Online Ethics Center
FOR ENGINEERING AND SCIENCE

Topics: Animal Subjects

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Description

A guide that provides information and resources on teaching responsible conduct of research that focuses on the topic of animal subject use. Part of the Resources for Research Ethics Education collection.

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Fundamental Questions

Humans have often used non-human animals for basic and biomedical research, but also for companionship, supporting those with disabilities or suffering from stress, protection, sources of medicine and clothing, entertainment, transportation, and food. Although the focus of this discussion is the use of animals in research, two fundamental questions are relevant to any use of animals:

1. Is the use ***beneficial***?
2. Even if beneficial, are some uses of animals ***unacceptable***?

Nominal Guidelines

Opinions among scientists, philosophers, and the general public about how to answer these questions are ***widely divergent***. However, at a minimum, scientists should always take the question of animal use seriously:

- **Critically evaluate the decision to conduct research with animal subjects**
  Both the spirit of regulations and good science requires thoughtful consideration as to what defines ***acceptable use of animals***.

- **Comply with regulations**
  No use of animals for the purposes of research, teaching, or testing should commence that is not explicitly part of an ***approved protocol***.

- **Protect animal welfare**
  Researchers have a responsibility to protect animals from all ***unnecessary suffering or pain***.

- **Promote responsible use of animal subjects**
  Researchers have a responsibility as mentors, as peers, and as trainees to ***initiate discussion, identify relevant regulations, and promote responsible studies*** involving animal subjects.

Background

> *Without the use of animals and human beings, it would have been impossible to acquire the important knowledge needed to prevent much suffering and premature death not only among humans, but also among animals.*
> Albert Sabin, Developer of Polio Vaccine (Sabin, 1992)

> *Virtually every major medical advance for both humans and animals has been achieved through biomedical research using animal models to study and find a cure for disease, and through animal testing, to prove the safety and efficacy of a new treatment.*
> C. Everett Koop, U.S. Surgeon General, 1982-1989 (UCSD, 2001)

Is Animal Research Useful?

The merits of animal research are widely accepted by scientists and largely appreciated by the general public:

- Biomedical research institutions, professional societies, and research scientists ***share an understanding of tremendous value gained from animal studies*** (e.g., FASEB, 2015).

- Polls of the general public historically have shown ***strong support for biomedical research*** with animals (Saad, 2010), although more recent polls suggest that the public is ***becoming more evenly divided*** (Funk and Rainie, 2015).

That said, the recognition of the benefits of animal research will depend greatly on precisely what question is being asked:

> *It would appear that people's attitudes toward experiments involving animals are likely to change depending on the beneficiary, purpose or necessity of the research.*
> (Ormandy et al., 2014)

For example, it is likely that someone who expresses general misgivings about animal research, but perceives the value of vaccines, will prefer that those vaccines be first tested for safety before being used in their children.

Is Animal Research Conducted Responsibly?

Foundations of Responsible Research

Animal research has tremendous utility because an understanding of ***the complex interactions of molecular, biochemical, and physiological mechanisms ultimately depends on studies in intact, living organisms***.

- The scientific enterprise and the integrity of research ***depend on the responsible, humane treatment of animal subjects***.
- To be performed, such studies depend on many genetic and environmental controls that are difficult, if not impossible, to achieve in studies with humans--yet the studies ***only have value if these controls are carefully maintained***.
- Furthermore, an experimental design that results in ***pain or suffering often decreases, if not eliminates, the scientific value of the experiment***.
- ***Irresponsible or inhumane treatment of animals*** harms the reputation of scientific institutions, endangers funding, and threatens the public image of science.

Failures of Responsible Research

While researchers typically recognize the need for responsible use of animals, poorly trained or inexperienced investigators may, for example:

- perform studies that ***deviate from approved protocol***
- provide ***inadequate care or feeding*** for animal subjects
- leave ***animals poorly attended*** during recovery from anesthesia and surgery.

Although these lapses may occur rarely, they are never acceptable.

It is hoped that the conduct of most researchers is principled and responsible, but this is not always the case. One of the most important early experimental scientists was Claude Bernard. Despite his fundamental and important contributions to science, his words suggest someone who did not recognize the suffering of the subjects of his research:

> To translate and paraphrase BernardBernard C (1865): Le physiologiste n'est pas un homme du monde, c'est un savant, c'est un homme qui est saisi et absorbé par une idée scientifique qu'il poursuit : il n'entend plus les cris des animaux, il ne voit plus le sang qui coule, il ne voit que son idée et n'aperçoit que des organismes qui lui cachent des problèmes qu'il veut découvrir.,
> *The physiologist is not a worldly man. He is a scientist seized and absorbed by scientific inquiry. He no longer hears the cries of the animals. He no longer sees the flow of the blood. He only sees his idea and the systems that conceal from him the questions he seeks to answer.*
> (Bernard, 1865)

In this context, it is noteworthy that some instances of animal abuse have been far worse than inadequate care or feeding.

> In 1984, ***head injury studies conducted with baboons*** at the University of Pennsylvania were found to exemplify the worst fears of those opposed to animal research. In studies with restrained baboons, researchers were testing the effects of rapid, traumatic head injury. Some of those researchers made comments suggestive of a callous, if not sadistic, attitude toward the experimental subjects. ***Videotapes documenting these abuses were obtained by an animal rights organization and were aired on national television***.

Despite the potential importance of what might be learned, such incidents reflect badly not just on one group of researchers, but on all of research.

Investigators who are irresponsible risk not just their own research project, but also the research of others at the same institution. Potentially, they ***also risk the public's willingness to support or allow any research with animal subjects***.

Opposition to Animal Research

The support for biomedical research is tempered in part by widespread misunderstanding about the general nature of research, and research with animals in particular, but also an impassioned opposition, by some groups, to any use of animals.

Arguments against the use of animals in research can broadly be divided into those that focus on the ***rights*** of animals and those that emphasize a ***utilitarian*** calculation to balance net benefits and harms.

Rights

Some in the animal rights movement rely on carefully reasoned, philosophical arguments that humans do not have the right to use animals for experiments (e.g., Regan, 1983), even if such studies might contribute important new knowledge about physiology or the mechanisms of disease in both humans and animals.

Utilitarian

Other opponents of animal research focus more on balancing benefits and harms

(e.g., Singer, 1975). The focus in this case is on claims that:

- Animals ***suffer needlessly*** in research
- Current medical advances were or could have been ***derived without the use of animals***
- Animal research has provided ***no useful data***
- There are ***negative consequences*** of animal research for humans (e.g., Greek and Greek, 2002).

While compelling arguments have been made to diminish the case made by Singer (Russell and Nicoll, 1996), it is important to remember that the principle of "the greatest good," is of paramount importance to Singer, who has even gone on record as saying studies in non-human primates for the purpose of Parkinson's Disease research could be defensible (Crowley, 2006). This is clearly contrary to the typical *Rights* argument.

Scientific Community Concerns about Animal Research

Singer is not the only one to have questioned the unmitigated value of animal research.

Frances Collins, director of the National Institutes of Health since 2009, noted:

> *The use of animal models for therapeutic development and target validation is time consuming, costly, and may not accurately predict efficacy in humans*
> (Collins, 2011)

John Ioannidis, a widely respected Stanford Professor of Statistics, Medicine, and Health Research and Policy, concluded from systematic reviews of the animal research literature that (Ioannidis, 2012):

> *Limited concordance exists between treatment effects in preclinical animal experiments and clinical trials in human subjects.*
>
> *[It is] nearly impossible to rely on most animal data to predict whether or not an intervention will have a favorable clinical benefit-risk ratio on human subjects*

This is consistent with an increasing body of literature noting a dismaying lack of reproducibility of published research (Prinz et al., 2011; Begley and Ellis, 2012). However, this doesn't necessarily mean that animal models *per se* are the problem.

First, not all uses of animals in research are the same:

> ***Animal models vary*** in their capacity for predicting efficacy or safety in humans (Greaves et al., 2004). Just as there are cases in which correlations are strong (e.g., lethal doses for anticancer drugs in mice with maximum tolerated dose in humans or that dogs can be better predictors "of human adverse effects than rodents or, surprisingly, monkeys"), there are others which have little correlation (e.g., rodents appear to be poor predictors of subjective adverse neurological reactions in humans).

Further, as pointed out by Ioannidis (2012), there are at least two reasons that research with animals might not be reliable:

> *Potential explanations for the failure of animal models to capture treatment effects in humans can be placed into two categories: First, both the human and animal results are accurate, but* ***human physiology and disease are not adequately captured by animal models****. Second, the animal* ***literature is susceptible to biases*** *in the study design, to reporting biases that distort the published evidence, or both. Indeed, although the scientific literature related to human clinical trials suffers from biases.*

Regulations and Guidelines

> *Enhancing the quality of animal studies will directly improve a quarter of the biomedical literature and may also benefit much of the other three-quarters that have an interface with animal research. Efforts are needed to minimize publication and other selective-reporting biases. Study design, conduct, and reporting can be improved—for example, by using the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines [Kilkenny et al., 2010]*
> (Ioannidis, 2012)

Roots of Regulation

Except for a set of guidelines for animal use recommended by the National Institutes of Health (NIH) in 1935, animal research in the United States was conducted with ***little public attention*** and virtually no oversight until the 1960s.

This changed with a report titled "Concentration Camps for Dogs", published in Life magazine in 1966, documenting ***brutal conditions and lack of care*** by suppliers of dogs to research laboratories (Cosgrove, 2014):

- Within the year, the ***first Animal Welfare Act*** was written and approved, calling for regulatory oversight of the suppliers of some animals.
- Within the next few years, the government and researchers approved ***further guidelines and regulations to reduce the risk that the privilege of working with animal subjects would be abused***.
- One of the most important outcomes was the ***NIH Policy for Animal Care and Use*** for institutions supported by the Public Health Service (PHS).

Regulations

The use of animal subjects is covered by numerous regulations.

Although many federal agencies have relevant regulatory controls, the two most important for biomedical research are the ***Public Health Service (PHS)*** and the

United States Department of Agriculture (USDA). Institutions are charged with implementing federal regulations primarily through the ***Institutional Animal Care and Use Committee (IACUC)***:

- **Public Health Service**
  The Health Research Extension Act of 1985 ('Animals in Research') is the legislative basis for PHS policy on use of animal subjects. The policy covers uses of living vertebrate animals for any PHS-supported research, research training, and biological testing (PHS agencies include but are not limited to the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA)).

- **United States Department of Agriculture**
  Animal Welfare Regulations, and specifically the Animal Welfare Act (AWA), are implemented by the Animal and Plant Health Inspection Service (APHIS) of the USDA. The AWA, first enacted in 1966 and amended periodically, covers the sale, handling, transport, and use of warm-blooded, vertebrate animals. At present, birds, rats, and mice that are bred for research, but not those that are wild, are specifically exempted from the Animal Welfare Regulations. The AWA, as amended in 1985, incorporates a variety of requirements to promote animal welfare, including minimization of pain and distress, consideration of alternative procedures, definitions of institutional responsibilities, and the establishment of IACUCs. In addition, institutions, businesses, or individuals covered under the AWA must be licensed or registered with APHIS. Facilities are inspected on an unannounced basis, and if deficiencies are not corrected by the subsequent inspection, consequences could include fines, or the suspension or revocation of licensing to use animals.

- **Institutional Animal Care and Use Committee**
  Although institutions are subject to federal oversight and inspection, day-to-day responsibility for complying with federal regulations is largely located within the IACUC. Under PHS policy, institutions are granted provisional responsibility for self-regulation after approval of an Animal Welfare Assurance by the Office of Laboratory Animal Welfare (OLAW). If the institution fails to meet its regulatory responsibilities, then OLAW can restrict or withdraw the assurance.

Guidelines

There is no presumption that animals may be sacrificed for research. Use of animals should only be considered if there is a legitimate scientific advantage to doing so, and even then the harm should be as little as possible.

Replacement, Reduction, and Refinement

Russell and Burch (1959) proposed three specific strategies for minimizing the pain and distress to animal subjects:

- ***Replacement***:
  When possible, conscious animals should be replaced with unconscious or insentient material in research, and higher animals should be replaced with lower ones.

- ***Reduction***:
  Fewer animals should be used if doing so will not compromise the significance or precision of a study.

- ***Refinement***:
  Procedures should be designed so as to minimize the incidence and severity of harm to the animal subjects.

These strategies have an ethical basis, but they also have ***practical advantages***. Research with animal subjects is expensive. If experiments can be conducted, for example, with mice rather than monkeys, with fewer animals, or without animals altogether, then the cost of those studies will generally be reduced.

ARRIVE Guidelines

Even if a case can be made that research is consistent with the principles of reduction, replacement, and refinement, the *research cannot be considered ethical if it doesn't also adhere to minimal precautions to favor research that will be reproducible*. A widely accepted set of such guidelines are those noted above for Animals in Research: Reporting In Vivo Experiments (Kilkenny et al., 2010).

Discussion

Case Study 1

Your colleague, Dr. Jay Mahata, is an NIH supported investigator who has an established collaboration with a field biologist, Dr. Ellen Yu, in another state. Dr. Yu does not receive any grant support for her research. Dr. Mahata sometimes receives blood and other tissue samples for analysis from the wild rodents that Dr. Yu traps for her research. Dr. Mahata has asked you to read his latest IACUC protocol prior to its formal submission. You know about his collaboration with Dr. Yu but note that it is not mentioned in the protocol. When you ask Dr. Mahata about this he says that he "does not have to report this activity to the IACUC because there are not any animal welfare concerns involved". He points out to you that he does not sacrifice the rodents or collect the blood and tissues. He maintains that the relevant animal welfare concerns are between Dr. Yu and her institution. Lastly, he suggests that because the NIH does not support her work, it does not have to conform to the same guidelines to which his own work is subject.

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Case Study 2

You are beginning a new post-doctoral position at the same time that your mentor is moving her laboratory into a new building. She is obsessive about animal care and wants to ensure that the colony of animals to be established in the new facility is healthy. You are assigned the task of developing a system of "sentinel" animals to monitor the health status of all new incoming shipments of animals as well those in the established animal colony. You establish a system that involves selected animals being sacrificed on a regular basis and screened for the presence of specific pathogens by a contract laboratory. Because these animals are not being used for research do you have to submit a protocol to the IACUC to cover these activities?

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Case Study 3

You are a graduate student working on a project that involves administering nerve toxins directly into the cerebrospinal fluid of rats by using a special infuser

connected to tubing that you have surgically implanted into the base of each rat's skull. Administering different nerve toxins to block specific effects of different types of drugs will help determine how the drugs work. After surgery, the nerve toxin is given, then a few days later the investigational drug is given to determine whether it will have an effect. This protocol has been approved by the Institutional Animal Care and Use Committee (IACUC) and is being funded by a grant from the Department of Defense. Over the past few weeks, you have carefully implanted a catheter into the base of each rat's skull, then infused the specified amount of nerve toxin. When you go to the vivarium to bring the rats to the lab to administer the investigational drugs, you find that a number of the rats are paralyzed or dead. You did not expect this. The lab director is currently out of town, so you go to the lab's senior graduate student, Tom, for advice. Tom will be able to complete his dissertation writing when this experiment is done and he has made it clear that he wants this experiment to run without delay. You ask him whether you should stop the experiment to determine why some of the rats are dead or paralyzed. He responds that stopping the experiment now would waste several weeks of work and delay completion of his dissertation. Stopping now may mean having to start over later and could result in using even more rats. He further explains that the IACUC might even prohibit restarting the experiment, so the rats would have died for nothing because the data would have to be obtained another way. He suggests that the paralysis and death of some of the rats may be due to your inadequate experience performing rat surgery or infusions, so further practice by continuing this experiment may result in better outcomes for the rest of the rats on which you perform surgery.

What do you do now? Do you continue performing surgery and infusions on the rats, knowing that more rats may be harmed? Do you stop the experiment and inform the IACUC, which risks earning the disfavor of Tom, with whom you have to work? How would you explain each course of action to the IACUC?

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1. Discuss the benefits of using animals in biomedical research and list at least three different studies that could be accomplished only with the use of animal subjects.
2. To what extent does your field of work depend on the use of animal subjects? To what extent is your work intended to benefit both humans and other animals?

3. Describe at least one instance in which abuse of animals in research resulted in public concern about the use of animals in research. Identify federal regulations that were apparently direct responses to such abuses.
4. Define the terms replacement, reduction, and refinement in the context of research with animal subjects.
5. What are the responsibilities of an IACUC?
6. In your institution, what minimal changes (e.g., increase in number of animals) to your protocol require review and approval of the IACUC? What changes are of a magnitude to require submission, review, and approval of a new protocol?
7. If you observed another investigator abusing the privilege of animal use, who should be notified?
8. Describe your criteria for the acceptable use of animals. Consider the importance and likelihood of benefits to be obtained, the nature of the species to be used (e.g., invertebrates versus vertebrates, primates versus non-primates, dogs or cats versus rats or mice), the number of animals to be used, and the extent of likely pain or suffering.
9. What forums are available in your institution to examine the ethical and/or legal ramifications of animal use? What, if anything, can you do to promote such discussion?

Resources

- OEC Animal Subjects Bibliography
  A bibliography of books, online resources, and articles on all aspects of animal use in research.

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Notes

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Resources for Research Ethics Education

Topics

Animal Use

Discipline(s)

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Research Ethics