MINUTES

HUMAN SUBJECTS RESEARCH ADVISORY COMMITTEE
Friday, May 11, 2007
CRC Medical Board Room
3:00 p.m.

Present

Dr. Michael Gottesman, Chair
Dr. Fabio Candotti, NHGRI
Dr. Robert Conley, NIDA
Dr. John Gallin, CRC
Dr. Christine Grady, CRC/DCB
Dr. Gilman Grave, NICHD
Dr. Maureen Hatch, NCI SS
Dr. Rohan Hazra, NCI
Dr. Barbara Karp, Combined Neurosciences IRB
Dr. Mitchell Max, NIDCR
Dr. Jerry Menikoff, Exec. Sec.
Dr. Koneti Rao, NIAID
Mr.Craig Wladyka, Protocol Administration Representative

Absent

Dr. Howard Austin, NIDDK/NIAMS
Dr. Marian Johnson-Thompson, NIEHS
Dr. Susan Olivo-Marsten, FELCOM
Dr. Robert Shamburek, NHLBI
Dr. Richard Wyatt. OIR

Guests

Dr. Lura Abbott, OHSR
Ms. Nilsa Almodovar, OPS, CC
Ms. Elaine Ayres, CRC
Dr. Frank Balis, NCI
Ms. Holli Beckerman Jaffe, OD
Ms. Marianna Bledsoe, OSP
Ms. Valerie Bonham, OGC
Ms. Katya Bratslavsky, NCI
Ms. Sarah Carr, OSP
Ms. Laura Cearnal, CC
Ms. Marjorie Gillespie, NINDS
Mr. Peter Glasz, NIDCR
Ms. Anne Gupman, NIDA
Dr. Emily Harris, NHGRI
Ms. Charlotte Holden, OHSR
Ms. Rosanne Hurwitz, NCI
Ms. Cathy Little, NIAAA
Ms. Jennifer Morris, NINDS
Dr. Joel Moss, NHLBI
Mr. Alex Noury, NINDS
Dr. James Ostell, NCBI
Dr. Maryland Pao, NIMH
Dr. Suzanne Pursley-Crotteau, NCI
Ms. Jeanne Radcliffe, NIMH
Dr. Laura L. Rodriguez, NHGRI
Dr. Stephen Sherry, NCBI
Dr. Julia Slutsman, NCI
Mrs. Janet Smith, OHSR (Ret.)
Ms. Patricia Sweet, NHLBI
Ms. Darlene Switalski, NIEHS
Ms. Jeanne Radcliffe, NIMH
Ms. Glynnis Vance, NIDDK
Ms. Gretchen Weaver, OGC/E
Ms. Gretchen Wood, NEI
Ms. Marcia Wright, OHSR
Dr. Jan Yates, NPCS

1. Minutes of the March 9, 2007 meeting. The minutes were approved without change.

2. Introduction. Dr. Gottesman re-introduced Dr. Jerry Menikoff, the new Director of OHSR, who was present at the January HSRAC meeting. Dr. Menikoff has a law degree as well as an M.D., was Chair of the University of Kansas IRB, and is an expert in human subjects research issues and bioethics. Dr. Menikoff said he was very pleased to be at NIH and looks forward to meeting all the IRB Chairs, Clinical Directors and Scientific Directors.

3, Standard consent language for conflict of interest. (Proposed language attached to the *Guidelines for Completing the Protocol Conflict of Interest Statement,* included with the agenda.) Ms. Ayres said that Dr. Kington has pointed out a loophole in the current *Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH* (February, 2007), in that contractors and non-NIH employees are not bound by it because NIH legally cannot collect financial information from them. They can be given the *Guide* with the expectation that they will disclose any conflict(s), or at least provide an assurance that they are in compliance with their own institutional guidance. Dr. Gottesman said this is a potential problem and wondered whether NIH PIs should be asked to get verbal assurance from outside collaborators that they do not, in fact, have any conflicts.

Dr. Rao said that overseas investigators, particularly in African and Asian countries, perceive the *Guide* as incomprehensible and too legalistic. He recommended simplifying the language. Research done overseas is normally expected to conform to the ethical standards of the countries where the research is taking place. Nevertheless, these are NIH intramural studies, and NIAID investigators are doing their best to educate their collaborators about the NIH standards.

Dr. Grady agreed that as the *Guide* has evolved is has become too long and complicated and asked why collaborators could not simply be asked whether or not they have a conflict of interest.

Dr. Conley noted that the document is aimed at current NIH employees, and requested more specificity about relating it to ongoing studies. Dr. Gottesman said the intent of the Guide is for it to relate to current studies and felt that the examples in section III make this clear.

Dr. Gallin said that NIH cannot ask outside investigators to follow NIH rules, but they can be asked if they are following the obligations of their own institutions. Ms. Beckerman Jaffe pointed out that there is no guarantee that non-NIH standards are adequate. However, NIH can control with whom it will collaborate.

Dr. Hazra said the problem arises not so much with non-NIH collaborators as with contractors. For instance, in drug trials, drug company employees often participate in the trial. Ms. Beckerman Jaffe added that such employees may not only be paid by the

sponsoring drug company but also have profit-sharing in the company. Dr. Gottesman pointed out that a conflict of interest statement can be written into contracts.

Dr. Grady said that she would recommend resisting the inclusion of all details of every collaborator's financial interest in consent documents. She also questioned why having an OMB-approved form as a questionnaire about conflict of interest for non-NIH employees is considered to be an obstacle. Dr. Gottesman said that in the beginning, it was important to move quickly to establish the "Guide," but as the environment has changed, it may be necessary to revisit the possibility of getting an OMB-approved form. He said that it is important for NIH leadership to maintain credibility and to watch out for major problems on this issue. Obviously the *Guide* continues to be an evolving document and changes will have to be made.

In the discussion about item 2 of the *Conflict of Interest Statements for Protocol Consent Forms* (attached to the agenda), it was agreed that last phrase ". . . and does not create a conflict of interest" should be deleted because it sends a mixed message. It was also suggested that this section be limited to cases where an investigator actually has *de minimis* stock in the manufacturer of the product being studied. However, it was pointed out that if an investigator who has *de minimis* stock were later added to a protocol, then reconsenting subjects might be required.

Dr. Karp asked whether the DEC would let IRBs know about investigators with *de minimis* holdings. Dr. Hazra said the NCI DEC already does this and noted that most such holdings are in stock of competing companies. Ms. Ayres pointed out that item 2 does not refer to competing companies. It was noted that stock must be sold if its value increases beyond the *de minimis* level and that stock may not be held in private companies, only in companies whose stock is publicly traded.

There was a suggestion that the second sentence of item 3 should be changed to read "Non-NIH investigators receive a copy of the Protocol Review Guide and are required to report that they are compliant with their own institutional conflict of interest guidelines." There was also a question about who would decide whether other institutional guidelines were adequate. Dr. Balis pointed out that it would be very difficult to get institutional guidelines from the very large number of institutions participating in some NCI protocols.

Dr. Gottesman decided that a small group would be formed to go over the language again and think about the issues, particularly with regard to extramural collaborators, contractors and international colleagues.

4. Protocol Conflict of Interest Statement and Guidelines (attached to the agenda). Ms. Ayres said additions have been made to the form in order to help investigators complete it and to enhance the ethical evaluation. The superscripts refer to the points in the *Guidelines for Completing the Protocol Conflict of Interest Statement*. She said the DEC needs more information about IND/IDE products and competitor products. Dr. Karp asked whether item 14 (products made by a commercial entity that is the subject of the

study) also included identification of scanners, magnets, etc., used in a study. Ms. Ayres said general studies using such products would not need to be reported. However, a magnet being studied under a CRADA as part of the protocol would have to be reported. Likewise, standard-of-care drugs or chemotherapy would only have to be reported if they were the subject of the protocol's hypothesis.

5. Genome-Wide Association Studies (GWAS) and Genetic Association Information Network (GAIN).

(a) Introduction. Dr. Gottesman noted the great strides that have been made in genome wide studies, such as recent Type II diabetes studies in Finland. He said that one of the key questions about genome wide association studies is whether or not they constitute human subjects research.

Ms. Holden said that Dr. Francis Collins and Dr. Elizabeth Nabel hope to meet with HSRAC to discuss GWAS and GAIN. In the meantime, several members of the GAIN Data Access Committee (DAC) are at this meeting, including Dr. Emily Harris, NHGRI (Chair), Dr. Christine Grady (Clinical Center), and Dr. Joel Moss (NHLBI).

(b) Overview of GAIN and GWAS. Dr. Laura Rodriguez, NHGRI, special assistant to Dr. Francis Collins, handed out a document entitled *Whole Genome Association Studies* (http://www.genome.gov/17516714) (Attachment 1); a list of GAIN Steering Committee members (Attachment 2), and illustrated her remarks with a power point presentation (Attachment 3). She prefaced her presentation by noting that the House of Representatives has recently passed legislation protecting individuals from genetic discrimination in employment and health insurance. The legislation is expected to go to the Senate in the next few weeks.

GWAS is "any study of genetic variation across the entire human genome (genotype) that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition (phenotype)."

GAIN is a public-private partnership between NIH, The Foundation for NIH and others, such as Pfizer, Perlegen, Affymetrix, etc., with the goal of encouraging whole genome association studies of common diseases.

dbGaP, the database of GWA studies, is managed by the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM). This is a central data repository which will provide a single point of access to basic information about NIH-supported GWA studies. It will also include genotyping DNA samples from participants in clinical studies that have already been conducted (contributed by GAIN) and will also accept GWAS datasets contributed from other sources. The guiding principle of GAIN is to make the results of whole genome association studies immediately available for the public benefit.

The NIH Committee on GWAS Policy was convened in April, 2006 with Dr. Elizabeth Nabel as Chair, and more than 20 members with wide IC representation. The Notice to Applicants for NIH GWAS was released on May 15, 2006, and the RFI on proposed NIH GWAS policy was released on August 30, 2006, with a final deadline of November 30, 2006. Six first round awards, with a large representation from mental health studies, have been made so far.

Investigators submitting GWAS data are expected to:

- provide descriptive information about their studies;
- submit **coded** genotypic and phenotypic data to the GWAS data repository;
- submit certification by the responsible IRB that it has reviewed and approved submission to the NIH, noting any limitations on data use based on the relevant informed consents; and
- submit an assurance from the responsible institution that all data are submitted to the NIH in accord with applicable law.

By the time NIH receives the incoming coded data, interaction with the subjects has already taken place and consents have been obtained. OHRP has confirmed that if there is a written agreement not to share the key to the code within the data, the data are not considered "human subjects data" under 45 CFR 46.

Investigators requesting GWAS data and their home institutions will:

- certify through Data Use Certification (DUC) that they agree to review informational material on GAIN data use;
- follow specified research use;
- disseminate research results broadly and acknowledge GAIN and contributing investigators in published or presented work;
- acknowledge GAIN policies on publication and intellectual property;
- submit brief annual updates on research progress and publications;
- agree not to identify research participants, not to transfer data to third parties, and to be identified within the GAIN database as an Approved User of GAIN data

Investigators and home institutions will be responsible for compliance with Federal, state and local policies such as HIPAA, 45 CFR 46 and local institutional review.

OHRP has confirmed that secondary data users will not be conducting human subjects research under 45 CFR 46.

The Data Access Committee (DAC), composed of Federal staff with expertise in whole genome association studies, and bioethics and privacy/confidentiality issues, reviews the incoming data access requests as well as annual reports. It checks for any sanctions on investigators and reviews research use statements to determine whether the proposed use is consistent with any data use limitations for each data set requested. The DAC also provides a summary of approved and disapproved users, applies criteria for

each research use and monitors productivity and any problems, such as data security breaches.

GAIN policies include a Data Use Review Board (DURB) to provide retrospective review of data distribution and use practices. A Working Group of the Advisory Committee to the Director (ACD) has been constituted to fulfill this role.

Contributing PIs will have the exclusive right to submit publications analyzing GAIN datasets for nine months after a genotype-phenotype dataset is made available. It is GAIN policy that GAIN data should be pre-competitive and the public will be best served if the data are placed in the public domain. Data will be available from GAIN in June, 2007.

(c) Website Demonstration (attachment 4). Dr. Ostell, NCBI, NLM provided a demonstration of how dbGaP works. It provides a central location of genotype and phenotype data and the associations between them to interested parties, who can see all study documents and variables in an organized and searchable web format. It also provides pre-computed analyses of the level of statistical association between genes and selected phenotypes. Dr. Ostell noted that the database includes data from the Framingham Heart Study (NHLBI) and the Age-Related Eye Diseases Study (AREDS) and gave a detailed overview of AREDS in the database. He described the elements of a phenotype and how they are organized within the database and how the database is acquiring genotype data.

There will be two levels of use for the database. (1) Unrestricted public use, which will allow users to browse and search projects and studies, including protocols, questionnaires, etc.; view phenotype and genotype summary data; identify studies of interest and view pre-computed or published associations. (2) Authorized Users, who will be permitted to download genotype/phenotype data for individuals.

Dr. Gottesman said that today's presentations were intended to provide HSRAC with a primer on GWAS and GAIN and additional presentations will be forthcoming. He noted that intramural PIs will want access to the database, and although OHRP has determined that its use is not human subjects research, PIs should check with OHSR beforehand and also obtain the approval of their SDs to certify that the request is appropriate. Dr. Karp hoped that some standard language would be developed to help contributing PIs with their consents. Dr. Harris said that the DAC checks that use of the database is consistent with the original informed consent(s) and is working with PIs in GAIN to review consent language, with the help of content experts in each IC. If there are questions, the DAC refers back to the PI and the approving IRB. Requests for access to the system will be accepted in June.

In the absence of any other business, the meeting concluded at 5:00 p.m. The next meeting will take place on Friday, July 13, 2007.

Attachment 1: Whole Genome Association Studies
Attachment 2: GAIN Steering Committee
Attachment 3: GWAS/GAIN power point presentation
Attachment 4: Website demonstration of the database