

Fostering Integrity in Clinical Research At Academic Medical Centers



Dr. Eve E. Slater, Assistant Secretary for Health, will give the keynote address at ORI's upcoming conference on protecting the integrity of clinical research at academic medical centers, September 9-10, 2002, in Baltimore, Maryland.

This conference will help institutions plan coherent activities to address integrity in clinical research. New approaches such as improved protocol design, oversight mechanisms, and educational techniques will be discussed, and practical approaches to running well-managed clinical research trials will be highlighted. Anyone who is in the chain of oversight for the collection and handling of clinical research data will benefit from attending this meeting.

Other confirmed speakers include Curtis Mienert, Johns Hopkins University School of Public Health; Michael Kalichman, University of California at San Diego; Greg Koski, Office for Human Research Protections (OHRP); Leonard Glantz, Boston University Schools of Medicine and Public Health; Henry Durivage, Theradex Systems, and Barbara Mishkin, Hogan & Hartson.

The conference, *Fostering Integrity in Clinical Research at Academic Medical Centers*, co-sponsored by the Association of American Medical Colleges, OHRP, and ORI, will be held at the Radisson Plaza Hotel near the Inner Harbor in Baltimore. For information, see the ORI web site or contact Tracy Morgan, phone 301-443-5330, or e-mail: tmorgan@osophs.dhhs.gov.

Research Guidelines Conference: Clarifying Nature of RCR

The practical problems related to the development of effective research guidelines will be examined by researchers, research administrators, and officials from scientific societies and professional and institutional associations during a conference at the Sheraton Hotel at Society Hill in Philadelphia, September 23-24, 2002.

The conference, *The Role of Institutional Rules, Guidelines, and Education in Promoting the Responsible Conduct of Research*, is part of a threefold effort undertaken by ORI to stimulate discussion about the relationship between research guidelines and the responsible conduct of research. The conference web site can be accessed through the ORI home page.

The ORI effort responds to recommendations made by the Institute of Medicine (IOM) and the National Academy of Sciences (NAS). The 1989 IOM report on *The Responsible Conduct of Research in the Health Sciences* recommended that "Universities, medical schools, and other research organizations should adopt guidelines to clarify the expectations of each institution about the professional standards to be observed by investigators in the conduct of research." The 1992 NAS report on *Responsible Science: Ensuring the Integrity of the Research Process*, recommended the "adoption of formal guidelines for the

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Research Applications Due November 15

The Research Program on Research Integrity (RPRI) has issued its third request for applications (RFA) with a deadline of November 15, 2002. The RFA may be accessed through the ORI home page.

The 30 applications received in response to the second RFA were reviewed in April. About 10 are expected to be funded by September.

Besides ORI, the RPRI is supported by the National Institute of Neurological Disorders and Stroke, the National Institute of Nursing Research, and the National Institute on Drug Abuse. ☺

Research Guidelines Conference

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conduct of research” because such action “can provide a valuable opportunity for faculty and research institutions to clarify the nature of responsible practices.”

Conference participants will be provided with a draft resource document for developing effective research guidelines for comment. A report on the *Analysis of Guidelines for the Conduct of Research Adopted by Medical Schools or Their Components* is on the ORI web site under Studies/Reports in the Publications section.

“We have taken the discussion format seriously,” Larry Rhoades, ORI project officer, said. “The program is designed to maximize audience participation. Each session has a question and answer period and small group discussion.” The agenda focuses on (1) guideline contents, (2) environmental factors affecting the development of effective guidelines, (3) the utility of guidelines, (4) educating staff about guidelines (5) implementing guidelines, and (6) assessing the impact of guidelines.

Advisory panel members are Margaret Dale, Harvard University; Julie Gottlieb, Johns Hopkins University; David Wright, Michigan State University; Jerry Rosenberg and Michael Zigmond, University of Pittsburgh, and Paul Friedman and Michael Kalichman, UC-San Diego. ☺

Can Survey Research Staff Commit Scientific Misconduct?

Can fabrication or falsification of data by lower-level staff who conduct surveys or interviews or administer questionnaires with human subjects constitute scientific misconduct? The answer is “yes.”

The Public Health Service (PHS) has made findings of scientific misconduct in several ORI cases involving this type of data. These misconduct cases involved the acquisition of data through questionnaires or interviews, administered face-to-face, over the telephone, or through the use of a computer interface. The data were used in a variety of research situations, ranging from epidemiological studies of diseases to the assessment of the effectiveness of therapeutic interventions, or of health services delivery systems.

Since questionnaires are often administered by individuals who are not members of the faculty or the professional senior research staff, institutional officials have questioned whether these individuals were actually members of the “scientific community” subject to PHS regulations on scientific misconduct.

The PHS regulations apply to any individual involved in proposing, conducting, or reporting research supported by PHS funds or proposed in applications for PHS funds, regardless of their position.

Institutional officials have also asked ORI about the relationship of common “data quality control” problems and possible scientific misconduct—that organizations involved in the conduct of surveys expect a certain incidence of “curbstoning” (i.e., fabrication or falsification of data “on the street”). When detected by regular “quality control” measures, the problem is often handled by purging the tainted data from the database.

Such “quality control” measures may serve a preventive and a detection function and ORI encourages their continued use. However, the data should not be destroyed because it might provide evidence of research misconduct. When evidence of

See *Survey Curbstoning* on page 7.

Institutions Report Increased Misconduct Activity in 2001 Annual Reports

Institutions reported the highest amount of misconduct activity since 1997 in their 2001 Annual Report on Possible Research Misconduct setting high water marks in five of six measures: institutions opening cases, new allegations, new cases, inquiries conducted and investigations conducted. Only the number of institutions reporting misconduct activity begun in, or prior to, 2001 slightly declined to 78 from the previous high of 82.

Sixty-one institutions opened 72 new cases to investigate 127 allegations. The new cases resulted in 67 inquiries and 20 investigations. The previous high marks in the last 5 years were 60 institutions, 64 new cases, 103 allegations, 59 inquiries, and 19 investigations.

The new allegations included 46 of falsification, 37 of fabrication, 17 of plagiarism, and 27 others. Some cases included more than one allegation. Organizations reporting new cases included 54 higher education institutions; 2 research organizations, 3 independent hospitals, 1 small organization, and 1 health organization.

In their submission, institutions report the receipt of an allegation, the type of misconduct, and the conduct of an inquiry and/or investigation. Reportable activities are limited to alleged misconduct involving PHS-supported research, research training or other research related activities.

The 78 institutions reporting misconduct activity conducted 86 inquiries and 46 investigations in response to allegations made in 2001 or before. Besides the 61 institutions that opened new cases, there were 17 completing old cases and 19 handling new and old cases. The number of inquiries conducted by an institution ranged from 0 to 3; the number of investigations ranged from 0 to 2. ☺

**2nd Research Conference on Research Integrity
November 16-18, 2002
See ORI Web Site for Details**

ORI Creates Program For Developing RCR Resources

ORI has established a Responsible Conduct of Research (RCR) Resource Development Program to facilitate the creation of instructional materials for general use in institutional RCR education programs. The program announcement is available on the ORI home page.

The program supports the development of instructional materials that address one or more of the following topics: Data acquisition, management, sharing, and ownership; mentor/trainee responsibilities; publication practices and responsible authorship; peer review; collaborative science; human research subjects; animal research subjects; conflict of interest and commitment, and research misconduct. Proposals must use the form provided on the ORI web site and be submitted via e-mail as an attachment to facilitate the review process.

The initial round of applications was solicited through the ORI web site, the RCR listservs, e-mail messages to institutional research integrity officers, and the *NIH Guide for Grants and Contracts* with a deadline of June 28, 2002. ORI intends to fund between 8 and 10 projects (total cost \$25,000 each) annually. Award decisions will be based on relevance to PHS research and the aforementioned RCR instruction areas, innovative quality, and potential for use by other institutions. Submission deadline will be February 1 each year with reviews conducted in March and awards made in May.

In 1992, the National Academy of Sciences report on *Responsible Science: Ensuring the Integrity of the Research Process* recommended that “scientists and research institutions should integrate into their curricula educational programs that foster faculty and student awareness of concerns related to the integrity of the research process.” In 1989, the Institute of Medicine report, *The Responsible Conduct of Research in the Health Sciences*, recommended that “universities should provide formal instruction in good research practices. This instruction should not be limited to formal courses, but it should be incorporated into various places in the undergraduate and graduate curricula for all science students.” ☺

Assessing Scientific Misconduct Allegations Involving Clinical Research

An allegation of wrongdoing in research involving human subjects must be assessed to determine under which Public Health Service (PHS) regulation or policy it should be handled. For ORI, the question is whether it is an allegation of scientific misconduct that falls under the PHS definition in 42 CFR Part 50, Subpart A. The following are examples of falsification and fabrication that have formed the basis for PHS findings of scientific misconduct in clinical research. Generally, these incidents occurred in the context of conducting clinical research or reporting data (internally or externally), publishing data or results, or including data or research records in grant applications or progress reports.

FALSIFICATION

- substituting one subject's record for that of another subject;
- falsely reporting to a data coordinating center that certain clinical trial staff, who were certified to perform the procedures on the subjects, had done so, when they had not;
- altering the dates and results from subjects' eligibility visits;
- altering the dates on patient screening logs and/or submitting the same log with altered dates on multiple occasions;
- failing to update the patients' status and representing data from prior contacts as being current;
- altering the results of particular tests on blood samples to show that the test accurately predicted a disease or relapse;
- backdating follow-up interviews to fit the time window determined by the study protocol; and
- falsifying the times that blood samples were drawn from human subjects.

FABRICATION

- creating records of interviews of subjects that were never performed;
- making up progress notes for patient visits that never took place and inserting them into the medical record to support published and unpublished research reports; and
- preparing records for calls and follow-up contacts to subjects who had already died.

PHS scientific misconduct regulations generally do **not** supersede or create an alternative to the established procedures for resolving fiscal or criminal improprieties or cases of abuse of animal and human subjects. In the absence of evidence of falsification or fabrication of the research record as described above, the following problems would **not** be considered as scientific misconduct by ORI, but would be forwarded to the appropriate agency, such as FDA and/or the Office for Human Research Protections (OHRP):

- failing to report an adverse event with a patient to the sponsor or the Institutional Review Board (IRB);
- deviating from the protocol (e.g., entering an ineligible subject in a trial, or administering an off-protocol drug);
- forging a physician's signature on medical orders;
- failing to obtain or properly document, informed consent;
- breaching human subject confidentiality; and
- failing to obtain IRB and/or Food and Drug Administration (FDA) approval for changes implemented in an approved protocol. ☹

CASE SUMMARIES

Joao Carlos deSales, San Francisco Department of Public Health (SFDPH): Based on the SFDPH investigation report and additional ORI analysis, the U.S. Public Health Service (PHS) found that Joao Carlos deSales, former study counselor at SFDPH, engaged in scientific misconduct by falsifying data supported by National Institutes of Health (NIH) subcontract SFP-N01-A1-35176-HMEISTERI-94 to SFDPH under the National Institute of Allergy and Infectious Diseases contract 5-N01-AI35176-019, "Domestic Master Contract for HIV Vaccine Efficacy Trials," awarded to ABT Associates, Inc. Specifically, from April through September 1999, Mr. deSales switched randomization assignments on four pairs of subjects and subsequently altered the research records to conceal his conduct. Mr. deSales' switching of the randomization assignments, if undetected, could have biased the study so as to invalidate the conclusions on the effectiveness of intensive counseling sessions on reducing the rate of new HIV infections.

Mr. deSales entered into a Voluntary Exclusion Agreement in which he voluntarily agreed for a 3-year period beginning April 4, 2002, to exclude himself from serving in any advisory capacity to PHS, and that any institution that submits an application for PHS support for a research project on which his participation is proposed, or which uses him in any capacity on PHS-supported research, or that submits a report of PHS-funded research in which Mr. deSales is involved, must concurrently submit a plan for supervision of his duties to the funding agency for approval. The supervisory plan must be designed to ensure the scientific integrity of his research contribution. A copy of the supervisory plan must also be submitted to ORI by the institution.

Atsushi Handa, M.D., Ph.D., National Institutes of Health (NIH): Based on an NIH report of an investigation, and additional ORI analysis during its oversight review, PHS found that Atsushi Handa, M.D., Ph.D., former visiting fellow in the intramural program of the National Heart, Lung, and Blood Institute, NIH, engaged in scientific misconduct by

falsifying and fabricating data published in two journals. Specifically, PHS found that Dr. Handa: (1) fabricated or falsified the following data in a paper published in *J. Gen. Virol.* 81:2077-2084, 2000: (A) data for the AAV-3 construct for days 2, 5, and 7 and data for the AAV-2 construct for days 5 and 7 in Table 1; (B) day 2 data in Table 2; and (C) Figure 4; and (2) falsified the following data in a paper published in *J. Gen. Virol.* 81:2461-2469, 2000: (A) Figure 3; and (B) data in Table 2; retracted at *J. Gen. Virol.* 82:2837, 2000. These actions were serious because the purported findings on the GV virus C/hepatitis G and AAV-2 viruses could have had major impact in areas such as hepatitis research and gene therapy.

Dr. Handa entered into a Voluntary Exclusion Agreement in which he voluntarily agreed for a 5-year period beginning April 4, 2002, to exclude himself from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government, and to exclude himself from serving in any advisory capacity to PHS. Additionally, he must submit a letter of retraction to the editor of the *Journal of General Virology* identifying the missing data as well as the falsified or fabricated data in Figure 3A and Table 2 of the paper published in *J. Gen. Virol.* 81:2461-2469, 2000. This retraction requirement will remain on the ALERT System until Dr. Handa sends, and ORI receives, a copy of the retraction letter that is consistent with the above language.

Matthew A. Lipski, Washington University in St. Louis (WUSL): Based on the WUSL investigation report and additional ORI analysis in the course of its oversight review of related records, PHS found that Matthew A. Lipski, former WUSL research patient assistant on a subcontract from Hipco, Inc., engaged in scientific misconduct by falsifying and fabricating data in research supported by NIH Phase II Small Business Innovation Research (SBIR) grant 2 R44 AG12317-03, "Effect of padded underwear on hip fracture incidence." Specifically, PHS found that Mr. Lipski falsified and fabricated data in a study examining whether wearing an undergarment with force

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distributing and absorbing pads positioned over the trochanteric regions of elderly nursing home residents could significantly reduce the number of hip fractures. From July 2000 through October 2000, Mr. Lipski falsified and fabricated observational patient data in multiple research records. Due to concerns over the reliability of all of Mr. Lipski's data, none of his data were used in the study. No publications required correction or retraction.

Mr. Lipski entered into a Voluntary Exclusion Agreement in which he voluntarily agreed for a 3-year period beginning March 20, 2002, to exclude himself from serving in any advisory capacity to PHS, and that any institution that submits an application for PHS support for a research project on which Mr. Lipski's participation is proposed or which uses him in any capacity on PHS supported research, or that submits a report of PHS-funded research in which he is involved, must concurrently submit a plan for supervision of his duties to the funding agency for approval. The supervisory plan must be designed to ensure the scientific integrity of his research contribution. A copy of the supervisory plan must also be submitted to ORI by the institution.

Aaron J. Morrow, B.S., Saint Louis University (SLU): Based on Mr. Morrow's admission, the SLU investigation report, and additional ORI analysis, the PHS found that Aaron J. Morrow, graduate student, SLU Graduate School, engaged in scientific misconduct by falsifying and fabricating data in research supported by National Institute of General Medical Sciences, NIH, grant 5 R01 GM54428-04, "Elucidation of the mechanisms of *in vitro* Golgi transport." Specifically PHS found that Mr. Morrow falsified data relating to the study of the mechanisms of protein transport using *in vitro* preparations. From October 1999 through January 2001, he falsified and fabricated data in his research notebook and produced false films and graphs of purported experiments to produce data for his thesis and misrepresent his progress. Mr. Morrow reported the falsified and fabricated data in: (1) laboratory group meetings;

(2) a poster presentation at the American Society for Cell Biology meeting in December 2000; and (3) a draft manuscript that he was preparing. Mr. Morrow also provided falsified data to his mentor, who unknowingly included it in a draft of NIGMS, NIH, application 2 R01 GM54428-05A2, "Elucidation of the mechanisms of *in vitro* Golgi transport." Given the extensive nature of Mr. Morrow's data falsification and fabrication, none of his research after July 2000 can be considered reliable. His actions adversely and materially affected the laboratory's ongoing research in protein transport mechanisms by creating uncertainty about all his experimental results, necessitating verification and repetition of experiments, preventing the reporting of results for publication, and preventing the principal investigator from submitting a competitive renewal application for a NIH grant.

Mr. Morrow entered into a Voluntary Exclusion Agreement in which he voluntarily agreed for a 3-year period to exclude himself from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government, and to exclude himself from serving in any advisory capacity to PHS.

Robert B. Tracy, Ph.D., University of Southern California (UCS) and University of California, Davis (UCD): Based on Dr. Tracy's admission, UCS and UCD reports, and additional ORI analysis in its oversight review, PHS found that Robert B. Tracy, Ph.D., former UCD doctoral student, and former USC postdoctoral student, engaged in scientific misconduct by falsifying and fabricating data in research supported by National Institute of Allergy and Infectious Diseases, NIH, grant R01 AI18987, "Mechanistic studies of genetic recombination," and NIGMS, NIH, grant 1 R01 GM56984, "Mechanism of DNA recombination at class switch sequences." Dr. Tracy's doctoral research at UCD involved the analysis of the mechanisms used by various enzymes to repair damaged DNA, while his postdoctoral research at USC dealt with the molecular mechanism used by B-lymphocytes when switching from

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producing one class of immunoglobulin to another. Specifically, PHS found that: (1) in 1996 and 1997, Dr. Tracy falsified research supported by NIH grant R01 AI18987, "Mechanistic studies of genetic recombination," while working on his UCD doctoral dissertation; he falsified Figure 6.2 of his Ph.D. thesis by adding discrete bands where there actually had only been a uniform smear of radioactivity, the effect suggesting an unobserved result, which was, therefore, falsified; the falsified image was not published; and (2) from 1998 to 2000, Dr. Tracy committed additional scientific misconduct while a USC postdoctoral research fellow funded by NIH grant R01 GM56984 "Mechanism of DNA recombination at class switch sequences." Dr. Tracy falsified values in Table 1 of supplemental web material that accompanied (Tracy, R.B., Hsieh, C.-L., & Lieber, M.B., "Stable RNA/DNA hybrids in the mammalian genome: Inducible intermediates in immunoglobulin class switch recombination." *Science* 288:1058-1061, 2000; the "Science paper"). In Table 1, Dr. Tracy misrepresented that lymphocytes from mice transgenic for ribonuclease H underwent significantly lower rates of isotope switching, when the actual data showed no such difference for IgG₁, IgG_{2b}, and IgE isotope classes. Dr. Tracy also falsified Figures 2 and 4 of the supplemental web material published with the *Science* paper in that the results were not representative of multiple independent experiments as he claimed. In addition, Dr. Tracy falsified Figure 2C of the *Science* paper, which represented a crucial control to establish his claim that RNA/DNA hybrids were limited to immunoglobulin switch regions, by publishing a blot that was not representative of his overall results. He also falsified Figures 4 and 7 of a second paper (Tracy, R.B., & Lieber, M.R. "Transcription-dependent R-loop formation at mammalian class switch sequences." *EMBO J.* 19:1055-1067, 2000) using the PhotoShop computer program to move bands or regions of a lane vertically relative to the rest of the gel, thus falsifying the size of molecules described in the paper. He reported these falsified data in the progress report for NIH grant 5 R01 56984-03. Dr. Tracy and his coauthors retracted both papers, in *Science* 289:1141, 2000, and in *EMBO J.* 19:4855, 2000, respectively.

Dr. Tracy entered into a Voluntary Exclusion Agreement in which he voluntarily agreed for 4 years beginning May 1, 2002, to exclude himself from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government, and to exclude himself from serving in any advisory capacity to PHS. ☹

IOM to Issue Report On Assessing Integrity

The *Assessing Integrity in Research Environments* report is scheduled for pre-publication on the National Academy Press web site in mid July and may be accessed through the ORI home page. The printed report will be published by September 30, 2002.

On October 10, 2002, an ORI-supported conference will be held at the National Academy of Sciences in Washington, D.C., to present the report to, and solicit comments from, the research community. Conference details will be posted on the ORI web site when they become available. ☹

Guidance for IRB Procedures Available


The Office for Human Research Protections (OHRP) has compiled a summary of the relevant regulatory requirements and guidance issued routinely by OHRP over the past several years. OHRP has posted guidance regarding written Institutional Review Board (IRB) procedures. This new guidance, dated April 2, 2002, can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wirbproc.pdf>. ☹

Survey "Curbstoning" is Misconduct (from page 2)

intentional fabrication or falsification of data in PHS-related research is detected in this way, the institutions should handle the case through the normal procedures for dealing with PHS scientific misconduct. Any investigative findings in these cases must be reported to ORI as required by PHS regulations. ☹

**Meeting Proposals
Due October 1**

ORI is seeking proposals from institutions, professional associations, and scientific societies that wish to collaborate with ORI to co-sponsor sessions at scientific meetings, symposia, conferences or workshops, on promoting research integrity or handling scientific misconduct allegations. Funding available generally ranges from \$2,000 to \$20,000.

October 1, 2002, is the next target date for receipt of applications. Instructions and an application form are available at <http://ori.dhhs.gov/html/programs/confprop.asp>. 

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ORI NEWSLETTER

The ORI Newsletter is published quarterly by the Office of Research Integrity, Office of the Secretary of Health and Human Services, and distributed to applicant or awardee institutions and PHS agencies to facilitate pursuit of a common interest in handling allegations of misconduct and promoting integrity in PHS-supported research.

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