Secretary's Advisory Committee on Human Research Protections

Inaugural Meeting
July 22, 2003
Washington, DC

Summary Minutes

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Hubert H. Humphrey Building
200 Independence Avenue S.W.
Washington, D.C., 20201

Secretary's Advisory Committee on Human Research Protections

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Members Attending

Chair Ernest D. Prentice, Ph.D.
Associate Vice Chancellor for Academic Affairs
and Regulatory Compliance
University of Nebraska Medical Center
Omaha, NE

Executive Secretary Bernard A. Schwetz, D.V.M., Ph.D.
Acting Director, Office for Human Research Protections
Rockville, MD

Thomas L. Adams, CAE
Chief Executive Officer
Association of Clinical Research Professionals
Alexandria, VA

Mark Barnes, J.D., LL.M.
Partner
Ropes & Gray
New York, NY

Celia B. Fisher, Ph.D.
Marie Ward Doty University Chair
Director, Center for Ethics Education
Fordham Univeristy
Bronx, NY

E. Nigel Harris, M.Phil., M.D., D.M.
Dean and Senior Vice President
for Academic Affairs
Morehouse School of Medicine
Atlanta, GA

Robert G. Hauser, M.D., F.A.C.C.
Senior Consulting Cardiologist
Abbott Northwestern Hospital
Minneapolis Heart Institute
Minneapolis, MN

Nancy L. Jones, Ph.D.
Associate Professor of Pathology
Department of Pathology
Wake Forest University School of Medicine
Winston-Salem, NC

Felix A. Khin-Maung-Gyi, Pharm.D.,
M.B.A., CIP
Chief Executive Officer
Chesapeake Research Review, Inc.
Columbia, MD

Susan Kornetsky, M.P.H.
Director, Clinical Research Compliance
Children=s Hospital
Clinical Investigation
Boston, MA

Mary L. Polan, M.D., Ph.D., M.P.H.
Professor and Chair
Department of Obstetrics and Gynecology
Stanford University School of Medicine
Stanford, CA

Susan L. Weiner, Ph.D.
Founder and President
The Children=s Cause, Inc.
Silver Spring, MD

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Documents

- Agenda
- Charter
- Membership Rosters
- HHS Protection of Human Subjects Regulations (45 CFR part 46)
- The Belmont Report
- NHRPAC Documents:
  - -Comment letter to the Food and Drug Administration (FDA) on decision to adopt 45 CFR part 46, subpart D, (excluding Section 46.408 (c)) |August 2001|
  - -Comment letter to HHS on 45 CFR 46 Subpart B |September 2001|
  - -NHRPAC Recommendations on HHS' draft Interim Guidance on Financial Relationships in Clinical Research |October 2001|
  - -Clarification of the Status of Third Parties |Revised April 24, 2002|
  - -NHRPAC Comment letter on Health Insurance Portability and Accountability Act Notice of Proposed Rule Making |April 2002|
  - -Report to NHRPAC from Social and Behavioral Science Workgroup on Public Use Data Files |April 2002|
  - -Draft Work product from the Genetics Workgroup |July 2002|
  - -Final Report to NHRPAC from Children's Workgroup
  - -Final Report to NHRPAC from Workgroup on Decisional Incapacity on Informed Consent and the Decisionally Impaired
  - -Final NHRPAC Recommendations on Confidentiality and Research Data Protections (Part 1) and Illustrative Overview of Federal Confidentiality Statues and Codes (Part 2)
- Prisoner Research-Subpart C (Slide Presentation by Karena Cooper)
- OHRP Request to NHRPAC |April 9, 2002|
- The HHS Protection of Human Subjects Regulations (45 CFR part 46, subpart C)
- Preamble to 45 CFR part 46, subpart C - *Federal Register* Notice, *1978*
- "Research Involving Prisoners," Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978
- OHRP Prisoner Research Guidance Document |May 23, 2003|
- "Waiver of the Applicability of Certain Provisions of HHS Regulations for the Protection of Human Research Subjects for HHS Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects" – *Federal Register* Notice, June 20, 2003
- OHRP Briefing Document for SACHRP on Subpart D: Research Involving Children
- The HHS Protection of Human Subjects Regulations (45 CFR part 46, subpart D)
- Additional Safeguards for Children in Clinical Investigations of FDA – Regulated Products – (45 CFR part 46, subpart D) *Federal Register* Notice

- 45 CFR part 46, subpart D Timeline: Relevant Statutes, Regulations and Federal Register Notices
- Letter to OHRP on 45 CFR part 46, subpart D process |February 2001|
- Algorithm for 45 CFR part 46, subpart D Analysis (45 CFR part 46 and 21 CFR part 50) by Dr. Robert M. Nelson
- "The Process of Federal Panel Review of Research Protocols Involving Children: Case Study: A Multi-Center Randomized Dose Response Study of the Safety, Clinical and Immune Response of Drynax® Administered to Children 2 to 5 Years of Age," Medical Research Law and Policy Report (BNA) 2002;1:613-615, by Nelson RM, Prentice ED, and Hammerschmidt DE
- Protection for Children in Research: HHS Report to Congress on the Children's HealthAct of 2000 |May 2001|
- Table on Development of Guidance on HHS 45 CFR part 46, subpart D Regulations: Uncompleted Tasks of NHRPAC
- Children's Research - Subpart D, slide presentation by Dr. Ernest Prentice, SACHRP Chairperson
- Executive Summary - "Preserving Public Trust: Accreditation and Human Research Participant Protection Programs," by the Institute of Medicine
- "Analysis and Perspective: The Institutional Review Board's Adverse Event Report Dilemma" Medical Research Law and Policy Report (BNA) 2002;1:339-343, by Prentice ED, Oki Gwenn, Gordon Bruce and Zaia John
- "Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials," by the National Institute of Health, June 5, 2000
- "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials," by the National Institute of Health, June 11, 1999
- "The NIH Policy for Data and Safety Monitoring," by the National Institute for Health, June 10, 1998
- Draft "Financial Relationships and Interest in Research Involving Human Subjects: Guidance for Human Subject Protection" – *Federal Register* Notice, March 31, 2003
- Standards for Privacy of Individually Identifiable Health Information Regulation Text (45 CFR pars 160 and 164)" by HHS
- "Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule," by HHS

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MORNING SESSION

Welcome, Opening Remarks, and Introduction of the Chairman of the Secretary's Advisory Committee on Human Research Protections (SACHRP)
Bernard A. Schwetz, D.V.M., Ph.D.
Dr. Schwetz welcomed members to the inaugural SACHRP meeting. He explained that the Committee will build on the work of the National Human Research Protections Advisory Committee (NHRPAC) in order to provide guidance to The Honorable Tommy G. Thompson, Secretary of the Department of Health and Human Services (DHHS). To help guide members in their deliberations, Dr. Schwetz outlined several expectations for the SACHRP meeting. These included:

- Identifying higher and lower priority issues for SACHRP to review during the next two years while maintaining the flexibility to address critical issues that arise unpredictably.
- Creating subcommittees to conduct transparent reviews of key issues such as additional protections for children.
- Defining the meeting calendar for the next two years and identifying important future agenda items.

Dr. Schwetz thanked the SACHRP official and *ex officio* members for coming to the meeting and encouraged everyone to participate. He explained that SACHRP can advise other departments under the Common Rule (Federal Policy for the Protection of Human Subjects), and urged SACHRP to regard the *ex officio* members as valuable resources. He concluded his opening remarks by introducing Ernest D. Prentice, Ph.D., who had graciously agreed to chair SACHRP. Dr. Prentice is the Associate Vice Chancellor for Academic Affairs and Regulatory Compliance at the University of Nebraska Medical Center.

Welcome, Committee Introductions
Ernest D. Prentice, Ph.D.
Dr. Prentice welcomed the official and *ex officio* members of SACHRP and thanked the public for attending. He acknowledged the accomplishments of NHRPAC under Chair Mary Faith Marshall, noting that their work will serve as a platform for pursuing the SACHRP agenda under Secretary Thompson. To facilitate this, he encouraged Susan

Kornetsky and Mark Barnes--both of whom are current SACHRP and former NHRPAC members--to share their perspectives during the discussions.

Introduction of SACHRP Members

Dr. Prentice invited SACHRP members to introduce themselves. They included:

E. Nigel Harris, **M.Phil., M.D., D.M.**, Dean and Senior Vice President for Academic Affairs, Morehouse School of Medicine

Dr. Harris is a rheumatologist by training and has a background in academic medicine.

Celia B. Fisher, Ph.D., Director, Center for Ethics Education, Fordham University

Dr. Fisher is a psychologist conducting studies on biomedical research ethics.

Thomas L. Adams, CAE, Chief Executive Officer, Association of Clinical Research Professionals (ACRP)

Mr. Adams represents an international association of 18,000 clinical research professionals.

Susan Weiner, Ph.D., Founder and President, The Children's Cause, Inc.

Dr. Weiner is an advocate for childhood cancer patients.

Mark Barnes, J.D., LL.M., Ropes & Gray

Mr. Barnes is an attorney representing organizations in the biomedical sphere including Institutional Review Boards (IRBs), academic institutions, and pharmaceutical companies. He also served as an AIDS advocate while on the faculty of Columbia University.

Robert G. Hauser, M.D., F.A.C.C., Senior Consulting Cardiologist, Abbott Northwestern Hospital, Minneapolis Heart Institute

Dr. Hauser is a trained cardiologist with a special interest in medical devices, particularly those used in the practice of cardiology.

Nancy L. Jones, Ph.D., Associate Professor of Pathology, Wake Forest University School of Medicine

Dr. Jones conducts basic research and is concerned about the ethics involved in translating bench research to clinical applications.

Felix A. Khin-Maung-Gyi, Pharm.D., M.B.A., CIP, Chief Executive Officer, Chesapeake Research Review, Inc.

Dr. Khin-Maung-Gyi is the founder and CEO of Chesapeake Research Review, Inc, an organization providing consulting services in the field of human research protection practices. He also is a Senior Policy Fellow at the University of Maryland Center for Drugs and Public Policy.

Susan Kornetsky, M.P.H., Director, Clinical Research Compliance, Children's Hospital
Ms. Kornetsky has worked full-time on IRB issues for 20 years.

Mary L. Polan, M.D., Ph.D., M.P.H., Professor and Chair, Department of Obstetrics and Gynecology, Stanford University School of Medicine
Dr. Polan is a reproductive endocrinologist who heads both a clinical practice and a research laboratory. She has a recent interest in international public health.

Introduction of SACHRP Ex Officio Members
Dr. Prentice also asked *ex officio* members to introduce themselves. Those in attendance included:

Peter R. Preuss, Director, National Center for Environmental Assessment, Environmental Protection Agency

John R. Livengood, Deputy Associate Director for Science, Office of Science Policy and Technology Transfer, Centers for Disease Control and Prevention

David Jacobs, Director, Healthy Homes and Lead Hazard Control, U.S. Department of Housing and Urban Development

Dr. David A. LePay, Senior Advisor on Clinical Science, Office of Science and Health Coordination, Office of the Commissioner, Food and Drug Administration

Tryn Stimart, representing Linda Beth Schilling, Director, Chemistry and Life Sciences Office, Advanced Technology Program, National Institute of Standards and Technology, U.S. Department of Commerce

Deborah Price, Chief of Staff, Federal Student Aid, U.S. Department of Education

Dr. Philip Rubin, Division Director, Behavioral and Cognitive Sciences, National Science Foundation

Patty Decot, Assistant Director for Regulatory Affairs and International Programs, BioSystems Directorate, U.S. Department of Defense

Christine Grady, representing Lana Skirball, National Institutes of Health

Dr. Lynn Cates, Assistant Chief Research and Development Officer, Program for Research Integrity Development and Education (PRIDE), Department of Veterans Affairs

Howard Bradley, Social Science Research Analyst, Office of Program Development and Research, Social Security Administration

Sally Flanzer, representing Francis D. Chesley, Jr., M.D., Director, Office of Research Review, Education, and Policy; Agency for Health Care Research and Quality

SACRHP's Mission and Role

Dr. Prentice noted that SACHRP's mission is to advise the Secretary of DHHS on all matters related to human subjects with a particular emphasis on special populations including children, neonates, decisionally impaired individuals, and prisoners. SACHRP also is mandated to address potential investigator conflicts of interest, international issues, research with individually identified samples, data, or information, and OHRP activities and plans.

Dr. Prentice explained the current human research protections philosophy, beginning with a quote from Secretary Thompson: "We must allow science and medical research to advance for the good of all Americans, but not at the expense of people who participate in clinical trials." This general philosophy evolved primarily in response to sentinel events and agents of change that occurred from 1998 to 2002, including:

- The 1998 HHS Office of the Inspector General (OIG) report on IRBs that indicted the system and identified deficiencies to be corrected.
- Successive Federal shut-downs of research at major academic and veterans' medical centers.
- The deaths of clinical trial participants Jesse Gelsinger, who participated in a gene transfer study at the University of Pennsylvania, and Ellen Roche, who was part of an asthma protocol at Johns Hopkins.

Many of these events were widely publicized in the media and fanned a general demand for change. SACHRP was created to respond to these issues.

SACHRP's charge, Dr. Prentice continued, is to determine "how best to protect the rights and welfare of human research participants while advancing science to benefit humankind." He added that SACHRP, like NHRPAC, probably will not complete its ambitious agenda by the end of its term.

<u>Review of NHRPAC Uncompleted Activities (Subparts C and D, etc.)</u>

Dr. Prentice observed that NHRPAC produced useful reports on several issues that SACHRP needs to review and update. For example, the reports on additional protections for children and decisionally impaired individuals left key areas unaddressed. Also, the regulations on additional protections for prisoners are 25 years old and need to be updated with concern for ethics and justice. Dr. Prentice added that IRBs and Federal agencies are eager to receive guidance on these challenging topics.

Committee Discussion

In response to Dr. Prentice's comments, members expressed a range of ideas and concerns. Mr. Barnes suggested that SACHRP follow up on NHRPAC's work on conflict of interest. Dr. Weiner noted that it is important for SACHRP to strike a balance between over- and under-protection in crafting its recommendations for additional protections for children. Dr. Prentice agreed, noting that IRBs are making inconsistent decisions in this area and definitely need guidance. Dr. Khin-Maung-Gyi recommended that the Committee discuss the impact of litigation on the field. Dr. Prentice observed that individual IRB members are now being named in complaints, and this is leading to:

- Difficulties recruiting volunteers to serve on IRBs and
- Demands for additional IRB documentation to respond to possible subpoenas.

Dr. Fisher commented that it is especially important to maintain research review transparency in the current litigious environment.

Prisoner Research--Subpart C

Presentation by Karena Cooper, M.S.W., OHRP

In 1978, DHHS adopted 45 Code of Federal Regulations (CFR) part 46, Subpart C to govern biomedical and behavioral research funded by the Department that involves prisoners as subjects. According to these regulations, DHHS shall not involve prisoners as research subjects unless:

- An IRB, which includes a prisoner representative on its roster, reviews the research proposal and makes the seven required findings specified in 46.305(a)(1)-(7).
- OHRP, as the DHHS Secretary's designate, determines that the research falls under one of the four permissible categories in 45 CFR 46.306(a)(2)(i)-(iv) for research involving prisoners.

Before making any findings, the IRB must determine whether the study involves "prisoners" as defined in Subpart C, 45 CFR 46.303(c). It can be a difficult, fact-specific inquiry to assess whether persons involuntarily detained in other facilities as an alternative to incarceration or prosecution in a penal institution meet the Subpart C definition of prisoner. Probationers, parolees, persons ordered by the court to attend non-residential community programs, and individuals released from prison to halfway houses would not be considered by OHRP to meet the Subpart C definition of prisoner.

After it is determined that "prisoners", as defined in Subpart C, are to be involved in the study, the IRB must decide whether the research falls under one of the four categories of permissible research involving prisoners listed in Subpart C, 45 CFR 46.306(a)(2)(i)-(iv).

- Categories 1 and 2: As defined in Subpart C, Category 1 (45 CFR 46.306(a)(2)(i)) involves the "study of the causes, effects, and processes of incarceration and criminal behavior." Category 2 (45 CFR 46.303(a)(2)(ii)) is the "study of prisons as institutional structures or of prisoners as incarcerated persons." For both categories, participants must face no more than minimal risk/inconvenience. "Minimal risk" is defined in Subpart C as: "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons." This varies from the definition in Subpart A and uses the healthy un-incarcerated individual as a point of reference.

- Categories 3 and 4: Category 3 (45 CFR 46.303(a)(2)(iii)) involves research on conditions affecting prisoners as a class. Category 4 (45 CFR 46.303(a)(2)(iv)) involves research on practices that are intended to improve the subject's health and well-being. Category 3 research triggers the requirement that the DHHS Secretary (delegated to OHRP) consult with experts and publish notice in the *Federal Register* for the intent to approve such research. Category 4 triggers the requirement for expert consultation if the study involves the assignment of

prisoners to a control group which may not benefit from the research. The consultation process takes at least six months from the time that OHRP receives the prisoner research certification from the institution/IRB.

If the IRB determines that the proposed research falls under one of the four categories of permissible research involving prisoners, it must then make the other six required findings, found in 45 CFR 46.305(a)(2)-(7). After the IRB has reviewed the proposed research involving prisoners, the Subpart C regulations require that the IRB's institution certify to OHRP that it made the required findings under 45 CFR 46.305(a). To comply with the certification requirement, the IRB must send a written prisoner research certification letter, along with the research proposal, to the OHRP. OHRP then makes its determination regarding the choice of category and responds to the IRB in writing. No prisoners may be involved in the proposed research until the completion of the prisoner research certification process. If the Secretarial consultation with experts was triggered by category 3 or 4, no prisoners may be involved until the completion of the consultation process and only if the DHHS Secretary approved the inclusion of prisoners in the research.

Looking at the larger issue of when Subpart C reviews are required, DHHS has determined that IRBs must review studies that are designed to be conducted in prison setting or using prisoners (as defined by Subpart C). Subpart C reviews also must be conducted of non-prison studies when a previously enrolled subject subsequently becomes a prisoner. An IRB may also be asked to prospectively review under Subpart C a non-prison study that involves study population at risk for incarceration, such as probationers or substance abusers.

Ms. Cooper identified a set of challenges the Subpart C reviews present to both IRBs and OHRP. IRBs often have difficulties finding qualified prisoner representatives. In addition, IRBs and OHRP have had difficulties applying the definition of "prisoner," determining what constitutes "minimal risk" in a prison, and deciding whether the research falls under one of the four permissible categories.

On behalf of OHRP, Ms. Cooper asked for SACHRP's guidance in meeting these challenges and in reviewing and updating the work done by NHRPAC to develop adequate prisoner protections. Specific guidance is requested to answer the following questions:

- Does the current Subpart C adequately ensure appropriate inclusions and exclusions of prisoners?
- What should the term "prisoner" encompass?
- What is the appropriate background and expertise for an IRB prisoner representative?

OHRP also would like recommendations about whether to expand the current four categories and retain the requirements that:

- Institutions must certify to the Secretary that the IRB has fulfilled its duties under Subpart C.

- The Secretary must ascertain that the research involves solely one of the delineated categories.

Committee Discussion

Dr. Prentice agreed that prisoner research protections need to be revised. He noted that DHHS-funded research must be certified by OHRP, but that the existing Prisoner Research Certification requirement is unique, unusual, and can unduly restrict research. Other highlights of the discussion included the following:

- Dr. Harris observed that genetics studies involving prisoners can have enormous implications, even if classified as minimal risk. Dr. Prentice explained that most IRBs do not regard genetics research as minimal risk.
- Dr. Khin-Maung-Gyi suggested that SACHRP provide guidance for bridging the gap between FDA and NIH requirements.
- Several members agreed that:
  - It was a matter of justice to ensure that prisoners have access to the latest experimental research.
  - Payment is a critical consideration in care.

Dr. Schwetz concluded the discussion by asking SAHCRP to provide OHRP with general and specific advice about NHRCAP's unfinished business so that OHRP could develop more comprehensive regulations.

Overview of 45 CFR 46, Subpart D and Related Issues

(Ernest Prentice, Ph.D.)

In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Biobehavioral Research issued its report recommending additional protections for children. This report was the basis for 45 CFR 46 Subpart D, Additional Protections for Children Involved as Subjects in Research, which was promulgated by DHHS in 1983. The Food and Drug Administration (FDA) adopted equivalent regulations as an enforceable "Interim Final Rule," 21 CFR 50, Subpart D in 2001. The FDA categories of pediatric research, 50.51--50.54, parallel the HHS categories 46.404--46.407. Dr. Prentice explained that the current additional protections for children are based on the risk-benefit escalation principle which states that "as the risk of the research increases in relation to the absence of direct benefit to the subject, the criteria for IRB approval under Subpart D categories become more stringent." Subpart D uses the standard of "minimal risk" as the threshold level of risk. Minimal risk means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests."

To help interpret the regulations, NHRPAC's guidance document recommends interpreting the phrase "daily life" as meaning "the daily life of healthy children in the general population." Also, in evaluating whether a given procedure or intervention qualifies as "minimal risk," NHRPAC guidelines recommend that IRBs "consider whether the risks are comparable to the risks that parents may ordinarily allow their children to experience in the course of daily life or as a consequence of routine tests using an *equivalence of risk basis."*

Dr. Prentice presented the four risk categories and summarized pertinent NHRPAC recommendations and gaps that remain to be addressed:

- Category 46.404 (or 50.51): Research studies in this category must not involve greater than minimal risk. The researcher must make adequate provisions for soliciting assent from children and permission from their parents or guardians. However, NHRPAC did not clarify "assent" and "permission."

- Category 46.405 (or 50.52): These studies involve greater than minimal risk, but present the prospect of direct benefit to the individual subjects. Risk must be justified by the anticipated benefit to the subjects, and:
  - The relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternate approaches.
  - Adequate provisions must be made for soliciting the assent of the children and permission of their parents and guardians.

  NHRPAC postponed defining "direct benefit."

- Category 46.406 (or 50.53): Qualifying studies involve greater than minimal risk and no prospect of direct benefit to individual subjects, but are likely to yield generalizable knowledge about the subjects' disorder or condition. Additional requirements are that:
  - The research risk represents a minor increase over minimal risk.
  - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
  - The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding of the subjects' disorder or condition.
  - Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

  NHRPAC defined "disorders" as medical in nature while a "condition" also can apply to preconditions. The National Commission interpreted "minor increase over minimal risk" as presenting "no significant threat to the child's health or well-being." HHS and FDA regulations provide no definition of the term, leaving this for IRBs to determine on a case-by-case basis. However, NHRPAC interpreted "minor increase over minimal risk" as a relative standard, allowing more risk for sick than for healthy children.

- Category 46.407 (or 50.54). This classification applies to research that is not otherwise approvable, but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. This is research that does not meet the requirement of the other Subpart D categories. A DHHS-OHRP/FDA panel of experts must review a 407/54 application, which includes the IRB's review, determination, rationale, and documentation. The public also must have an opportunity to comment. HHS/FDA reviews the experts' recommendations and public comments before making a final decision.

NHRPAC did not formulate recommendations on 46.407 studies, as there were relatively few of them. However, since 2001 the number of 46.407 reviews has been increasing.

Subpart D Issues

Dr. Prentice provided an initial list of Subpart D issues that need SACHRP's attention. Categories 46.404 and 406 need to be reviewed, clarified, and updated as needed. The requirements for 46.405 need to be reviewed and additional recommendations made. Assent, consent, and permission issues need to be reviewed across the categories. In addition, recruitment and incentives in pediatric research, as well as controlled trials using placebos, need to be reviewed. Another key priority is determining whether SACHRP should be a venue for 46.407 reviews.

Dr. Prentice suggested that the Institute of Medicine (IOM) report on pediatric research due in March 2004, could serve as the platform for the Committee's discussions of 46.404-406. However, in the interim, 46.407 should be SACHRP's highest Subpart D priority. Dr. Prentice added that OHRP is now looking at the 46.407 review process, focusing on efficiency, effectiveness, transparency, and validity. SACHRP's recommendations and guidance about this process would be greatly appreciated.

Drs. Schwetz and Prentice asked SACHRP to determine whether a subcommittee should be created to facilitate improvement of the 46.407 review process. In the past, the reviews were closed and reviewers provided individual recommendations rather than a consensus report. The subcommittee structure would enable OHRP to require reviews to be conducted in a public forum and in compliance with Federal Advisory Committee Act (FACA) for public involvement. The subcommittee would be composed of experts drawn from SACHRP and outside organizations; members would formulate a consensus and submit it to the Committee.

Before inviting SACHRP's comments, Dr. Prentice publicly thanked OHRP staffer Leslie Ball for her help developing the Subpart D presentation even though she could not be there at the meeting.

Committee Discussion

Dr. Harris asked whether SACHRP would have enough time to conduct 46.407 (also called "407") reviews and accomplish its other goals. Dr. Prentice explained that based on Federal regulations, it was logical that 407 reviews be conducted under SACHRP's auspices. Dr. Schwetz added that, because HHS is consolidating the work of advisory committees, SACHRP would be the ideal mechanism for housing the subcommittee and ensuring that regular, transparent, meetings of experts be held to conduct 407 reviews.

Members expressed concerns about the volume of reviews growing over time, both as part of the current trend and in response to the availability of a consistent review process, assuming that SACHRP or a similar group continues in existence. Dr. Schwetz anticipated that SACHRP, in some form, would exist for the foreseeable future and that an on-going mechanism for conducting 407 reviews would be maintained. In addition,

Dr. Schwetz noted that OHRP staff would be available to support the subcommittee's work. Mr. Barnes suggested that SACHRP take on responsibility for 407 reviews as requested, but also monitor the amount of time and effort the reviewing process required. Dr. Fisher identified two definitions of an advisory group: one develops criteria and processes, and the second evaluates this system in practice. She expressed reservations about whether a single advisory group could fulfill both roles appropriately.

Dr. Prentice reinforced the importance of developing a transparent, efficient 407 review mechanism that encouraged institutions to submit for 407 reviews when appropriate. At present, IRBs often try to avoid 407 reviews because they are complex and can involve long delays. He suggested that SACHRP develope a pediatrics subcommittee focusing on 407 reviews. This subcommittee would draw on the expertise of SACHRP members as well as others in field recruited with assistance from OHRP. SACHRP would provide a general review function for the subcommittee.

During further discussion, Dr. Schwetz explained that two SACHRP members usually would be required to serve on a subcommittee, but one might be sufficient if serving as chair. Mr. Barnes suggested that subcommittee members be asked to develop consensus reports for 407 applications that would, when appropriate, include discussions of major issues that SACHRP needed to review. Dr. Fisher recommended that the SACHRP member serving as subcommittee chair recuse him/herself from the SACHRP vote. Ms. Kornetsky observed that this plan made sense in light of NHRPAC's experience.

SACHRP members asked about specific aspects of the SACHRP mandate. Dr. Prentice explained that it includes both addressing international issues and improving communications among HHS/FDA, OHRP, and IRBs. Regarding the latter point, Dr. Polan observed that Federal regulations must be interpreted consistently and information must be communicated in a timely fashion; this is critical for reducing delays in the IRB process.

Delays are caused by fear of litigation as well as poor communication, Dr. Prentice observed. Reducing litigation is not among SACHRP's current priorities, but could occur as a result of the accreditation of human research protection programs.

Accreditation would alter the research community culture in positive ways, Dr. Prentice explained. The utility of accreditation is supported by:

- Extrapolations from animal research accreditation programs and
- The results of recent reviews of human research protection programs conducted by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

AAHRPP's findings also indicate that the entire institutional human research protection program--investigator education and the place of the IRB in the institutional culture, as well as the IRB itself--should be reviewed by an accrediting body. This broad external oversight encourages institutions to provide needed staff and resources, Dr. Prentice explained. Dr. Weiner added that accreditation would reduce the widespread variations in approvals for pediatric research that currently exist across the country.

Dr. Fisher raised concerns about the costs of accreditation. Committee members suggested that institutions might consider banding together or working with independent IRBs to reduce costs. In other cases, a centralized IRB, similar to the one supported by the National Cancer Institute (NCI), might be put in place or IRB reviews might not be needed from all sites involved in some collaborative studies.

Administering the Oath of Office to SACHRP Members

The Honorable Tommy G. Thompson

Dr. Schwetz introduced The Honorable Tommy G. Thompson, Secretary of the Department of Health and Human Services, and Vice Admiral Richard H. Carmona, M.D., M.P.H., F.A.C.S., who is the U.S. Surgeon General and was serving as the Acting Assistant Secretary for Health. In his comments, Secretary Thompson noted the importance of SACHRP's work, which protects the rights of humans involved in vital medical research. The Secretary thanked each member for his or her willingness to serve on the Committee and explained that the group had been selected based on their experience, commitment, and dedication. He then administered the Oath of Office. After members were sworn in, Dr. Prentice thanked Mr. Thompson and Dr. Carmona on behalf of SACHRP.

AFTERNOON SESSION

SACHRP Priority-Setting Discussion Part I

Dr. Prentice reviewed the seven items on the priority-setting agenda:

1. Explore the option of creating SACHRP Subcommittees to:
    - Review certain proposed research involving:
        - Pregnant women, human fetuses or neonates in accordance with the requirements of subpart B (45 CFR 46.207);
        - Prisoners, in accordance with the requirements of subpart C (45 CFR 46.306(a)(2)(iii) and (iv); and
        - Children, in accordance with the requirements of subpart D (45 CFR 46.407)
    - Assist the full Committee in advising the DHHS Secretary about whether the proposed research should be conducted or supported by the Department.
2. Advise DHHS about the responsible conduct of research involving special populations, including prisoners and children.
3. Advise DHHS on its role, if any, in the accreditation of human research protection programs by non-Federal accrediting bodies.
4. Review adverse event reporting (AER) requirements under DHHS/FDA regulations.
5. Review the role of Data Safety Monitoring Boards (DSMBs) relative to IRBs.
6. Discuss other topics raised by SACHRP members.
7. Address short topics (e.g., conflict of interest guidance, Health Insurance Portability and Accountability Act, central IRBs).

Reviewing Pediatric 407 Applications
Members discussed whether SACHRP should be the parent committee for 45 CFR 46 Subpart D (407) panel reviews. Currently, Dr. Prentice explained, if an IRB receives a protocol requesting DHHS funds for a study that involves children and cannot be approved under 46.404-06, the Board may send the research proposal for DHHS review at the 407 level. The DHHS review is convened by OHRP and conducted in a closed session. Dr. Prentice suggested that SACHRP appoint a subcommittee to review pediatric 407 applications. The subcommittee would submit their recommendations to SACHRP for a brief, general review. The chair and some members would be drawn from SACHRP; experts from other organizations also would serve on the subcommittee.

***Motion*:** Mr. Barnes moved that SACHRP appoint a subcommittee to review pediatric 407 applications. Two SACHRP members would serve as co-chairs, with other SACHRP members and experts in the field (selected by HHS and SACHRP) completing the subcommittee roster. The subcommittee would conduct reviews and submit their report to SACHRP for further consideration. During the deliberations, the co-chairs would recuse themselves. The motion was seconded.

Discussion of the Motion: Members were concerned that SACHRP not become a rubber stamp for the subcommittee. They suggested that subcommittee members develop a consensus report for each proposal to ensure that SACHRP understands the complex issues involved. Mr. Barnes added that each report should include a précis that would bring any differing points of view on key issues to SACHRP's attention.

Other discussion points included the following:

- Timing: Dr. Prentice recommended that SACHRP and any subcommittees meet a minimum of three times per year. Dr. Fisher asked whether this would be sufficient time to complete all business, especially considering that SACHRP and subcommittee meetings would be transparent and open to the public.
- Availability of expert opinions: Concern was expressed that critical expertise would not be available to SACHRP if the co-chairs recused themselves.
- Guidance for IRBs: It was suggested that SACHRP begin by assessing the 407 review process and develope guidelines for IRBs, including items such as what documentation is needed for the review.
- Dr. Fisher suggested the Committee address overall SACHRP responsibilities, roles, and structure before moving to subcommittee issues. Dr. Harris added that there seemed to be a conflict between SACHRP's role developing guidelines and its role reviewing applications based on the guidelines.

Dr. Prentice asked OHRP to develop a detailed plan for the 407 review process that SACHRP could assess.

Action: The motion was tabled pending further discussion.

The Algorithm for Subpart D Analysis (45 CFR 46 and 21 CFR 50)
OHRP has disseminated the draft algorithm to some IRB community members and received informal comments, Dr. Prentice reported. Dr. Schwetz noted that OHRP found

the draft very useful for explaining the review classification process and the rationale for moving from one section of the regulations to another. However, the algorithm has never been formally adopted. Dr. Prentice suggested that SACHRP look at the document and, given that review time was limited, do one of the following:

- Defer consideration of adoption,
- Approve the document in principle,
- Approve the draft formally unless reconsideration is requested during a specified period of time, or
- Approve the document as a straightforward illustration of the regulations.

Committee Discussion

Dr. Khin-Maung-Gyi observed that the document was useful to IRBs. However, he added, the algorithm would be more helpful if it clearly indicated that researchers do not have independent access to 407 reviews and if it included guidance for different types of IRBs. Dr. Prentice noted that this draft could not be adopted by OHRP with inclusion of the FDA information and asked SACHRP to assume that the FDA information would be eliminated. Dr. LePay added that FDA:

- Has a similar panel structure for 54 reviews,
- Uses a subcommittee of an existing committee for the reviews, and
- Is moving toward a separate pediatric committee.

Once the pediatric committee is established, Dr. LePay continued, FDA will determine whether the committee or one of its subcommittees will conduct 54 reviews. At present, FDA is communicating with OHRP about constructing the committee structure.

In further discussion, members suggested that:

- The algorithm needed an introductory statement to explain its purpose, especially how IRBs can use it as a classification aid.
- SACHRP be given more time to study the algorithm as it was not on the agenda.

Dr. Prentice asked whether further consideration of the algorithm should be deferred. Mr. Barnes suggested that a subcommittee be formed to review the algorithm comprehensively, in conjunction with NHRPAC recommendations and gaps. The algorithm could be considered by a standing subcommittee on pediatrics issues. Other members suggested that 407 issues be addressed before moving to the algorithm.

Establishment of a Subpart D Pediatrics Subcommittee

Motion: Dr. Fisher moved that a Subpart D Pediatrics Subcommittee be formed to focus initially on 407 issues and then to identify and review other pediatrics issues. The motion was seconded.

***Action*:** The motion was approved unanimously.

Related Discussion: Members asked that they be provided information in advance of Committee discussion so that they might be well prepared to make decisions on complex issues.

Public Comment

There were no statements or questions from the audience.

SACHRP Priority-Setting Discussion Part II

Advising DHHS on Accreditation

Dr. Prentice explained that there are two non-Federal accrediting bodies for human research protection programs, AAHRPP and the Partnership for Human Research Protection, Inc., (PHRP). He asked SACHRP to consider what roles the Committee, OHRP, and FDA might play in advancing meaningful accreditation and in encouraging institutions to become accredited.

Dr. Weiner noted that double accreditation is a concern in the research community and urged DHHS to establish a single set of standards. Dr. Polan agreed, adding that academic health centers would be well served if they had to comply with only one set of standards rather than the several layers of requirements imposed by various accrediting organizations. She asked SACHRP to avoid adding an additional layer of accreditation requirements.

Highlights of the ensuring discussion included the following:

- Mr. Adams suggested that SACHRP establish a subcommittee to work with OHRP and FDA to develop voluntary accreditation standards and provide national education on the topic.
- Mr. Barnes expressed concern that conflicts of interest might arise in a subcommittee effort because many SACHRP members are involved with either AAHRPP or PHRP. He noted that it might be too soon to try to determine which accrediting body will become the leader in the field. However, he suggested that the standards of both groups be compared to existing basic Federal requirements and that standards exceeding these requirements should be identified.
- Ms. Kornetsky advised SACHRP not to tackle accreditation standards yet. She observed that a natural experiment is occurring to determine which accrediting body's standards will be generally applied. She also said that the animal research certification experience was a pertinent model for SACHRP's consideration and one that supported limited Federal involvement. For now, Ms. Kornetsky encouraged SACHRP to focus on promoting the importance of accreditation.
- Dr. Harris observed that it is important for institutions to recognize that certain accrediting bodies have acceptable standards. To promote this, he suggested that SACHRP focus on developing a certification process for these bodies. In addition, he believes that accreditation will lead to a cultural shift among institutions that would not be achievable otherwise.

Dr. Schwetz stated that OHRP also believes accreditation for human research protection programs will lead to a cultural shift. OHRP will help ensure that this cultural shift takes place in a timely manner by promoting accreditation and enabling it to become a self-propagating process seen as vitally important by institutions. In addition, Dr. Schwetz agreed with Ms. Kornetsky's comments that a natural experiment is occurring and that the animal research accreditation experience is a pertinent model for SACHRP. He also

said that neither OHRP nor FDA wants to intervene in the non-governmental accreditation process, but the existence of two accrediting bodies may create challenges.

Dr. Khin-Maung-Gyi suggested that SACHRP's discussion of accreditation should focus on the broader category of research sites and include those not associated with IRBs. To facilitate this, the Committee should address the general issue of promoting human research protection programs. In addition, regulatory mandates should be expanded so that independent research sites have an incentive to become accredited. He also encouraged SACHRP to understand the regulatory burdens on clinical research sites. Noting that many audits are duplicative, he suggested that regulatory agencies collaborate on ways to recognize each other's overview and compliance programs.

Dr. Prentice invited representatives from both IRB accrediting organizations to speak extemporaneously.

- Marjorie Speers, Ph.D., Executive Director, AAHRPP, thanked the group for their work and offered to provide information to SACHRP. She noted the importance of ensuring that accrediting agencies are accountable.
- Jessica Briefer French, Assistant Vice President, PHRP explained that the organization is a collaborative program developed by the National Committee for Quality Assurance (NCQA), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). She noted that the PHRP hopes to lessen the burden on research sites by eliminating duplicative oversight, and added that "deemed" accreditation can streamline the accreditation process.

Dr. Fisher asked about SACHRP's mandate regarding accreditation; specifically, whether the Committee should: (1) explore the pros and cons of accreditation, (2) discuss accreditation by Federal or other bodies, and (3) develop and critique accreditation standards. Dr. Harris asked whether SACHRP should be certifying accrediting bodies. Dr. Schwetz explained that SACHRP has a narrower mandate and asked for Committee input on whether OHRP should be doing more than simply observing the natural accreditation experiment underway. Mr. Adams recommended that SACHRP focus on encouraging institutions to get accredited by the existing non-Federal organizations.

Several members addressed the merits of accreditation and providing rewards for institutions that become accredited:

- Ms. Kornetsky suggested that OHRP review whether accreditation increases compliance with regulations. Dr. Schwetz agreed that it would be useful to determine whether there is a relationship between accreditation and the reduction of severe problems. He added that any criteria for monitoring accreditation that SACHRP recommends would apply to all agencies under the Common Rule.
- Mr. Barnes asked SACHRP to consider how Federal agencies could encourage accreditation. He suggested that the Government provide institutions with some sort of reward, short of certification, for participating in the voluntary accreditation process. In cases where the accrediting organization's standards exceed Federal requirements, providing incentives is especially important. At

present, the only incentive is that accreditation may provide IRBs with some protection in law suits.

- Dr. Prentice and Mr. Barnes suggested that, as an incentive, accredited institutions receive fewer routine HHS and/or FDA inspections. Drs. Schwetz and LePay explained that it would be premature to reduce the number of inspections before links between accreditation and performance are established. Dr. Schwetz noted that, as a first step towards developing linkages, OHRP might determine if certain criteria could be monitored and specific key items put into the accreditation curriculum. Dr. LePay explained that routine FDA inspections serve an educational purpose and enforcement-related inspections target specific issues not necessarily resolved by accreditation.

Committee members noted challenges related to the collection and interpretation of accreditation data. Dr. Harris questioned whether sufficient data could be collected quickly enough to validate the importance of accreditation in a timely manner. Dr. Hauser commented that accreditation should not be seen simply as a set of measurable outcomes because this does not allow full consideration of whether accreditation helps prevent unfortunate events.

Establishment of a Subcommittee on Accreditation

***Motion*:** Dr. Hauser moved that SACHRP establish a subcommittee on accreditation. Its purposes would be to examine the background of accreditation, look at the organizations that currently accredit IRBs, review the possible benefits of accreditation, and recommend roles for DHHS--specifically OHRP and FDA--in the accreditation process. The motion was seconded.

***Discussion of the Motion*:** Dr. Fisher reopened the issue of potential conflicts of interest on an accreditation subcommittee. Dr. Polan suggested balancing the subcommittee membership so that each accrediting group is equally represented; this would help eliminate potential conflicts of interest while allowing the subcommittee to benefit from members' specialized expertise. Dr. Jones suggested that accreditation should be addressed by SACHRP as a whole rather than by a subcommittee.

Concerns also continued to be raised about whether SACHRP would be reviewing the standards of either accrediting group. Mr. Barnes revisited his earlier idea, suggesting that SACHRP articulate differences among AAHRPP, PHRP, and Federal requirements and then communicate this information to the IRB community. Dr. Prentice observed that it was premature for SACHRP to examine the standards of AAHRPP or PHRP. He recommended that SACHRP first focus on encouraging accreditation.

Dr. Hauser explained that the intent of his motion was for SACHRP to:

- Educate the IRB community
- Encourage accreditation
- Make recommendations about how institutions and Government would benefit from accreditation

His intent was not to suggest or recommend that SACHRP review the accrediting bodies' standards. After this clarification by Dr. Hauser, SACHRP voted.

Action: The motion passed unanimously.

Subcommittees and Presentations: Structure and Topics

Dr. Prentice recommended that SACHRP limit itself to three subcommittees. He also explained that:

- OHRP and SACHRP will provide names of individuals to serve on the proposed subcommittees. SACHRP members also can volunteer to serve as members or co-chairs.
- The subcommittees will not normally meet publicly. However, they can at the discretion of the Co-Chairs and OHRP.
- Subcommittees are to reach consensus and forward their recommendations to SACHRP for final review.
- OHRP will provide a road map for the Pediatrics 407 Subcommittee; this may assist other subcommittee in resolving process issues. (The development of road maps for these subcommittees may be a future agenda item.)

SACHRP reviewed possible topics for the third subcommittee. Dr. Prentice suggested that AERs and DSMBs be considered together as the subcommittee topic. Dr. Fisher suggested that the subcommittee examine the role of independent practitioners in conducting research and in recruiting participants for DHHS-funded studies. Ms. Kornetsky asked that OHRP's current work and priorities be considered in developing a topic for the third subcommittee. In response, Dr. Schwetz identified the following issues:

- Central IRBs
- International programs (e.g., capacity to conduct large-scale studies, leveraging OHRP/FDA efforts, cross-national ethics)
- OHRP's educational activities (e.g., evaluating the entire enterprise, identifying the greatest human research protection program risks, determining whether educational efforts are targeted correctly to address these risks)

Ms. Kornetsky remarked that the investigator community is becoming increasingly concerned about central IRBs. Dr. Prentice noted that IRB review of AERs also is becoming a major concern among IRBs. Messrs. Barnes and Adams suggested expanding the AER topic to encompass a discussion of current legal challenges faced by IRBs. Dr. Polan suggested that OHRP might be able to leverage its international efforts by working with IOM, which is expanding its work in other countries.

Members discussed whether some topics might be better addressed through subcommittees or as presentations made to the full committee. Dr. Schwetz asked SACHRP to determine which mechanism would be most appropriate for addressing the prisoner research issues. Dr. Prentice commented that Subparts B and C were more complex than Subpart D. This being the case, it might be better to address Subparts B and C after the Pediatrics Subcommittee had worked through some of the general

subcommittee process issues. Dr. Schwetz noted that recent IRB and FDA activities concerning responsibility for AERs also should be considered as a possible future topic.

Mr. Barnes identified three topics for future presentations: liability issues, international concerns, and AERs/DSMBs. He suggested that a presentation be made on each topic during the next meeting. Each presentation would last up to 1.5 hours and focus on key issues, problems, and solutions. SACHRP would determine whether subcommittees should be established on the topics based on the presentations. Mr. Barnes also noted that:

- Dr. Prentice has a presentation on adverse events/DSMB issues.
- Possible aspects of the litigation presentation include: types of suits and their dispositions, public and non-public settlements, and the implications of these recent suits and settlements.

Dr. Fisher observed that SACHRP's mission statement identifies vulnerable populations as a key priority. As a result, she asked that additional subcommittees be formed to review the issues related to prisoners and the decisionally impaired. Ms. Kornetsky noted that SACHRP is small and has limited time; she suggested that the Committee start on a smaller scale with goals for the pediatrics and accreditation subcommittees. Dr. Schwetz commented that vulnerable populations were an important priority, but not the only priority. SACHRP needs to remain flexible and prepared to tackle additional critical issues as they arise.

Dr. Fisher asked what other topics should be considered and what the subcommittees should accomplish by the next meeting. Dr. Harris suggested that the next meeting include subcommittee updates and presentations on other key topics. Dr. Prentice commented that litigation issues cannot be solved by SACHRP and suggested that the issues be addressed in a presentation rather than being considered by a subcommittee. Building on the idea that presentations could serve as the platform for future subcommittees, Ms. Kornetsky added that SACHRP could invite the speakers to join the subcommittees, as was done by NHRPAC.

Dr. Prentice presented a possible SACHRP structure and plan based on the afternoon discussion. SACHRP would establish three subcommittees, one addressing Subpart D pediatric issues with an initial focus on 407 reviews, a second focused on accreditation, and a third reviewing Subpart C prisoner research issues. Presentations would be made at future meetings by internal or external experts, individually or in groups, on topics of importance; initial presentations might concern AERs/DSMBs or litigation. Committee members suggested the following additions and modifications:

- Liability issues, such as the legal vulnerability of IRBs and those submitting information to them, should be included in the litigation presentation.
- Central IRBs, including the NCI model, should be considered among the immediately upcoming presentation topics.
- The FDA might be a resource for the presentations on AERs and central IRBs.
- International issues should be considered as a component of each topic.

Establishment of a Subpart C Prisoner Research Subcommittee
***Motion*:** Based on the foregoing comments and the SACHRP mission, Dr. Prentice proposed that SACHRP establish a subcommittee to focus on Subpart C issues.

Action: The motion passed unanimously.

Wrap-Up and Future SACHRP Meetings
Dr. Prentice asked members to e-mail their priority topics for the next meeting to him. These will be used to set the agenda. Christine Grady noted that NIH and FDA are currently assessing how to organize the AER system. Dr. Prentice suggested that an update on this project be added to the agenda for the next meeting. In addition, Dr. Prentice encouraged members to volunteer to serve on, and co-chair, subcommittees and to nominate others who might serve. OHRP will follow-up on this request as well as making arrangements for the next two SACHRP meetings, including one more in 2003. Dr. Prentice thanked the participants and adjourned the meeting.

ACTION ITEMS

OHRP will:

- Assist in identifying experts to make presentations at SACHRP meetings and to serve on subcommittees.

- Provide a roadmap for the Pediatrics 407 Subcommittee; other subcommittees also may use this map to help resolve process issues. (The development of road maps for these subcommittees may be a future agenda item.)

- Follow up on Dr. Prentice's request that SACHRP members send him their priority items for future agendas, indicate their interest in joining subcommittees, and nominate others who might serve.

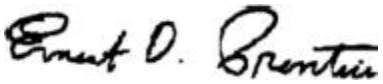
- Make arrangements for the next two SACHRP meetings, including one more session in 2003. This includes:
  - Contacting Christine Grady and arranging for SACHRP to be updated on the NIH/FDA AER project at the next meeting.
  - Arranging for subcommittees to meet in public, including placing advanced notice of the meetings in the *Federal Register*.

Secretary's Advisory Committee on Human Research Protections

Inaugural Meeting
July 22, 2003
Washington, DC

Certification of the Summary of Minutes

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



9/8/2003

Ernest D. Prentice, Ph.D., Chair Date