research, there actually is a separate AIDS budget and clearly stated that these are not fungible funds. Dr. Hyman also mentioned that it is vital for NIMH to continue supporting robust basic research.

Discussion

Ms. Lydia Lewis said that it continues to frustrate members of the mental health community that many physicians as well as members of the public do not recognize mental illnesses as real diseases. She said that it is important to deliver this science-based message to the general public. In response, Dr. Hyman said that this message is being heard in some sectors, particularly regarding schizophrenia and autism. It will help as basic research provides additional insights into the components of the brain that are involved in additional specific diseases. Although many physicians are not properly trained to deal with such illnesses, former practices based on beliefs that blamed many mental conditions on one's parents are being replaced by an understanding of the biological bases of those conditions.

sequence of the human genome began on a large scale in 1999, and is ahead of schedule and under budget, according to Dr. Collins. The overall program has reached a number of important milestones, including genomic sequences of several model organisms, including yeast, *Escherichia coli*, C. elegans, and, very recently, the fruit fly *Drosophila melanogaster*. After genomic mapping was done in adequate detail, sequencing of the human genome began as a pilot project in 1996, with a goal of determining the entire sequence by 2005. During the past 14 months, however, progress has steadily accelerated, and the sequencing completion date has been moved up to 2003 with a "working draft" (90% of sequence in high accuracy) this year.

By late March, about two-thirds of the human genome sequence was available in working draft form, and about 20 percent was considered unequivocally finished, according to Dr. Collins. The sequencing of chromosome 22, for example, was completed and published late in 1999. At least a dozen new disease-associated genes have been identified because specialists in those diseases have free and immediate access to sequence data through GenBank. The NIH position on patenting of gene sequences is that stringent criteria for their utility need to be satisfied before patents are issued. In other words, the bar for obtaining patents needs to be set high.

d(set h)-s s hJ0romave

Although the death in 1999 of a young man who was participating in a gene therapy protocol has focused attention on this area of research, public concern could well be directed more broadly to include other areas of clinical research, according to Dr. Ellis. An important consideration is that the need for research protection has received attention from President Clinton, who directed all federal departments in 1994 to assure compliance with applicable protective measures and has spoken out on this subject several times since then. In addition, members of the National Bioethics Advisory Commission (NBAC) in 1997 recommended universal protection for research subjects, regardless of whether protocols received federal funding or were protected under FDA regulations. Moreover, several congressional committees held hearings early during 2000 on this subject.

Discussion

In response to a comment from Ms. Barbara Lackritz, Dr. Ellis said the candidate subjects may demand to know full details about a protocol in which they have been asked to participate and that no one should sign an informed consent agreement until being fully satisfied with the disclosures. He also said that students involved in conducting research studies involving human subjects often do not receive adequate training from their mentors.

Ms. Lydia Lewis said that the NBAC 1998 report on research involving subjects with mental disorders is misleading inasmuch as some individuals with mental disorders can make fully informed decisions about participating. Dr. Ellis said that the title of that report is at fault and that NBAC members took great care to indicate that not all mental disorders lead to impaired decision making.

In response to a question from Dr. Isaac Montoya, Dr. Ellis said that systematic clinical evaluations intended to develop generalizable knowledge fall under the broad definition of research; thus, individuals who participate in such evaluations are entitled to full protection under current federal guidelines.

In response to a question from Mr. Bob Roehr about OPRR moving from NIH to DHHS, Dr. Ellis said that the office is under-staffed, with only two full-time investigators, an average investigational period of 23 months, and 163 cases now under investigation. The caseload could be much higher if the office operated proactively. Nonetheless, the recent wave of high-profile investigations and enforcement actions has intensified interest in protecting human subjects. For example, attendance at recent OPRR-sponsored workshops has increased substantially.

Dr. Wendy Baldwin, NIH Deputy Director for Extramural Research, said that IRBs may not have adequate resources in terms of information and funding to fulfill their mandates. A Web site is being established to provide useful information to IRBs, and steps are being taken to provide additional funding, possibly by raising the current 26 percent cap on indirect cost recovery from NIH research grants. In addition, a committee at NIH is reviewing how regulatory burdens could be reduced or simplified in ways that would make the job of IRBs easier, particularly in cases of multi-site clinical trials in which duplicative regulatory efforts often are required. NIH also has several training programs in bioethics for members of the research community, and a research program was recently begun whose aim is to better understand behaviors needed to achieve informed consent. Finally, NIH is working on a guidance document for investigators conducting research that involves subjects whose decision-making capabilities are impaired.

Ms. Rosemary Quigley recommended that COPR establish a working group, perhaps including COPR Associates among its members, to help deal with the many public misunderstandings that surround research involving human subjects. Ms. Debra Lappin said that it would be helpful for Dr. Baldwin to participate further during COPR deliberations and to explain more completely issues revolving around IRB operations.

April 7 Discussion

Dr. Kirschstein said that care needs to be taken to explain to potential research subjects that such trials can mean that some of them will receive placebos or best-available conventional care rather than a particular experimental treatment. She also said that sometimes individuals refuse to participate because they do not understand how such trials are structured. Mr. Roehr said that the line between standard health care and treatment within clinical research projects is not so clear as it was a decade ago. Moreover, with other issues involving the participation of managed care organizations in clinical research programs in flux, COPR potentially can influence such organizations to be more receptive to having their members participate in clinical trials.

In response to a question from Mr. Doug Yee, Dr. Baldwin said that, although there are many partnerships involving university scientists and researchers in companies and these investigators embrace the principles of bioethics, there is currently not enough research being conducted on the ethical issues, practices, and principles involving human subjects.

Current Activities, Future Directions for COPR

[Thursday and Friday segments of the COPR deliberations are combined in this section.]

COPR Activities Presentation

COPR member Ms. Vicki Kalabokes, who moderated this session, said that the council is mandated to exchange information with the public. Although the breadth of capabilities among current COPR members is considerable, there is interest in expanding the capabilities by more actively involving the 225 COPR Associates in some of the council's activities.

Ms. Cate Timmerman of Palladian Partners, a contractor who is assisting the NIH, described salient demographic features of the COPR Associates. She said that they are associated with institutions in 37 states, and about one-quarter of them are interested in multiple diseases; other information is available as part of a database to which COPR members are entitled access because they are considered federal employees while they are engaged in NIH-related activity. She also said that NIH communicates frequently with the Associates, providing them a newsletter and other items describing ongoing COPR and COPR-related activities.

Ms. Anne Thomas, Director of the NIH Office of Communications and Public Liaison, said that COPR members can contact COPR Associates to determine whether they will participate in specific COPR-related activities. She said that she would draft a prototype message for this purpose that COPR members subsequently could review. Dr. Ruth Kirschstein said that, as a matter of privacy, individuals among the Associates may decline to participate or even to be contacted about pending COPR activities.

Mr. Bob Roehr asked whether additional information that would enable COPR members to contact and collaborate with members of the Institute advisory councils could be made available. Dr. Montoya suggested establishing a formal link between COPR and the members of those councils. Dr. Kirschstein said that one-third of the members of those councils are public representatives who help in deciding where to allocate NIH resources and thus the councils serve a different purpose from COPR.

Several suggestions were presented for how to communicate with and best involve the Associates in COPR activities. Ms. Pam Fernandes recommended that communications between COPR and the Associates be centralized, not fragmented and diffuse. Mr. David Frohnmayer said that COPR Associates might be affiliated with COPR by serving as members of working groups. Ms. Barbara Lackritz said that grouping Associates according to their interests might be helpful. However, Mr. Doug Yee recommended that the Associates not focus on their specialty interests when collaborating on COPR activities. Ms. Rosemary Quigley said that assigning each of the Associates to specific COPR members would help to personalize their contacts with the council.

Dr. Ted Castele said that it is important to define carefully what to expect from the Associates. Dr. Isaac Montoya suggested that the Associates help with future GPRA assessments. After further discussion, there was wide agreement among COPR members that the Associates should be considered as a pool of talented individuals from which to draw for involvement in specific, task-oriented assignments. Ms. Timmerman said that, as specific needs arise, there are efficient ways to contact all the Associates and to offer them opportunities to participate in COPR activities.

Ms. Thomas agreed to draft a general message for this purpose and also to enlist Associates to help the general public to better understand NIH through outreach efforts. Mr. Yee said that Rotary Clubs and other general public service organizations offer many opportunities to reach the general public with information about

Mr. Roehr said, and others agreed, that setting explicit priorities for COPR by establishing a series of working groups risks excluding potentially important issues from the future agenda. Dr. Luz Claudio said that having a checklist of key issues would be helpful for COPR members. Mr. David Frohnmayer said that potential issues identified during the course of this (April 2000) meeting should be critically reviewed.

Dr. Isaac Montoya said that evaluating the success of COPR presents a challenge, with one possibility being to rely on public opinion polls. In response to a comment from Ms Fernandes, who said that keeping records of COPR accomplishments would help toward such evaluations, Dr. Kirschstein urged all members of COPR also to keep their own list of COPR activities.

In response to a comment from Ms. Lackritz, Dr. Kirschstein recommended that COPR establish a working group to deal with research involving under-served communities. Mr. Roehr said that it is important to undertake this effort across all the Institutes at NIH, as the public perspective changes shape in each different context. Dr. Kirschstein said that Mr. Roehr should take the lead in establishing a group to work with other public advisors at NIH. Dr. Yvonne Maddox said that inviting those public members to a COPR meeting could prove valuable in enlisting their cooperation. Mr. Roehr agreed to form such a working group.

Ms. Thomas asked COPR members to form a working group to develop a process for identifying and recruiting new members to replenish the council as current members depart. Ms. Thomas emphasized that whatever selection process was used to bring new members onto the Council would need to take into account an appropriate balance of many diverse factors, including gender, biomedical interests, and geographic representation. Ms. Kalabokes agreed to coordinate this working group.

Several other items were suggested for inclusion on the agenda of the next meeting: pain research; clustering of diseases and environmental factors; a review of

- **NIDCR—**National Institute of Dental and Craniofacial Research
- **NIDDK—**National Institute of Diabetes and Digestive and Kidney Diseases


NIH...Turning Discovery Into Health

- Leonard Tamura

Executive Summary

Dr. Ruth Kirschstein began the Fourth Meeting of the Director's Council of Public Representatives (COPR) by briefing COPR members on uncertainties facing NIH because the Congress has not yet passed an ap

October 31–November 1, 2000 Meeting Minutes | Director's Council of ...

Ms. Rosemary Quigley summarized some of her experiences as one of several COPR members who served on the NIH Working Group on Gene Transfer Clinical Trials. The Working Group concluded that the intense focus by the public on gene transfer research helps to set it apart from other types of clinical research, according to Ms. Quigley. She also said that it was valuable for several individuals to be representing the general public on the Working Group because even the bioethicists who serve on that body appear to bring a distinct viewpoint to its deliberations, but the public members can better represent the public at large. She said that the Working Group was trying to amend the process for reviewing research on gene transfer to improve its oversight without making the process too formal. The scope of that oversight remains limited to those research proposals involving genuinely novel activities, about ten percent of overall activities in gene transfer clinical research.

Ms. Quigley said that the Working Group also recommended that RAC reviews be conducted before any patients are enrolled in a particular clinical trial and that communications improve between the NIH RAC and FDA. However, those efforts are complicated because the NIH RAC and FDA adhere to different, mandated procedures when reporting serious adverse events associated with clinical trials, making it difficult to reconcile the differences in their current practices.

Mr. Robert Roehr said that, although he supports the NIH Working Group's recommendations, he would like to see data from gene transfer clinical trials treated more openly, and for the review process to be modeled after NIH rather than FDA practices. He said that he favors increased public participation, and suggested that a more open process will encourage patients to enroll in clinical trials. Subjects are more likely to protect themselves if they better understand experimental procedures through a process for informed consent that is more open.

Ms. Debra Lappin said that having COPR members serve on the Working Group was valuable, and that their presence helped to demarcate important differences between the NIH and FDA. She agreed with Mr. Roehr that NIH should go further toward openly reporting serious adverse events associated with gene transfer

October 31–November 1, 2000 Meeting Minutes | Director's Council of ...

said that his goal is to improve the current system and to provide robust protections to human subjects participating in research. These reforms will benefit not only patients, but also the science being done. Dr. Murray said that NBAC invited several groups of human subjects to provide input to the commission. He also noted that IRBs would benefit if they included more lay representatives as members.

In response to a comment from Dr. desVignes-Kendrick about the erosion of trust toward researchers among minority groups, Dr. Koski said that such populations have been approached in the wrong way and that it is essential to provide all populations with equal protection from research risks. He said that reaching out to such populations and respecting their needs represents an important challenge for the research community to meet. Dr. Kirschstein said that the NIH Women's Health Initiative has enrolled a very large number of women from minority groups and is implementing a number of special measures to develop their trust. Dr. desVignes-Kendrick agreed that such measures are needed to help in overcoming health disparities. Ms. McCabe said that training efforts are being stepped up to provide more health care professionals drawn from such communities.

In response to a question from Ms. Quigley about what COPR might contribute, Dr. Murray said that some suggestions, such as developing closer contacts with human subjects, provide a good start. He said that knowing COPR's opinions on whether measures to protect human subjects should be applied to both privately and publicly funded research and whether there should be a federal office with oversight over all such research would be helpful. Dr. Koski urged COPR to share its views directly with the OHRP advisory committee that will soon begin to meet.

Mr. Roehr suggested that market forces and efforts to better inform patients about clinical trials would improve protective measures and might also induce more lay individuals to participate in designing clinical trials that better meet their health needs.

Ms. Lackritz praised the prototype document on informed consent described earlier by Ms. McCabe. In response to a question from Ms. Anne Thomas about how that document is being distributed, Ms. McCabe said that it has been sent to all IRBs and to cancer patient advocacy groups and to cancer research and treatment centers. She also said that other NIH Institutes are adapting the document for use in research settings where other diseases are being studied. Mr. Roehr said that he hopes that large components of the document will remain intact regardless of the settings in which it is being used. Dr. Kirschstein said that the IOM has been asked to provide advice on how to foster wide use of this prototype document.

COPR Business Items, Wednesday, November 1, 2000

Dr. Kirschstein acknowledged andahat

Dr. Montoya thanked Ms. Gorman for her help in coordinating the working group's efforts, which overlap extensively with those of the working group headed by Ms. Lappin that is focusing on human research protections. His working group, which has developed an outline of its plans, is considering what format of a report would be most helpful to NIH. So far, the input for this report has come mainly from communities connected to members who serve on the working group, but plans call for reaching out more broadly. One consistent comment from those who have been contacted is to try to define underserved populations not so much in terms of racial-ethnic distinctions but in terms such as geography, disabilities, and socioeconomic and educational factors.

Rotation and Transition Working Group—Vicki Kalabokes

Ms. Kalabokes said that the members of the working group conferred by telephone to consider how the first and subsequent rotations from membership on the NIH COPR should be handled. For the first phase, enough members identified themselves as willing to rotate off active membership, that the question of finding an equitable selection process for those who are first to retire was easily resolved. In terms of finding the first set of replacements, former NIH Director Dr. Harold Varmus had agreed that the COPR Associates would make up the primary pool of candidates for the next new group. The six new COPR candidates will primarily be selected from the COPR Associates pool. The six COPR members rotating off active membership of the council will end their terms on March 31, 2001. The six new members will be selected by February 2001 and will officially begin their terms as of April 1, 2001. However, for subsequent selection rounds, the members of this working group will work with NIH staff to make sure an open call for nominations is widely distr

October 31–November 1, 2000 Meeting Minutes | Director's Council of ...

IRB—Institutional Review Board

NBAC—National Bioethics Advisory Commission

NCI—National Cancer Institute

NCRR—National Center for Research Resources

NCMHD—National Center on Minority Health and Health Disparities

NEI—National Eye Institute

NIAMS—National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIBIB—National Institute for Biomedical Imaging and Bioengineering

NICHD—National Institute of Child Health and Human Development

NIDA—National Institute on Drug Abuse

NIDCR—National Institute of Dental and Craniofacial Research

NIDDK—National Institute of Diabetes and Digestive and Kidney Diseases

NIEHS—National Institute of Environmental Health Sciences

NIH—National Institutes of Health

NIMH—National Institute of Mental Health

NINDS—National Institute of Neurological Disorders and Stroke

*NINR—*National Institute of Nursing Research

NHGRI—National Human Genome Research Institute

NLM—