
University of Arizona Program in Research Integrity Education Monthly Newsletter

A Federally Mandated Compliance Education Program

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This month the Program in Research Integrity Education (P.R.I.E.) newsletter focuses on the topic of “*Human Subjects*.” We are continuing to highlight each month one of the nine core instructional areas in the Responsible Conduct of Research (RCR). Last month the topic of “*Data Management*” was discussed, and this month we are focusing on the topic of *Human Subjects*. The information presented is authored by Michael Kalichman and P.D. Magnus and may be viewed at the *RCR Education Resources* web site, which is:

<http://rcrec.org/r/index.php>.

Responsible Conduct of Research (RCR)

P.D. Magnus and Michael Kalichman,
September 2002

Human Subjects

Background

Advances in human health and welfare ultimately depend on research with human subjects. Properly controlled studies with human subjects are essential to verify any conclusions about normal physiology, mechanisms of disease, effectiveness of treatment, learning, or behavior. Unfortunately, not all human studies have been justifiable and useful. Human cruelty can be perpetrated in the name of research. Some of the best known examples occurred in Nazi Germany. Investigations following the war uncovered many atrocities, such as studies in which subjects were immersed in very cold water to gauge how long it would take to die of hypothermia. The discoveries of these abuses were the basis for the Nuremberg trials and development of the Nuremberg Code (1949), the first international codification of minimal expectations for the conduct of research involving human subjects. Some of the most important provisions of the Code were that experiments with human subjects should occur only in the context of a clear scientific rationale and only with subjects who have freely chosen to participate.

Harm to unwilling subjects under the guise of research has not been unique to the Nazis. During World War II, the U.S. conducted medical experi-

ments on people not competent to consent and on subjects without their knowledge (Vanderpool, 1996). In 1932, prior to the start of World War II, 400 African American males with syphilis had been entered into a study at Tuskegee, Alabama with the intended purpose of documenting the natural course of their disease (Rivers et al., 1953; Jones, 1993). Although treatments of some presumed efficacy were available, these were withheld while the study participants were led to believe that experimental procedures (such as spinal taps to examine cerebrospinal fluid) were for the purpose of therapy. By the 1950's, penicillin was available and known to be highly effective against syphilis, but it also was withheld. The surviving participants were only given treatment in 1972, after the nature of the study became publicly known, 23 years after publication of the Nuremberg Code. Recognition of problematic studies published in the medical and social science literature resulted in the appointment of a federal commission to identify fundamental principles that should govern human subjects studies. The final product of this commission was the Belmont Report (1979). It defined the three ethical principles that now guide studies with human subjects in the U.S.

Rules and regulations

Seventeen federal agencies have regulations governing the conduct of research involving human subjects. Examples of agencies with human subject requirements include the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Science Foundation (NSF), and the Departments of Defense, Education, Justice, and Veterans Affairs.

Recent concerns about protection of human subjects have resulted in new federal requirements for researchers to receive instruction in the responsible conduct of research (RCR). In June of 2000, the DHHS announced a requirement calling for education of all key personnel working on PHS-funded studies with human subjects (NIH, 2000). In December of 2000, the Office of Research Integrity (ORI) announced a new PHS policy extending the requirement for instruction in RCR to all staff with substantive involvement in PHS-funded research or

training (PHS, 2000). Although now suspended (ORI, 2001), this requirement is likely to be reintroduced in the near future.

Different agencies define “human subject” in different ways, but it includes (at minimum) any living person who is involved in research either as an experimental subject or as a control. The scope of activities included under the definition of “research” is quite broad. One federal regulation defines research as any “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.” (Code of Federal Regulations for Department of Health and Human Services 45CFR46.102(d)).

Human subject protections are a shared responsibility of principal investigators, other personnel involved in studies with human subjects, and the Institutional Review Board (IRB). Although most institutions are concerned primarily with regulations of DHHS and FDA, investigators are obligated to identify any special regulations or guidelines implicated by the project funding source or by the institution in which the study is performed.

The IRB is a primary mechanism for institutional protection of human subjects. An IRB is designed to be an advocate for potential and actual research subjects. Under both DHHS and FDA regulations, the IRB has responsibility to approve or disapprove all covered research activity, requiring for instance that subjects are given enough information to be able to provide informed consent. The IRB must conduct periodic reviews of research to ensure continued protection of the welfare of human subjects and compliance with relevant regulations.

The membership of an IRB is defined to include at least five members. The membership must include at least one person whose concerns are primarily scientific, one with nonscientific concerns, and one person who is both unaffiliated with the institution and unrelated to anyone from the institution. As appropriate, the IRB should also seek out special expertise for the review of projects presenting unusual ethical, legal, social, or scientific considerations. The IRB membership cannot consist of members from only one profession. Additionally, any member with conflicting interest should be excluded from the review process.

The diverse membership of the IRB is designed to protect the interests and welfare of human research subjects.

Principles

The three principles listed below are from the Belmont Report (1979). At least three important premises underlie these principles. The first is that studies with human subjects are necessary for improvements in health and welfare. Second, to conduct such research is a privilege, not a right, extended to researchers by society, institutions, and the research subjects themselves. Finally, neither the risks nor the costs of any research study should outweigh the likely benefits.

1. Respect for persons

“Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.”

2. Beneficence

“Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.”

3. Justice

“An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly... For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.”

Guidelines

Research that involves humans is subject to regulation. No procedure or study should be performed that is not explicitly exempted or a part of an approved protocol. Applicable regulations include requirements for adherence to IRB-approved research protocols, maintenance of documentation and records, obtaining approval prior to initiation of changes, and reporting of adverse

events. Investigators are responsible for identifying all applicable regulations and complying with them.

Think about issues of responsible conduct.

Responsible conduct of research involving human subjects requires much more than complying with regulations. The spirit of the regulations and of good science both require that researchers critically review what is known and give thoughtful consideration to what defines an acceptable study. This consideration is necessarily an ongoing process. Factors to be considered include changes in our best understanding of the science, of the risks and potential benefits, of alternative methods for study, and so on. The decision to conduct a study with human subjects carries both ethical and regulatory responsibilities to protect the welfare and interests of those subjects, to design the study so as to minimize risks to subjects, and to obtain adequate training for protecting the interests and welfare of the research subjects.

Make sure the use of human subjects is both justifiable and necessary.

A prerequisite for the responsible research involving humans is a realistic examination of the probability and magnitude of both the risks and the benefits of the research. Investigators must assess whether the risks are reasonable in relationship to the benefits to the individual subjects and the knowledge to be gained.

It is not enough that a proposed line of work is found to be justifiable; it is also necessary to consider whether alternative methods would be preferable. Any study involving human subjects is likely to involve at least minimal inconvenience and risks; other studies may carry more or less significant physical, social, psychological, or financial risks. Can the same information be obtained with less cost or risk by a less invasive study, by the use of fewer subjects, or by studies of other species?

Informed Consent

Investigators conducting a research study with human subjects have an absolute responsibility to ensure that consent to participate has been given freely and is based on an understanding of the risks and benefits. The Belmont principle of respect for persons requires that researchers avoid invading privacy, maintain confidentiality of data, and obtain informed consent. Federal regulations outline numerous requirements for informed consent, including general requirements, basic and additional elements, criteria for waiving informed consent, and documentation for informed consent. The basic assumption underlying the regulations is that subjects need certain information so they can exercise self determination. Informed consent is often needed even for studies in the social sciences that impose little or no inconvenience, but still present

the risk of a loss of privacy or confidentiality. Although some costs or risks may be more injurious than others, it must be up to the potential research subject, not the research investigator, to decide whether such costs or risks are outweighed by the benefits of participation.

The most visible indication of “informed consent” is a document to be signed by the research subject. This document is important because it provides a consistent body of information that the investigator and the IRB have agreed is necessary for individuals to provide their informed consent. Unfortunately, subjects may sign such forms without understanding them. Differences in language, levels of comprehension, or retention of what has been read can make subjects fail to appreciate what they have agreed to. Also, the risks of participating in a research project may be overlooked because of the perception that physician scientists, and other health professionals, are clinical caregivers and not researchers. For these reasons, informed consent typically requires a dialogue with the potential subject to ensure that the content of the document is understood. Similarly, circumstances may change during the course of an ongoing study. If those circumstances might have an impact on subjects' willingness to continue with participation, then the investigator has an obligation to provide that new information. Informed consent is not a single event, but an ongoing process.

Not all subjects are able to give true informed consent. In some cases, it is difficult to ensure that consent is given freely, such as in prison populations. In other cases, it may be difficult to convey the necessary information or to verify an understanding in people with reduced decision-making capacity—such as subjects with some developmental disabilities, some psychiatric disorders, or advanced dementia. For all subject populations in which autonomy is diminished, research investigators are responsible for meeting ethical and regulatory obligations to protect the right for self-determination of any prospective or current research subject.

Children also require special consideration. Parents can give permission for their child's participation in research; depending on age and maturity level of the child, however, it may also be appropriate to obtain “assent” from the child.

Resources

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Next month the featured RCR topic will be:

"Animal Subjects"

Message to UofA Instructors of Conduct/Ethics

From: Michael D. Mumford, Ph.D.
George Lynn Cross Distinguished Research Professor
Director, Center for Applied Social Research
University of Oklahoma
455 W. Lindsey St., Room 705
Norman, OK 73019-2007

As you may know, many well-published cases in recent years have brought to light the potential for research misconduct to undermine the integrity of the scientific enterprise. While it is encouraging that institutions across the nation have responded to the need to emphasize responsible conduct of research by establishing training programs, more research on the most effective strategies for educating researchers about RCR issues is needed. To this end, the Office of Research Integrity and the National Institutes of Health are sponsoring a project taking place during this summer and the upcoming academic year aimed at assessing the impact of RCR training courses on researchers' ethical decision-making.

I am contacting you to ask for your assistance in informing instructors who teach courses in ethical conduct in social, biological, and health sciences at your university about this initiative. You could assist us by forwarding an email message to instruc-

tors or by providing us with instructor contact information.

Instructors who agree to participate will be asked to encourage course participants to complete a series of online measures assessing ethical decision-making and to complete a short course description. Their participation in this effort will provide valuable guidance to individuals and institutions that are designing and/or evaluating programs aimed at enhancing ethical decision-making. Moreover, participants will have access to feedback about their trainee's performance which will provide insight into the strengths of their course and guide future efforts in curriculum.

To learn more about this project, we encourage you to visit www.ou-research.com. Please feel free to contact us at scientificdecisionmaking@ou.edu.

**UNIVERSITY OF ARIZONA
RESEARCH SUPPORT SERVICES GROUP
(RSSG)**

**HUMAN SUBJECTS
PROTECTION PROGRAM**

⇒**Highlights**⇐

Conference Announcement

The Office for Human Research Protections (OHRP) and Duke University School of Medicine will sponsor a National Human Subject Protections Conference entitled, "***Crossing the Line: What is Acceptable Risk?***" on Monday, September 25 and Tuesday, September 26, 2006, at the Sheraton Imperial Hotel and Convention Center in Durham, North Carolina. Co-sponsors of the conference are the University of North Carolina at Chapel Hill, North Carolina State University, Family Health International, RTI International, National Institute of Environmental Health Sciences, Copernicus Group IRB, U.S. Environmental Protection Agency, and Department of Veterans Affairs.

This conference will focus on the concept of "*acceptable risk*" in the conduct of biomedical and behavioral research. Topics during this two day conference will include the risks associated with research on environmental hazards in emergency research and in psychiatric studies, including the use of placebos in study design and continuing assessment of subject competency and the effects of recent information concerning anti-depressants on the design of psychiatric studies. Breakout sessions will focus on risks particular to vulnerable populations. The faculty will include academic experts who will address key topics and issues in biomedical and behavioral research. In addition, representatives from the OHRP, U.S. Food and Drug Administration, National Institutes of Health,

National Institute of Environmental Health Sciences, U.S. Environmental Protection Agency, and Department of Veterans Affairs will provide federal regulatory updates.

This conference should be of special of interest to those persons currently serving or about to begin serving as members of IRBs as well as investigators, legal counsel, patient advocates, public health officials, privacy officials, compliance officers, laypersons, sponsors and contract research professionals.

Dates: September 25-26, 2006

Title: *Crossing the Line: What is Acceptable Risk?*

Location: Sheraton Imperial Hotel and Convention Center, Durham, NC

**Host: Duke University School of Medicine
Registration**

Contact: Faten Habib, B.S.

IRB Education

**Duke University School of Medicine, Durham,
NC**

919-668-5104 Telephone

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News from HIPAA.....

**OCR Publishes Disaster Recovery
Planning Tool**

The Department of Health and Human Services (HHS) has published a new web-based interactive decision tool designed to assist emergency preparedness and recovery planners in determining how to access and use health information about persons with disabilities consistent with the HIPAA Privacy Rule. The tool will guide emergency preparedness and recovery planners through a series of questions regarding how the HIPAA Privacy Rule applies to a particular disclosure. By helping users focus on the source of the information being disclosed, to whom it is being disclosed, and for what purpose, users will better meet the needs of the elderly or persons with disabilities in the event of an evacuation. While the tool's initial purpose focused on emergency planning for persons with disabilities, it is applicable to most emergency planning efforts. The intended audiences include covered entities as well as emergency preparedness and recovery planners at the local, state and federal levels. **[Go to OCR's Emergency Preparedness Planning and Response page.](#)** ↗



Good Laboratory Practices (GLP)

POSITION PAPER OF THE WORKING GROUP ON GOOD LABORATORY PRACTICE:

"OUTSOURCING" OF INSPECTION FUNCTIONS BY GLP COMPLIANCE MONITORING AUTHORITIES

This document was endorsed by the Working Group on Good Laboratory Practice at its 20th Meeting on 4 April 2006 and declassified by the Joint Meeting on 10 June 2006. It reiterates the decisions and the recommendations related to the role and responsibilities of governments, national GLP compliance monitoring authorities and inspectors as set out in the 1989 Council Decision-Recommendation on Compliance with Good Laboratory Practice [C(89)87(Final) and its Annexes, as concerns outsourcing of inspection functions.

To view this document, please follow this link: [Position Paper of the Working Group on Good Laboratory Practice: 'Outsourcing' of Inspection Functions by Glp Compliance Monitoring Authorities](#)

University of Arizona – Animal Care Quality Care for Research Animals



Changes to Requirements in the Documentation Section on the IACUC Animal Protocol Review Form

Recently, the UA was visited by the United States Department of Agriculture Animal Care Veterinarian. The visit included inspection of the animal facilities and records. The inspector indicated that our current IACUC protocol form is not specific enough to ensure that the search for alternative techniques (3R's: Replace, Reduce, Refine) is adequately addressed. She also did not find evidence in most protocols that databases specifically geared to address alternatives were commonly used by researchers at the UA.

To address the concerns, which could result in citations for violation of the Animal Welfare Act, the IACUC is requiring that all literature searches performed after AUGUST 1, 2006, must include at least one search engine that can address alternative techniques. Examples of acceptable data bases include:

- ALTWEB: <http://altweb.jhsph.edu/>
Alternatives to Animal Testing on the Web serves as a gateway to alternatives news, information and resources on the Internet and elsewhere.

- ALTBIB: <http://toxnet.nlm.nih.gov/altbib.html>
This site is under the National Library for Medicine.
- AnimAlt-ZEBET Database: <http://www.dimdi.de/static/en/db/index.htm>
This German site provides a full-text database of alternative methods (3Rs) to animal experiments in biomedicine and related fields (Click on Databases, then Databases A-Z, and then on AnimAlt-ZEBET)
- ECVAM SIS (Scientific Information Service) Database: <http://www.nc3rs.org.uk/category.asp?catID=3>
Provides factual and evaluated information on advanced non-animal methods for toxicology assessments; offers full method descriptions, including development and validation status.
- INVITRODERM: <http://www.invitroderm.com/> Provides alternatives to skin irritation/corrosion testing in animals.
- ALTWEB Pain Management (Anaesthesia/ Analgesia) Database: http://apps1.jhsph.edu/altweb/aadb/aadb_search.cfm Information about anesthesia and analgesia for most commonly used laboratory animals.
- ALTWEB Humane Endpoints Database: <http://apps1.jhsph.edu/altweb/humane/> Designed to help researchers find the earliest "endpoint" that is compatible with the scientific objectives of their research, i.e., the earliest point at which an experimental animals pain and/or distress is terminated, minimized, or reduced.
- European Resource Centre for Alternatives in Higher Education (EURCA): <http://www.nc3rs.org.uk/category.asp?catID=3>
Information about alternatives to using animals in higher education.

The following sites can help you develop strategies for searching for alternatives and can link you to data bases that will perform the searches:

- Animal Welfare Information Center: Alternatives: http://riley.nal.usda.gov/nal_display/index.php?info_center=3&tax_level=1&tax_subject=183.
This site provides many avenues to consider for searches and gives information on how to design your search for alternatives.
- Databases section of the University of California Center for Animal Alternatives (UCCAA) website: http://www.vetmed.ucdavis.edu/Animal_Alternatives/database.htm

- FRAME Guide to Searching for Alternatives: <http://www.frame.org.uk/Searching%20for%20Information/Search%20Guide%20Index.htm>.

If you have questions regarding this new requirement, please contact one of the following individuals:

Richard Vaillancourt, Chair IACUC:
626-4374
vaillancourt@pharmacy.arizona.edu

Susan Wilson-Sanders, IACUC member:
626-1066
wilson-s@u.arizona.edu

Paula Johnson, IACUC member:
621-3483
pauladj@email.arizona.edu



Radiation Control

Laser Radiation Protection Course

Registration is required. To register, send completed Form RC-088 ([RC-088 Form](#)) to the Radiation Control Office, PO Box 245101, Campus. Hand-delivered forms may be dropped off at the Radiation Control Office, 1717 E. Speedway, Suite 1201, the Babcock building. **Registration date and time will be confirmed via email.**

Questions regarding registration can be directed to the RCO at 626-6850 or rcohelp@u.arizona.edu.

Requesting Accommodations for a Disability:

Persons with a disability may request a reasonable accommodation, such as a sign language interpreter, by contacting the Disability Resource Center at the following telephone number, 621-3268, or by emailing Diane Mayer at dmayer@u.arizona.edu. Requests should be made as early as possible to allow time to arrange the accommodation.

Institutional Biosafety Committee



Bulletin



Work with Infectious Agents at the University of Arizona

Research or teaching activities involving infectious agents must be conducted with prior approval by the Institutional Biosafety Committee (IBC). Researchers and students must follow requirements as specified in the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories Manual as the minimum containment required for this work.

Containment requirements may be subject to modification by the IBC.

Upcoming Conferences/Workshops

September 14-15, 2006

Statistics, Images, and Perceptions of Truth: Detecting Research Bias and Misconduct

Birmingham, AL

Co-sponsor: University of Alabama School of Medicine

September 25-26, 2006

Crossing the Line: What is Acceptable Risk?

Durham, NC

Co-sponsor: University of North Carolina at Chapel Hill

<http://dukeohrp2006.org/>

September 28-29, 2006

New Capabilities, Emerging Issues and Responsible Conduct in Data Management

Baltimore, MD

Co-sponsor: University of Maryland-Baltimore

October 15-18, 2006

49th Annual Biological Safety Conference

Boston, MA

absa@absa.org

October 16-17, 2006

Fourth Annual RCR Expo

Quebec City, Canada

Contact: LNguyen-Khoa@osophs.dhhs.gov

December 1-3, 2006

Research Conference on Research Integrity

Tampa, FL

Co-sponsors: Association of American Medical Colleges, American Association for the Advancement of Science

Abstracts due: April 28, 2006 (see ORI web site for details on submitting abstracts and to obtain a conference schedule: <http://ORI.hhs.gov>).

Questions should be addressed to Nick Steneck at nsteneck@umich.edu.

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*The P.R.I.E. newsletter is researched
and compiled by Ruth Kurash Daniels.*

Words of Wisdom:

“Kind words may be short ... but their echoes are endless.”

— Mother Teresa