Chapter 3. The Protection of Human Subjects

The use of human subjects in research benefits society in many ways, from contributing to the development of new drugs and medical procedures to understanding how we think and act. It also can and has imposed unacceptable risks on research subjects. To help ensure that the risks do not outweigh the benefits, human subjects research is carefully regulated by society.

Case Study

Two weeks into the new semester, the professor in Mary's course on family health gives the class a special assignment that was not on the course syllabus. Over the next week, everyone in the class is to talk with three classmates who are not in the course about the way their families deal with medical emergencies and chronic illness. Next week they should come to class prepared to report on their interviews. The Professor warns them, however, that in talking about their conversations they should not mention any names to protect the privacy of their classmates.

The assignment makes Mary uneasy. In her basic psychology course last semester she learned about some of the rules pertaining to the use of human subjects in research. However, when she raises her concerns with her professor, he assures her that her informal conversations with classmates are not research and therefore not subject to regulation. Moreover, since she will not be mentioning any names, there are no privacy issues to worry about.

Should Mary be content with these assurances and conduct the interviews?

If she still has concerns, where should she turn for advice?

Did the professor act properly in giving this assignment to the class?

Investigators who conduct research involving humans that is subject to regulation must comply with all relevant Federal regulations as well as any applicable state and local laws, regulations, and policies related to the protection of human subjects. They are also expected to follow other relevant codes that have been formulated by professional groups. To meet these responsibilities requires, among other things:

- ✓ **knowing what research is subject to regulation,**
- ✓ **understanding and following the rules for project approval,**

- ✓ **getting appropriate training, and**
- ✓ **accepting continuing responsibility for compliance through all stages of a project.**

If you expect to use or study living humans in your research, no matter how harmless that use may seem, and receive Federal funding, familiarize yourself with your responsibilities and check with someone in a position of authority before making any contacts or undertaking any work.

3a. Federal regulations

Society protects the welfare of individuals in many ways, but it did not specifically address the issue of the welfare of research subjects until after World War II. Following the War, widespread concerns about atrocities committed during the War in the name of research led to the formulation of a code for human subjects research known as the Nuremberg Code (1947). Although not binding on researchers, the Nuremberg Code and the later Declaration of Helsinki (1964; latest revision and clarification, 2002) provided the first explicit international guidelines for the ethical treatment of human subjects in research.

The Nuremberg Code and Declaration of Helsinki did not put an end to unethical human subjects research. During the Cold War, U.S. researchers tested the effects of radiation on hospital patients, children, and soldiers without obtaining informed consent or permission to do so. Through the 1950's and 1960's, well after antibiotics effective for the treatment of syphilis were discovered, scores of African-American males in a long-term syphilis study (conducted by the U.S. Public Health Service in Tuskegee, Alabama) were not offered treatment with the new drugs so that researchers could continue to track the course of the disease. These and other questionable practices raised serious public concern and led eventually to government regulation.

Excerpts, Nuremberg Code (1947)

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

http://www.hhs.gov/ohrp/references/nurcode.htm

To prevent these and similar abuses from continuing, in 1974 Congress required the Department of Health, Education and Welfare (HEW, currently Health and Human Services—HHS) to clarify its rules for the use of human subjects in research. With this mandate in hand, HEW codified its procedures under Title 45 of the Code of Federal Regulations, Part 46 (45 CFR 46). (At roughly the same time, the FDA codified its rules for human subjects research under 21 CFR 50 and 56.)

Congress also called in 1974 for the creation of a National Commission for the Protection of Human Subjects of

Biomedical and Behavioral Research. During the 4 years it met, the Commission issued a number of reports on the protection of research subjects and recommended principles for judging the ethics of human subjects research (discussed below).

In 1991 most Federal departments and agencies that conduct or support human subjects research adopted a common set of regulations for the protection of human subjects referred to as the "Common Rule" (45 CFR 46, Subpart A). Additional requirements on three sensitive research areas are also included in 45 CFR 46:

- ✓ **Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.**
- ✓ **Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.**
- ✓ **Subpart D – Additional Protections for Children Involved as Subjects in Research.**

Together, 45 CFR 46, Subparts A-D, provide a comprehensive articulation of society's expectations for the responsible use of human subjects in research.

Authority for enforcing the HHS regulations for the protection of human subjects who participate in research conducted or supported by HHS now rests with the Office for Human Research Protections (OHRP) in the Office of Public Health and Science (OPHS). If you have specific questions about the Federal requirements for the protection of human subjects, contact your local institutional officials, OHRP (for research conducted or supported by HHS), or appropriate officials at the department or agency conducting or supporting the research.

3b. Definitions

Researchers are responsible for obtaining appropriate approval before conducting research involving human subjects. The need for approval rests on three seemingly obvious but not always easy-to-interpret considerations: 1) whether the work qualifies as research, 2) whether it involves human subjects, and 3) whether it is exempt. All three considerations are discussed in the Common Rule and guide decisionmaking about the use of human subjects in research. The authority to make decisions about the need for approval rests with the Institutional Review Board (IRB, discussed below) or other appropriate institutional officials.

Research. The Common Rule defines research as "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (§ 46.102(d), see box, next page, for full definition). This means that a project or study is research if it:

- ✓ **is conducted with the intention of drawing conclusions that have some general applicability and**
- ✓ **uses a commonly accepted scientific method.**

The random collection of information about individuals that has no general applicability is not research. Scientific investigation that leads to generalizable knowledge is.

Human subjects. Human subjects are "living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information" (§ 46.102(f), see box, next page, for full definition). Humans are considered subjects and covered by Federal regulations if the researcher:

- ✓ **interacts or intervenes directly with them, or**
- ✓ **collects identifiable private information.**

45 CFR 46. 102
Protection of Human Subjects – Definitions

(d) **Research** means a 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.

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(f) **Human subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

If one of these two conditions applies and if the project or study qualifies as research, then institutional approval is needed before any work is undertaken.

Exempt research. Some studies that involve humans may be exempt from the requirements in the Federal regulations. Studies that fall into the following categories could qualify for exemptions, including:

- ✓ **research conducted in established or commonly accepted educational settings;**
- ✓ **research involving the use of educational tests;**

- ✓ **research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if unidentifiable or publicly available;**
- ✓ **research and demonstration projects which are conducted by or subject to the approval of department or agency heads; or**
- ✓ **taste and food quality evaluation and consumer acceptance studies.**

It is critically important to note, however, that decisions about whether studies are exempt from the requirements of the Common Rule must be made by an IRB or an appropriate institutional official and not by the investigator.

3c. IRB membership and deliberations

Federally funded research that uses human subjects must be reviewed and approved by an independent committee called an Institutional Review Board or IRB. The IRB provides an opportunity and place for individuals with different backgrounds to discuss and make judgments about the acceptability of projects, based on criteria set out in the Common Rule.

Under the Common Rule, IRBs must have at least five members and include at least one scientist, one non-scientist, and "one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution" (§ 46.107(d)). IRBs have authority to approve, require modification of (in order to secure approval), and disapprove all research activities covered by the Common Rule. They also are responsible for conducting continuing review of research at least once per year and for ensuring that proposed changes in approved research are not initiated

without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject.

IRBs weigh many factors before approving proposals. Their main concern is to determine whether (§ 46.111(a)):

- ✓ **risks to subjects are minimized;**
- ✓ **risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;**
- ✓ **selection of subjects is equitable;**
- ✓ **informed consent will be sought from each prospective subject or the subject's legally authorized representative;**
- ✓ **informed consent will be appropriately documented;**
- ✓ **when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and**
- ✓ **when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.**

Researchers should consider each of these issues before completing their research plan and submitting it to an IRB for approval.

Making decisions about whether human subjects will be treated fairly and appropriately or given adequate information requires judgments about right and wrong (moral judgments). In the 1979 Belmont Report, the National Commission recommended three principles for making these judgments:

- ✓ **respect for persons** and their right to make decisions for and about themselves without undue influence or coercion from someone else (the researcher in most cases);
- ✓ **beneficence** or the obligation to maximize benefits and reduce risks to the subject; and

The Belmont Report (1979)
Ethical Principles and Guidelines for the Protection of Human Subjects of Research

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

✓ **justice** or the obligation to distribute benefits and risks equally without prejudice to particular individuals or groups, such as the mentally disadvantaged or members of a particular race or gender.

While this list does not exhaust the principles that can be used for judging the ethics of human subjects research, it has nonetheless been accepted as a common standard for most IRB deliberations. Knowing this, researchers should spend time considering whether their work does provide adequate respect for persons, appropriately balances risks and benefits, and is just.

3d. Training

To help assure that researchers understand their responsibilities to research subjects, the National Institutes of Health (NIH) currently requires

> …education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects. (http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)

Many institutions, including NIH, provide this training through special Web-based programs that summarize essential information and in some cases require some evidence of mastery. A description of the education program and who was trained must be included in applications for grants and contracts before they will be considered.

3e. Continuing responsibility

Once a project has been approved by an IRB, researchers must adhere to the approved protocol and follow any additional IRB instructions. This, unfortunately, is where a few researchers and institutions have occasionally run into problems and temporarily had their "assurance" (FWA - Federalwide Assurance) suspended. The continuing responsibilities that researchers have include:

✓ **enrolling only those subjects that meet IRB approved inclusion and exclusion criteria,**

Federalwide Assurance (FWA)

The Federal Policy (Common Rule) for the protection of human subjects at Section 103(a) requires that each institution "engaged" in Federally supported human subject research file an "Assurance" of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects. The requirement to file an Assurance includes both "awardee" and collaborating "performance site" institutions.

Under the Federal Policy (Common Rule) at Section 102(f) awardees and their collaborating institutions become "engaged" in human subject research whenever their employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain, release, or access individually identifiable private information for research purposes.

In addition, awardee institutions are automatically considered to be "engaged" in human subject research whenever they receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. The awardee is also responsible for ensuring that all collaborating institutions engaged in the research hold an OHRP approved Assurance prior to their initiation of the research.

http://www.hhs.gov/ohrp/assurances/assurances_index.html

- ✓ **properly obtaining and documenting informed consent,**
- ✓ **obtaining prior approval for any deviation from the approved protocol,**
- ✓ **keeping accurate records, and**
- ✓ **promptly reporting to the IRB any unanticipated problems involving risks to subjects or others.**

While research institutions are increasingly monitoring the progress of human subjects research, the primary responsibility for conducting experiments as approved still lies with the individual researchers and staff who conduct the experiments.

3f. Ethical issues

Despite the many rules governing research with humans, tough choices continually arise that have no easy answers.

Informed consent. It is widely agreed that research subjects should be fully informed about experiments in which they may participate and give their consent before they enroll. However, some subjects, such as children, some adults with impaired decisionmaking capacity, and some critically ill patients, cannot give informed consent, either because they are not old enough to understand the information being conveyed or because they have lost their ability to understand.

These and other problems could be eliminated by forbidding researchers to do studies that raise difficult questions about respect for persons, beneficence, and justice, but this would make it difficult or even impossible to get some crucial information needed to make informed decisions about medicine and public health. Since children do not respond to medicines in the same way as adults, it is important to include children in some clinical trials. However, it is not easy to decide when they should be included and how consent can/should be obtained.

Right to withdraw. It is widely agreed that research subjects should have the right to withdraw from experiments at any time, but in some cases they cannot. In the final stages of development, mechanical hearts are tested on patients whose own heart is about to fail. But if it has not failed, and once the mechanical heart replaces the weakened heart, there is no turning back. The patient can technically withdraw from the experiment and undergo no further testing, but he or she cannot withdraw from the conditions imposed by the experiment, no matter how distressing living with the mechanical heart might be. Knowing this, under what conditions should these experiments be allowed?

Risk without benefit. In one recent experiment, researchers wanted to test whether a common surgical procedure used to relieve arthritis pain had any benefits. To gather information about benefits they designed a clinical trial in which subjects in the control group received sham surgery. An operation was performed, but the common surgical procedure was not performed.

The researchers in this case complied with all regulations, which included thorough IRB review. None of the patients experienced any adverse effects, and the study concluded that the common surgical procedure did not provide significant benefits. However, since surgery always involves some risk, the subjects in the control group were placed at risk without any expectation that they would benefit. Should this be allowed, and if so, under what circumstances?

These and other questions must ultimately be answered by IRBs during the review process. Researchers who serve on IRBs need additional training to help them deal with the growing complexities of biomedical, social, and behavioral research. Researchers who use human subjects in research should seriously consider having some formal training in bioethics so that they can participate in the critical reasoning process needed to respond to the complex moral issues raised by the use of human subjects in research.

Questions for discussion

1. Why should some research on humans be exempted from regulation?

2. What other criteria could be used to identify necessary members for IRBs?

3. What should subjects know about proposed research and their protection before they enroll as subjects?

4. What other principles could be used for evaluating the ethics of human subjects research besides respect for persons, beneficence, and justice?

5. Should subjects be allowed to enroll in experiments that either promise no direct benefit to them or cannot provide them with the opportunity to withdraw completely?

Resources

Policies, Reports, and Policy Statements

Directives for Human Experimentation: Nuremberg Code. 1949. (available at: http://www.hhs.gov/ohrp/references/nurcode.htm)

Federal Policy for the Protection of Human Subjects, 45 CFR 46, Subpart A (2005). (available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)

National Institutes of Health. *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health,* 1995. (available at: http://www.nihtraining.com/ohsrsite/guidelines/graybook.html)

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General Information Web Sites

Food and Drug Administration. *Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators*, 1998. http://www.fda.gov/oc/ohrt/irbs/default.htm

National Institutes of Health. *Standards for Clinical Research within the NIH Intramural Research Program*, 2000. http://www.cc.nih.gov/ccc/clinicalresearch/index.html

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Additional Reading

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How do researchers decide which animals are used in research?

4. The Welfare of Laboratory Animals

Animal research is as carefully regulated as human research, but for different reasons. With humans, regulation stems from the need to assure that the benefits all humans gain from human research do not impose unacceptable burdens on some research participants. Animals may benefit from the information gained through animal experimentation and some research with animals is conducted specifically for the purpose of improving animal health (veterinary medicine and animal husbandry research). But most animal research is conducted primarily for the benefit of humans, not animals. Moreover, unlike humans, animals cannot consent to participate in experiments or comment on their treatment, creating special needs that should be taken into consideration in their care and use.

The special needs of animals have evolved over time into policies for the appropriate care and use of all animals

Case Study

After many years using fish and frogs to study brain function, Dr. Ruth Q. encountered some problems that can be explored only using new animal models. For the near future, she plans to turn to mice or rats, but eventually may have to do some research using cats or dogs. To help prepare the way for this new research, she decides to put a note about her plans in the progress report for her current research grant, which runs out next year.

The day after she gave a draft of the progress report to her long-time research assistant, he came to her with a troubled look on his face. Although he never told her, the main reason he applied for the job in her laboratory many years ago was the fact that she did not use warm-blooded animals in her research. If she changed her animal models as planned, he would have to quit his job and had no prospects for getting another position that paid as well and was as rewarding.

Does Dr. Q. have any obligation to consider her research assistant's views before she redirects his research?

Why are objections raised to the use of some animals in research and how can those objections be answered?

Why are there more objections to using some animals in research compared to others?

involved in research, research training, and biological testing activities. Researchers can meet their responsibilities by:

- ✓ **knowing what activities are subject to regulation,**
- ✓ **understanding and following the rules for project approval,**
- ✓ **obtaining appropriate training, and**
- ✓ **accepting continuing responsibility for compliance through all stages of a project.**

If you expect to use or study living animals in your research, regardless of the level of invasiveness, familiarize yourself with your responsibilities and check with someone in a position of authority before making any plans or undertaking any work.

4a. Rules, policies, and guidelines

The current rules, policies, and professional guidelines for the responsible use of animals in research are the product of roughly 50 years of ongoing discussion between government, the public, animal care professionals, and

Animal Welfare Act as Amended (7 USC, 2131-2156)

Section 1.

(a) This Act may be cited as the **"Animal Welfare Act."**

(b) The Congress finds that animals and activities which are regulated under this Act are either in interstate or foreign commerce or substantially affect such commerce or the free flow thereof, and that regulation of animals and activities as provided in this Act is necessary to prevent and eliminate burdens upon such commerce and to effectively regulate such commerce, in order—

(1) to insure that animals intended for use in research facilities or for exhibition purposes or for use as pets are provided humane care and treatment;

(2) to assure the humane treatment of animals during transportation in commerce; and

(3) to protect the owners of animals from the theft of their animals by preventing the sale or use of animals which have been stolen.

http://www.nal.usda.gov/awic/legislat/awa.htm

PHS Policy on Humane Care and Use of Laboratory Animals (Amended, August 2002)

II. Applicability

This Policy is applicable to all PHS-conducted or supported activities involving animals, whether the activities are performed at a PHS agency, an awardee institution, or any other institution and conducted in the United States, the Commonwealth of Puerto Rico, or any territory or possession of the United States.

http://grants2.nih.gov/grants/olaw/references/phspol.htm

researchers. The conclusions reached through these discussions are laid out in two key sources of information for researchers who use animals in their work: Federal regulations and professional guidelines.

Federal regulations. Over the last 50 years, Congress has addressed the responsible use of animals in research on a number of occasions and drafted two important statutes:

- ✓ **the 1966 Animal Welfare Act (revised 1970, 1976, 1985, and 1990) and**
- ✓ **the 1985 Health Research Extension Act, Sec. 495.**

The former broadly assigns authority for the responsible transportation, care, and use of animals to the United States Department of Agriculture (USDA), as implemented by Title 9 of the Code of Federal Regulations. It covers animals used "in research facilities or for exhibition purposes or for use as pets." The latter law delegates authority for the responsible use of animals in "biomedical and behavioral research" to the Secretary of Health and Human Services (HHS), acting through the Director of the National Institutes of Health (NIH) and the Office of Laboratory Animal Welfare (OLAW), NIH.

Researchers who use animals in research, including observational research, or teaching, can come under the jurisdiction of the USDA animal welfare regulations and/or

the PHS Policy on Humane Care and Use of Laboratory Animals (hereafter, PHS Policy), which carries out the provisions of the 1985 Health Research Extension Act. They therefore should be familiar with both.

Guidelines. In the late 1950's, a group of animal-care professionals formed the "Animal Care Panel" (ACP) specifically for the purpose of establishing a professional standard for laboratory animal care and facilities. Their work led to the publication of a comprehensive and influential *Guide for Laboratory Animal Facilities and Care* (1963, revised 1965, 1968, 1972, 1978, 1985, and 1996). The current edition, now called the *Guide for the Care and Use of Laboratory Animals,* or *Guide*, as it is commonly referenced, was prepared by a committee appointed by the National Research Council of the National Academy of Sciences and provides guidance on:

- ✓ **Institutional Policies and Responsibilities;**
- ✓ **Animal Environment, Housing, and Management;**

Guide for the Care and Use of Laboratory Animals (1996)

The Guide for the Care and Use of Laboratory Animals (the Guide) was first published in 1963 under the title Guide for Laboratory Animal Facilities and Care and was revised in 1965, 1968, 1972, 1978, and 1985. More than 400,000 copies have been distributed since it was first published, and it is widely accepted as a primary reference on animal care and use. The changes and new material in this seventh edition are in keeping with the belief that the Guide is subject to modification with changing conditions and new information.

The purpose of the Guide, as expressed in the charge to the Committee to Revise the Guide for the Care and Use of Laboratory Animals, is to assist institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate. The Guide is also intended to assist investigators in fulfilling their obligation to plan and conduct animal experiments in accord with the highest scientific, humane, and ethical principles. The recommendations are based on published data, scientific principles, expert opinion, and experience with methods and practices that have proved to be consistent with high-quality, humane animal care and use.

http://www.nap.edu/readingroom/books/labrats/preface.html

- ✓ **Veterinary Medical Care; and**
- ✓ **Physical Plant.**

The *Guide* is widely accepted by both government and research institutions as the most authoritative source of information on most animal care and use questions. The PHS Policy requires that PHS-funded institutions use the *Guide* as a basis for developing and implementing an institutional program for animal care and use.

4b. Definitions

The term "animal" is defined differently in the statutes, codes, policies, and guidelines that govern animal research. Federally funded research is guided by two key definitions:

- ✓ **The PHS Policy, which applies to all PHS-funded activities involving animals, defines "animals" as "any live, vertebrate animals used or intended for use in research, research training, experimentation, or biological testing or for related purposes."**
- ✓ **The Federal Code that implements the Animal Welfare Act (Title 9) covers warm-blooded animals but excludes "[b]irds, rats of the genus Rattus and mice of the genus Mus bred for use in research, and horses not used for research purposes and other farm animals…."**

Many institutions apply uniform and consistent standards to all activities involving animals regardless of the source of funding or legal requirements as a way of ensuring broad compliance with all regulations covering the care and use of animals in research.

Researchers are not authorized to make decisions about covered or excluded research themselves. Therefore, anyone who plans to use animals in research, teaching, testing and other covered activities is well advised to assume a broad definition and to consult with their institutional committee (see below) before ordering animals or beginning work.

4c. Institutional organization

The task of assuring that researchers adhere to the regulations and guidelines for the responsible care and use of animals is generally recognized to be an institutional responsibility. Institutions vest authority for animal care and use in an "institutional official" (IO), who in turn appoints the Congressionally mandated Institutional Animal Care and Use Committee (IACUC), administers institutional care and use units at institutions that are large enough to have such, and handles other general matters relating to the care and use of animals at that institution.

IACUCs. Following the provisions of the 1985 Health Research Extension Act, PHS Policy, USDA regulations, the *Guide*, and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) require research institutions to establish an IACUC. IACUCs oversee and evaluate all aspects of the institution's animal program, procedures, and facilities. Its members must include a doctor of veterinary medicine, one researcher who uses animals in research, and one person who is not affiliated with the institution. Many IACUCs also have a researcher who does not use animals or a member who has some grounding in ethics.

IACUC Members are appointed by their institution, but they have considerable independent authority. Their responsibilities include:

- ✓ **reviewing and approving all animal use research proposals,**
- ✓ **reviewing the institution's animal care program,**
- ✓ **inspecting (at least twice a year) the institution's animal facilities,**
- ✓ **receiving and reviewing concerns raised about the care and use of animals, and**
- ✓ **submitting reports to the Institutional Official.**

IACUCs also have independent authority to suspend projects if they determine that they are not being conducted

in accordance with applicable requirements. This authority comes directly from Congress through the Health Research Extension Act and can be exercised independent of any other institutional administrative authority.

Animal care and use units. Research institutions with large animal research programs generally have centralized animal care and use units that provide veterinary support, training in procedures, and advice on analgesics, anesthesia, euthanasia, and occupational health and safety. While the staff employed in these units cannot approve research protocols for the institution or make decisions specifically assigned to the institutional IACUC, as animal care professionals they are an excellent local source of information about the responsible care and use of animals in research.

4d. Federal and voluntary oversight

OLAW, USDA, and a voluntary accreditation program (Association for Assessment and Accreditation of Laboratory Animal Care—AAALAC) are charged with or assume the task of assuring that research institutions live up to their responsibilities for the care and use of animals in research.

OLAW. OLAW relies on an "assurance" mechanism to monitor institutional compliance with the PHS Policy. An "Assurance" is a signed agreement submitted by a research institution confirming that it will:

- ✓ **comply with applicable rules and policies for animal care and use,**
- ✓ **provide a description of the institution's program for animal care and use,**
- ✓ **maintain an appropriate IACUC, and**
- ✓ **appoint a responsible IO for compliance.**

The Assurance is considered the cornerstone of a trust relationship between the institution and the PHS and grants considerable authority to institutions for self-regulation.

Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International

AAALAC International is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. ...

More than 700 companies, universities, hospitals, government agencies and other research institutions in 29 countries have earned AAALAC accreditation, demonstrating their commitment to responsible animal care and use. These institutions volunteer to participate in AAALAC's program, in addition to complying with the local, state and federal laws that regulate animal research.

http://www.aaalac.org/about/index.cfm

An OLAW-approved Assurance and compliance with PHS policy are considered terms and conditions of receiving PHS funds. Compliance is monitored by OLAW through annual mandatory institutional reporting to OLAW and in the event of noncompliance, serious deviations from the *Guide*, or IACUC suspensions. OLAW conducts limited site visits and reviews, and if necessary conducts investigations of reported noncompliance. Institutions that fail to submit an Assurance or to live up to the terms of their Assurance can have their approval to use animals in research, teaching, and testing suspended.

USDA. The animal welfare regulations also have mandatory reporting requirements, but USDA is an inspection-based system carried out by USDA Veterinary Medical Officers. Rather than allowing institutions to "assure" their own compliance, USDA visits sites, either announced or unannounced, to check whether institutions are in compliance. If violations are found, the institution is then subject to administrative fines and penalties.

Accreditation programs. Animal use programs can be, and most large ones are, accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. AAALAC is "a private nonprofit organization that promotes the humane treatment of animals in science through a voluntary accreditation

program." It is governed by a Board of Trustees representing scientific, professional, and educational organizations. Its Council on Accreditation is composed of animal care and use professionals and researchers who conduct the program evaluations that determine which institutions are awarded accreditation.

AAALAC relies on widely accepted guidelines, such as the *Guide*, and other peer-reviewed resources when evaluating an institution's animal research program. During the accreditation process, AAALAC accreditors evaluate all aspects of an institution's animal research program. If an institution meets AAALAC's standards, it receives an accreditation for a specified period of time and can use this accreditation to demonstrate its commitment to high standards for the care and use of animals.

4e. Principles for the responsible use of animals in research

There is a range of views about the morality of animal experimentation. Antivivisectionists hold that humans have no right to place their own welfare above the welfare of animals and therefore all animal experimentation is immoral. Many animal welfare organizations find that some scientifically necessary experimentation is acceptable, but that it should be kept to a minimum and conducted on animals low on the phylogenetic scale, in ways that minimize pain and suffering. Many scientists feel that extensive animal experimentation is necessary and moral, provided it is based on sound scientific practices and utilizes quality animal care, along with minimization of pain and distress.

To help researchers and IACUCs make decisions about the responsible and appropriate use of animals in research, the Federal government has adopted nine *Principles for the Utilization and Care of Vertebrate Animals used in Testing, Research, and Training* (see box, next page). These principles specify requirements for planning and conducting research and are useful to investigators and IACUCs. When questions

arise, PHS policy and USDA regulations provide further criteria for researchers and IACUCs to consider in assessing protocols.

Further practical advice on ways to assure appropriate respect for animals can be found in the "three Rs of alternatives" devised by Russell and Burch in 1959:

- ✓ **Replacement—using non-animal models such as microorganisms or cell culture techniques, computer simulations, or species lower on the phylogenetic scale.**
- ✓ **Reduction—using methods aimed at reducing the numbers of animals such as minimization of variability, appropriate selection of animal model, minimization of animal loss, and careful experimental design.**
- ✓ **Refinement—the elimination or reduction of unnecessary pain and distress.**

US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

[Researchers should:]

1. follow the rules and regulations for the transportation, care, and use of animals;
2. design and perform research with consideration of relevance to human or animal health, the advancement of knowledge, or the good of society;
3. use appropriate species, quality, and the minimum number of animals to obtain valid results, and consider non-animal models;
4. avoid or minimize pain, discomfort, and distress when consistent with sound scientific practices;
5. use appropriate sedation, analgesia, or anesthesia;
6. painlessly kill animals that will suffer severe or chronic pain or distress that cannot be relieved;
7. feed and house animals appropriately and provide veterinary care as indicated;
8. assure that everyone who is responsible for the care and treatment of animals during the research is appropriately qualified and trained; and
9. defer any exceptions to these principles to the appropriate IACUC.

http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples/

Although PHS Policy is not explicit in addressing refinements, the requirements to use appropriate animal models and numbers of animals and to avoid or minimize pain and distress are, for all practical purposes, synonymous with requirements to consider alternative methods that reduce, refine, or replace the use of animals. USDA animal welfare regulations require a written narrative of the methods used and sources consulted to determine the availability of alternatives.

Knowing the concerns society has about the use of animals in research, researchers should be prepared to explain why they are using a particular species in their research; why pain or discomfort cannot be avoided; why it may be necessary to sacrifice the animals; and why non-animal options cannot be used to gather the same information or to achieve the same ends, based on the principles set out in the *U.S. Government Principles* and other sources of guidance.

4f. Broader responsibilities

Even with all of the care and review that currently is used to assure the responsible use of animals in research, animal research is still controversial and raises concerns that cannot easily be set aside.

Pain and suffering. Some experimental information cannot be gained without subjecting animals to pain and suffering. Researchers who study the effects of severe trauma, such as child abuse, can learn a great deal about physiological change by subjecting animals to different levels of pain and suffering. This can be done by administering mild electric shocks, forcing animals such as rats to swim until they reach exhaustion, or subjecting them to other traumatic treatments. How much pain and suffering is acceptable in experiments is not easily determined.

Concern for different species. There is widespread agreement that some animals, such as primates and

household pets, deserve more protection than other animals, such as worms and clams. There is less agreement about the relative protection that is needed for species within general groups of animals, such as cats, dogs, pigs, rabbits, mice, and rats. What moral considerations set one species apart from another when making decisions about the use to which it can be put in experiments?

Unnecessary experiments. Members of the public disagree about the use to which animals can reasonably be put in research, testing, and teaching. Animals are used to test the safety of experimental drugs, but should they also be used to test the toxicity of chemicals or cosmetics (as once was common, but has largely been abandoned)? Should they be used to train surgeons to do elective surgery? Do researchers sometimes use more animals in an experiment than is absolutely necessary or use animals when other means of testing would provide the same information?

Discussions about the responsible use of animals in research are not likely to dissipate in the near future. If animals are essential to your research and cannot be replaced; if you cannot reduce the number without compromising the experiment; and if you cannot further refine your methods to reduce pain and suffering, then presumably you have done all you can to meet your responsibility. However, do not forget that society does not have to permit the use of animals in research. It can seek to protect animals through complex and expensive regulations if it loses confidence in the research community's ability to regulate itself.

Questions for discussion

1. Should all animals used in research be treated the same or are there reasons to treat some animals differently than others?
2. Are there some animals that should not be used in research?
3. What circumstances justify pain and suffering of experimental animals?
4. How should research animals be procured? How should they be housed and treated during experiments?
5. How should members of IACUCs be selected? What constituencies should be represented on IACUCs?

Resources

Policies, Reports, and Policy Statements

National Academy of Sciences. Institute of Laboratory Animal Resources Commission of Life Sciences. *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 1996. (available at: http://www.nap.edu/readingroom/books/labrats/)

National Institutes of Health. *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*, Bethesda, MD: National Institutes of Health, nd. (available at: http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples)

Public Health Service. *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, Washington, DC: GPO, 2002. (available at: http://grants2.nih.gov/grants/olaw/references/phspol.htm)

United States. Congress. *Animal Welfare Act*, PL 89-544, 1966. (available at: http://www.nal.usda.gov/awic/legislat/awa.htm)

United States Department of Agriculture. *USDA Animal and Plant Health Inspection Animal Care Policy Manual*, Washington, DC: GPO, nd. (available at: http://www.aphis.usda.gov/ac/polmanpdf.html)

General Information Web Sites

Association for the Assessment and Accreditation of Laboratory Animal Care. *Home Page*. http://www.aaalac.org/

National Institutes of Health. Office of Laboratory Animals Welfare. *Home Page*. http://grants2.nih.gov/grants/olaw/olaw.htm

United States Department of Agriculture. Animal Care Program. *Home Page*. http://www.aphis.usda.gov/ac/

Additional Reading

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