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# University of Arizona Program in Research Integrity Education Monthly Newsletter

## *A Federally Mandated Compliance Education Program*

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October 1, 2006

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This month the Program in Research Integrity Education (P.R.I.E.) newsletter focuses on the topic of “*Conflict of Interest and Commitment.*” We are continuing to highlight each month one of the nine core instructional areas in the Responsible Conduct of Research (RCR). The recently published editorial in the *Journal of the American Medical Association (JAMA)* authored by Catherine D. DeAngelis, MD, MPH, (*JAMA*. 2006;296:996-998), published online August 7, 2006, entitled, “The Influence of Money on Medical Science,” is recommended reading, and is also confirmation of the need for researchers to be educated in the subject of *conflict of interest and commitment.*

The information presented below 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>.

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### **Responsible Conduct of Research (RCR)**

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P.D. Magnus and Michael Kalichman,  
September 2002

### **Conflict of Interest and Commitment**

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#### **Background**

Although scientists have a professional, fiduciary, and ethical interest in the responsible conduct of research, these interests may be compromised by personal interest. A common worry is that financial interest in the outcomes of research can result in unethical behavior or criminal misconduct.

Although discussions about conflict of interest generally focus on financial interests, it is equally plausible that interests other than financial could compromise the responsible conduct of research. Examples of non-financial interests that might conflict with the integrity of science include career advancement, publishable results, service to patients or students, fame, power, or family and friendships. Another potential conflict can come in the form of conscience. An individual might suffer a conflict of interest if the mission or expectation of the institution is not compatible with his or her personal values.

Of course, having a personal interest does not necessarily mean acting irresponsibly. Although some might take personal interest as a motivation for misconduct, it is obvious that not all individuals would make this choice.

Conflicts of interest are not merely a hypothetical problem. Financial conflicts are associated with altered outcomes of research. Stelfox et al. (1998) reviewed the literature in 1995 and 1996 for reports on the safety of calcium channel antagonists. They classified reports as being supportive, neutral, or critical of these drugs. They found that 100% of authors of reports supporting calcium channel antagonists had financial relationships with drug companies, while only 43% of authors of reports critical of the drugs had such connections with drug companies. Many different hypotheses might explain this trend, but one lesson is that it would be valuable to know if a published study was supported by industry.

#### **Rules and regulations**

A variety of regulations and guidelines govern the disclosure and management of conflict of interest. Although many of the concerns addressed could be generalized to any form of conflict of interest, the explicit problem in nearly all cases is financial. The most relevant of these are federal regulations, notably those of the Public Health Service (PHS) and National Science Foundation (NSF).

Professional societies and journals are an important source for guidance on the management of conflicts of interest. These are quite variable in their scope and rarely enforced, but two examples are noteworthy. The first is a policy statement from American Society of Gene Therapy (ASGT), and the second is the published requirements for publication in the *New England Journal of Medicine*. In a statement adopted in April of 2000, the ASGT concluded that “investigators and team members directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options, or comparable arrangements in companies supporting the trial.” (Woo, 2000) As early as 1984, the *New England Journal of Medicine* requested that, “all

authors disclose to [the Editor] any associations they had with businesses that could be affected by their work – including direct employment and consultancy, stock ownership, and patent-licensing arrangements.” (Angell and Kassirer, 1996)

*[PHS and NSF policies are substantially the same regarding conflicts of interest (PHS, 1995; NSF, 1995). Under PHS policy: “...investigators are required to disclose to an official(s) designated by the institution a listing of Significant Financial Interests ... that would reasonably appear to be affected by the research proposed for funding by the PHS.” The institutional official(s) are responsible to review “those disclosures and determine whether any of the reported financial interests could directly and significantly affect the design, conduct, or reporting of the research and, if so, the institution must, prior to any expenditure of awarded funds, report the existence of such conflicting interests to the PHS Awarding Component and act to protect PHS-funded research from bias due to the conflict of interest.” Significant Financial Interests are defined to be, “...anything of monetary value, including, but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights).”]*

Federal regulations defer, in part, to institutional definitions of conflicts of interest. Not surprisingly, institutional standards vary greatly. Regarding stock ownership, most use the federally defined threshold of \$10,000 or 5% of total shares as a definition of significant financial interest that must be declared. However, some institutions have been somewhat stricter. For example, Harvard scientists are prohibited from working for a company in which they have more than \$20,000 in stock (Brainard, 2000).

### **Principles**

Perhaps the adverse consequences of conflicts of interest will eventually be mitigated by the structure of science – objectivity, blinding of experimenters, repetition of studies, peer review, disclosure, and so on. In practice, this strategy does not address the harms to subjects in clinical trials, misinformation entering the literature, and increased cynicism about science.

#### **Conflicts of interest increase the temptation to commit misconduct.**

Conflicts of interest do not necessarily amount to research misconduct. If the potential gain is large, however, then principles that guide responsible conduct in research may be compromised.

#### **Conflicts of interest increase the risk of unintentional bias.**

Unintentional bias can be a more serious threat than deliberate misconduct, because even those who are biased would be unaware of the ways in which their actions were effected.

For example: Because research is expensive, the research interests of individual scientists are likely to drift toward those topics, methods, and approaches for which support is available. In the design of experiments, scientists may be unconsciously biased to choose, or stick with, approaches likely to provide “marketable” findings, rather than those designed to increase basic understanding of mechanisms. In the collection of data, a researcher with significant financial interests may unwittingly introduce bias into enrollment of subjects for a clinical trial, into evaluation of data dependent on subjective judgments, or even into the reading of objective measurements. Finally, unintentional bias could alter choices about data selection, statistical methods, and presentation of results.

#### **Conflicts of interest can lead to harmful misperceptions of scientists and the scientific enterprise.**

When large sums of money are involved, it may be difficult for the public, legislators, the judicial system, and even colleagues to be convinced that results were not biased for personal gain. Perceived impropriety can result in consequences as damaging as if intentional misconduct had been committed. With increased media, governmental, and public scrutiny, a researcher's reputation, research funding, and employment can depend as much on perceptions of integrity as on integrity itself.

### **Guidelines**

Beyond the existing rules, the following are guidelines generally applicable to the management of conflicts of interest and commitment:

#### **Avoid and minimize conflicts**

Everyone has different interests, and eventually these will come into conflict. Although it is not possible to avoid all sources of conflict, it is in the best interests of the scientific community and the individual scientist to recognize conflicts of interest and to take steps to nullify or mitigate those conflicts; for instance, sell shares in the company, turn down research support, or abandon a project.

#### **Disclose interests**

If conflicts cannot be avoided, then those conflicts should be disclosed. At minimum, the institution and any other parties with a significant interest should be made aware of the extent and nature of the conflict. This includes the audience at meeting presentations as well as journal editors (before submitting or refereeing manuscripts).

## Manage potential for conflict

Disclosure is often not enough because of the risks of bias, the temptation for irresponsible conduct, public and regulatory concerns about the possibility of misconduct, and the appearance of impropriety. For every step of the research process, attempts should be made to isolate the conflicted individuals from all decision-making functions. For example, steps should be taken to maximize the objectivity of patient selection, data collection, the selection of data for publication, and interpretation of the findings. These functions should be the responsibility of, or should at least be reviewed by, an unconflicted individual or group.

*[Disclosure usually occurs only for financial interests, and such disclosure is not routine in the biomedical literature (Krimsky et al., 1998). In a survey of 789 scientific papers published by Massachusetts scientists in the leading journals of cell and molecular biology, Krimsky and his colleagues contacted the authors and found that 34% of the articles had at least one Massachusetts author with a significant financial interest. Despite this high rate of financial interests, Krimsky et al. reviewed 62,000 papers and found that only about 0.5% included disclosure statements. Unfortunately, even as financial conflicts and the risks for bias are increasing, a minimal expectation that those conflicts would be disclosed is not being met].*

In summary, it is important to understand that both the potential for conflicts of interest and the strategies for dealing with those conflicts are evolving. Considering the potential for misperceptions of a researcher's motives, it is best to assume that good intentions are not enough.

## Resources

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Next month the featured RCR topic will be:

"Publication"

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

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**HUMAN SUBJECTS  
PROTECTION PROGRAM**

≧Highlights≦

**Emergency Use Exemption**

The Food and Drug Administration (FDA) provides patient access to investigational drugs and devices outside the standard research mechanism. This process is known as an emergency use exemption. The following outlines the steps needed to obtain an emergency use exemption.

- 1) Determine whether the use of the investigational drug fulfills the FDA criteria for emergency use: (a) a life-threatening situation exists in which no standard acceptable treatment is available, and (b) there is not sufficient time to convene a quorum for full-board review and approval.
- 2) The next step would be to determine if the sponsor requires an Institutional Review Board (IRB) acknowledgement letter. The letter must document compliance with FDA requirements for emergency use indicating that a life-threatening situation does exist and that there is insufficient time to convene the IRB.
- 3) The IRB Chair or designee (with appropriate medical knowledge) needs to review the investigator's letter and confirm that (a) and (b) above are met. The letter generated by the IRB indicates knowledge of or notification of the emergency use of the test article rather than approval of its use.

Subsequent uses of the test article are to be reviewed using the standard IRB review.

Patients must be given information in which the investigational nature of the test article is explained. A standard research consent form is inappropriate and often the Sponsor will supply the consent document. The Institutional Review Board (IRB) is not responsible for the review and approval of the consent form if criteria are met for emergency use.

**Exception From Informed Consent Requirement\*\***

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative *unless both the investigator and a physician who is not otherwise participating in the clinical investigation* certify in writing all of the following [21 CFR 50.23(a)]:

- (1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal representative.
- (4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

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\*\*Food and Drug Administration Information Sheets: Guidance for Institutional Review Boards and clinical investigators, September 1998. Access date 16 September 2006.

<http://www.fda.gov/oc/oha/IRB/toc.html>.



**News from HIPAA.....**

**Groups Commit to HIPAA  
Standardization**

More than 20 leading healthcare organizations have committed to making it significantly easier for physicians and other health professionals to verify patient insurance information one of the biggest administrative challenges identified by providers, Council for Affordable Quality Health Care (CAQH) announced last week. By March 31, 2007, these organizations will electronically exchange eligibility and benefits information according to operating rules developed through the CAQH Committee on Operating Rules for Information Ex-

change (CORE). Operating rules build on existing standards, such as HIPAA, to make electronic transactions more efficient, predictable and consistent, regardless of the technology.

Read more at:

<http://www.hipaadvisory.com/news/newsarchives/2006/0914caqh.htm>

Jeniece Poole, Privacy Officer  
Office of the Vice President for Research  
[jpoole@email.arizona.edu](mailto:jpoole@email.arizona.edu)

## Good Laboratory Practices (GLP)

**Be Aware:**

### **Good Quality Practices are Important!!!**

FDA Fines American Red Cross \$4.2 Million for Failure to Meet Established Blood Safety Laws.

*The amended consent decree requires ARC to:*

- Establish clear lines of managerial control over a newly established comprehensive quality assurance system in all regions;
- To enhance training programs;
- To improve computer systems, records management, and policies for investigating and reporting problems, including adverse reactions.

Again and again **record keeping** and **training compliance** are the cause of most warning letters from the FDA. As the University of Arizona, Quality Assurance officer, I am available to University laboratories to train or review record keeping and regulatory issues.

Marilyn M. Marshall, SpM  
Quality Assurance Officer  
Office of the Vice President for Research  
621-1469 (p), 621-1429 (f)

## **Institutional Biosafety Committee**



### *Bulletin*



### **Emergency Procedures Response to Biosafety Incidents**

**From the Office of  
Occupational & Environmental Safety**

The following steps should be followed to respond to biosafety incidents:

1. Determine if the spill or release poses a threat outside the lab;
2. Notify others in the vicinity to avoid exposure;
3. Contain and clean up the spill with lab personnel if possible;
4. Call 911 if there is a threat outside the laboratory and begin evacuation;
5. If outside cleanup assistance is needed, call UofA IBS Office at 621-5279; OES Office phone number is: (225) 578-5640;

6. If injuries are involved, decontaminate the injured before transport if possible, and provide technical information to medical personnel regarding the agent involved.

Source:

[http://app1003.lsu.edu/pubsafety/oes.nsf/\\$Content/Emergency+Procedures?OpenDocument#biosafety](http://app1003.lsu.edu/pubsafety/oes.nsf/$Content/Emergency+Procedures?OpenDocument#biosafety)

## **University of Arizona – Animal Care Quality Care for Research Animals**



Office of Laboratory Animal Welfare  
Guidance on PHS Policy on Humane Care and Use of Laboratory Animals Provided in  
**Frequently Asked Questions**

**Notice Number: NOT-OD-06-101**

### **Key Dates**

Release Date: September 11, 2006

### **Issued by**

Office of Laboratory Animal Welfare (OLAW),  
Office of Extramural Research  
(<http://grants.nih.gov/grants/olaw/olaw.htm>)

This Notice announces the availability of a series of Frequently Asked Questions (FAQs) at <http://grants.nih.gov/grants/olaw/faqs.htm> about the PHS Policy on Humane Care and Use of Laboratory Animals (PHS Policy) (<http://grants.nih.gov/grants/olaw/references/phspol.htm>).

### **Background**

Between 1990 and 2003 OLAW (and its predecessor the Division of Animal Welfare, Office for Protection from Research Risks) published a number of articles in journals and magazines such as ILAR News, Lab Animal, and Contemporary Topics that provided guidance or commentary for the Institutional Animal Care and Use Committee (IACUC) community concerning issues associated with the PHS Policy. In the early 1990s, OPRR also issued a number of “Dear Colleague” letters addressing various PHS Policy requirements and related issues.

### **Frequently Asked Questions Posted**

Nearly 60 FAQs are now posted that address a significant number of the topics previously addressed in the publications noted above. The information in the FAQs is updated and supersedes previously published guidance or commentary. However, in many instances the previously published material provides additional information or elaboration, and is therefore available through hyperlinks provided on the FAQ site.

In addition, the FAQs provide guidance on topics not previously addressed, including the

Freedom of Information Act, post approval monitoring, HVAC malfunctions/failures, and rodent cage density.

Institutions are encouraged to review the FAQs and make use of this new resource. As necessary, OLAW will update the site with new FAQs.

### **Inquiries**

For questions or further information, contact:

Office of Laboratory Animal Welfare

Phone: 301-496-7163

Fax: 301-402-2803

E-mail: [olaw@od.nih.gov](mailto:olaw@od.nih.gov)

### **Source:**

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-101.html>



## **Radiation Control**

### **Radiation Machines**

All radiation-producing machines are registered with the Arizona Radiation Regulatory Agency (ARRA). It is important to notify the Radiation Control Office (RCO) if you plan to move your radiation-producing machine. Additionally, if you plan to purchase or acquire a radiation-producing machine you must notify the RCO, additional shielding requirements may be required.

**No one is allowed to work with radiation producing machines until they have received appropriate training.** At the University of Arizona, this is a two-part process: Radiation Machines Protection Course ([RMPC](#)) and on-the-job training. The Radiation Worker Data Sheet & Training Record, Form [RC-088](#), **must** be completed by each person who will be working with radiation producing machines and submitted to the RCO to be registered for the RMPC. All employees and students who work with radiation producing machines are required to attend and receive a passing score **prior to beginning work.**

(See [Training Policy](#)).

Approval Holders are not required to attend the RMPC, but are required to attend an Approval Holder Orientation (AHO) prior to beginning work with radiation producing machines and then again every three years.

During initial training with the Approval Holder, it is essential to become familiar with the characteristics and the safe use of the machines you will be using. At any time you need information about a radiation-producing machine, the RCO is available as a resource.

### **Audits**

The RCO will inspect each machine Approval annually. During the audit, several areas are reviewed including all training records for each individual. A copy of the certificate from the *Radiation Machines Protection Course* should be available for review.

Use logs, interlock checks, postings, and service logs are reviewed. Security, interlocks, and warning lights will be tested. A radiation survey is performed.

Call the Radiation Control Office at 626-6850 or email [rcohelp@u.arizona.edu](mailto:rcohelp@u.arizona.edu) for assistance.

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## **Upcoming Conferences/Workshops**

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### **October 15-18, 2006**

49<sup>th</sup> Annual Biological Safety Conference

Boston, MA

[absa@absa.org](mailto:absa@absa.org)

### **October 16-17, 2006**

*Fourth Annual RCR Expo*

Quebec City, Canada

Contact: [L.Nguyen-Khoa@osophs.dhhs.gov](mailto:L.Nguyen-Khoa@osophs.dhhs.gov)

### **November 15-18, 2006**

2006 Annual HRPP Conference... *A Commitment to Ethical Research: Advancing the Mission of Human Research Protection Programs*

[broskin@primr.org](mailto:broskin@primr.org)

### **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

To obtain a conference schedule: <http://ORI.hhs.gov>.

Questions should be addressed to Nick Steneck at

[nsteneck@umich.edu](mailto:nsteneck@umich.edu).

### **February 16, 2007**

American Association for Laboratory Animal Science (AALAS) Symposium

Embassy Suites Hotel, Phoenix, AZ

[Submit your abstract form](#) for your paper or poster by November 15, 2006.

Address questions to: Grace Aranda at 621-3931, or email [www.azaalas.org](http://www.azaalas.org)

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### **University of Arizona Program in Research Integrity Education staff:**

Alice C. Langen, Director, Research Compliance  
Ruth K. Daniels, Program Coordinator and Editor of the P.R.I.E. Newsletter [rhk@u.arizona.edu](mailto:rhk@u.arizona.edu)

P.R.I.E. – Program phone number: (520) 626-6282

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

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### *Words of Wisdom:*

*“Humor is by far the most significant activity of the human brain.”*

— Edward De Bono