Should federal law allow or require IACUCs to engage in ethical review of animal research projects?

Or

Should federal law regard IACUCs as "ethics committees?"

Plan of discussion

1. Nature of ethical review.
2. Current federal statutory law: How Congress answered the question in 1985.
3. Why the question has re-emerged.
4. Some problems and issues.

Perfectly clear

- Animal research is a necessary tool in preventing, alleviating, and curing human and animal disease.
- There is enormous agreement in the research community about ethically appropriate aims of animal research and ethically appropriate means of achieving these aims.
- The vast majority of animal research projects are in fact conducted for ethically sound reasons and in ethically sound ways.

Perfectly clear

- The need to consider the advisability of legally authorized or required IACUC ethical review does not imply that there are widespread or serious ethical problems in animal research.
- Or that IACUCs – or anyone else – should be legally required to engage in ethical review of animal research.

Hypothetical Scenario

Imagine that IACUCs were to be allowed or required by federal law to reject animal research projects they find to be ethically inappropriate or to require modifications in project aims or procedures in order to comport with what they regard as ethical requirements. Imagine that you are an IACUC member at an American university, and that the IACUC is presented with the following proposal.*

*Not all aspects of the protocol are presented here.

The proposed experiment will simulate first-hand cigarette smoking in Rhesus monkeys to examine whether various new potential therapeutic agents can alleviate or reverse resulting emphysema in these animals, and ultimately in humans. Emphysema of different levels of severity will be induced in different monkeys, and selected agents will be administered in various dosages to determine their effectiveness in alleviating or reversing symptoms of the disease.

Should federal law allow or require IACUCs to engage in ethical review of animal research projects?

"Ethical review"

- Synonymous with "full ethical review, "complete ethical review."
- Examination and assessment of all aspects of an animal research project – including its scientific or medical aims – on ethical grounds.
- Ability to approve or disapprove the project, or to require modifications in any aspect of the project, on ethical grounds.

Ethical review: Some questions

- Do the aims or potential results of the experiment justify its uses and treatment of the animals?
- Are any harms done to the animals justified by the project's probable or likely benefits?
- Is it ethically acceptable to use this species to obtain this kind of benefit?
- Is it ethically acceptable to subject this species to these experiences to obtain this kind of benefit?

"Limited ethical review"

- Examination and assessment of some aspect or aspects of an animal research project – not including its scientific or medical aims.
- Application of an ethical standard or standards to some aspect or aspects of the project.
- Ability to approve, disapprove, or require modifications in these aspects based on adherence to or deviation from these ethical standards.

In the hypothetical emphysema study

- The IACUC is considering whether the investigator can, consistently with the scientific aims of the project, reduce the pain or distress the monkeys might experience by modifying the proposed restraint procedures by not using restraint chairs. Limited ethical review.
- The IACUC is considering whether it is ethically acceptable to simulate first-hand smoking and cause pain or distress in monkeys to develop drugs that might alleviate or cure resulting emphysema. Ethical review or full ethical review.

"Scientific review"

- Synonymous with "full scientific review," "complete scientific review," or what the NIH calls "scientific or technical merit review."
- Determining whether all aspects of the project – including its scientific or medical aims – are sound from a scientific standpoint.
- Ability to approve or disapprove the project, or to require modifications in any aspect of the project, on scientific grounds.

Scientific review: Some questions

- In the case of an animal experiment, is there reason to think that the species is or might be shown by the experiment to be a good model for the disease or condition under study?
- Are the proposed procedures and uses of animals scientifically appropriate to address the project's scientific aims?
- Does the investigator possess sufficient knowledge and expertise to perform the proposed procedures properly?
- Does the investigator possess sufficient facilities, funding, and staff to perform the proposed procedures properly?

"Limited scientific review"

- Examination and assessment of some aspect or aspects of an animal research project – not including its scientific or medical aims.
- Application of scientific or technical standards to such aspects of the project.
- Ability to disapprove or require modifications in these aspects based on adherence to or deviation from these standards.

In the hypothetical emphysema study

- The IACUC is considering whether the investigator can, consistently with the scientific aims of the project, reduce the pain or distress the monkeys might experience by modifying the proposed restraint procedures by not using restraint chairs. Limited scientific review (as well as limited ethical review).
- The IACUC is considering whether monkeys are a good model for understanding emphysema in humans. Scientific review.

Ethical review includes scientific review

- Full ethical review must involve some scientific review which determines that, at the very least, project aims and procedures are not problematic from a scientific standpoint.
- *If the project does not address scientific questions relevant to the disease or matter under study, or if it is unlikely, for scientific or technical reasons, to achieve its aims, the project cannot justify its use of animals in general, and certainly cannot justify any pain or distress it might cause the animals (if it causes any pain or distress).*

In the hypothetical emphysema study

- If monkeys are not a good model for human emphysema, the project is ethically unacceptable.
- If monkeys are a good model, but the proposed cigarette-smoking simulation procedures are unlikely to induce the desired levels of severity of emphysema, the project is ethically unacceptable.
- If monkeys are a good model, and the proposed procedures are scientifically appropriate, but the investigator lacks sufficient funding and facilities to undertake the project properly, the project is ethically unacceptable.

Current Statutory Law

How Congress thought it answered the question about IACUC ethical review in the Animal Welfare Act (AWA) amendments of 1985 and the Health Research Extension Act (HREA) of 1985

Current statutory law summarized

- See Appendix in PDF for AWA and HREA provisions.
- IACUCs may not engage in ethical review. They may not evaluate the aims or general character of projects on ethical grounds.
- IACUCs may not engage in scientific merit review. They may not assess the scientific quality of project aims or of the technical procedures intended to achieve these aims.

Current statutory law summarized

- IACUCs do engage in limited ethical review: They must assure compliance with a number of legally-mandated ethical principles, the most general and important of which is that animal pain or distress must be eliminated or minimized consistently with project aims.
- IACUCs do engage in limited scientific review: They must be satisfied that experimental procedures in fact comport with ethical or technical principles required by law, for example, that in fact there are no alternative procedures that would subject the animals to less pain or distress and are consistent with project aims.

HREA: Legislative history

"The animal care committees have *no authority to interfere with research decisions, goals, or methods*. The committees have *no authority to 'second guess' or review the appropriateness of research*. The authority of the committees is *limited to review of the care and treatment of animals* pursuant to guidelines established by the NIH."

House Conference Report, 1985, pp. 746-747, italics added

AWA: APHIS regulatory policy

"Alternatives or alternative methods, as first described by Russell and Burch in 1959, are generally regarded as those that incorporate some aspect of replacement, reduction, or refinement of animal use in pursuit of the minimization of animal pain and distress *consistent with the goals of the research*. … However, *methods that do not allow the attainment of the goals of the research are not, by definition, alternatives*."

Animal Care Resource Guide, Policy 12, italics added

At present: An ethical review void

- IACUCs may not engage in full ethical review of project aims (and as will be noted later are not qualified to engage in kinds of scientific review that are necessarily part of ethical review).
- NIH scientific review groups (SRGs) have the expertise to assess scientific merit (when reviewing NIH grant applications), and do consider whether projects are medically important and thus have important ethical goals, but SRGs do not engage in full ethical review.

An ethical review void

- Put another way, federal statutory law does not now allocate the task of comprehensive and sustained ethical review of animal research projects to anyone.

Why is the ethical review question back – and more important than ever?

❶ A review void acceptable?

- At a time when adherence to ethical standards in science in general and animal research in particular is regarded as essential, is it acceptable that the law does not require sustained ethical review of animal experiments?
- Even if the vast majority of animal research projects are in fact conducted for ethically appropriate reasons and in ethically appropriate ways.
- And especially if some experiments (e.g., the hypothetical monkey emphysema study) at least raise serious ethical questions.

❷ Promotion of public support?

- US public support for biomedical animal research is unimpressive and may be waning. (See Appendix in PDF).
- Might not IACUC ethical review – and the ability of the research community and government to assure the public that there is such review – promote public support for animal research?

❸ Law in other countries

- Ethical review by institutional committees or government officials is legally required in many countries, including the UK and members of the EU.
- In the UK and EU, it must be demonstrated that any *harm* done to animals in research a project is *justified* by the *likely benefits* of the project. (See Appendix in PDF.)
- If, as many in the research community believe, animal research practices should be harmonized internationally, shouldn't IACUC ethical review be required in the US?

❹ Eighth edition of the *Guide*

"Certain animal use protocols include procedures or approaches that require special consideration during the IACUC review process due to their potential for unrelieved pain or distress or other animal welfare concerns. … For these and other areas the IACUC is obliged to weigh the objectives of the study against potential animal welfare concerns." (p. 27.)

❺ Research community acceptance

Citing the statement in the *Guide* quoted in the last slide, AAALAC requires that an IACUC in an accredited institution must perform a "harm/benefit analysis," in which it would "weigh the potential adverse effects of the study against the potential benefits that are likely to accrue as a result of the research." AAALAC, *Accreditation: Frequently Asked Questions. C.3. Harm-benefit analysis,* http://www.aaalac.org/accreditation/faq_landing.cfm.

❺ Research community acceptance

- Report of the Joint Working Group on Harm-Benefit Analysis in Animal Experiments of the American Association for Laboratory Animal Science (AALAS) and the Federation of European Laboratory Animal Science Associations (FELASA). *JAALAS* , 2016, vol. 50(1S), pp. 1-20; 21-42.
- Harm-benefit analysis is now a common subject of sessions in professional meetings.

❻ Support of ethical review by OLAW

Via the *Guide* (including the passage from the *Guide* quoted above)

"The IACUC shall confirm that the research project will be conducted in accordance with the Animal Welfare Act insofar as it applies to the research project, and that the research project is consistent with the *Guide* unless acceptable justification for a departure is presented." *PHS Policy,* para. IV(C)(1), p. 13.

❻ Support of ethical review by OLAW

Via *US Principles* and other PHS review criteria

"Although not intended to conduct peer review of research proposals, the IACUC is expected to include consideration of the U.S. Government Principles in its review of protocols. Principle II calls for an evaluation of the relevance of a procedure to human or animal health, the advancement of knowledge, or the good of society. Other PHS Policy review criteria refer to sound research design, rationale for involving animals, and scientifically valuable research. Presumably a study that could not meet these basic criteria is inherently unnecessary and wasteful and, therefore, not justifiable." *Frequently Asked Questions: PHS Policy on Humane Care and Use of Laboratory Animals*, http://grants.nih.gov/grants/olaw/faqs.htm.

Why regulatory overextension

- See this topic in Appendix in PDF.
- In a nutshell: NIH has applied the *PHS Policy*, including *US Principles* Principle II, which were originally designed for NIH intramural research and can and do equire ethical review for such research, to NIH-funded extramural research governed by the HREA, regarding which Congress prohibits IACUC ethical review.
- For a detailed account, see J. Tannenbaum,"Ethics in Biomedical Animal Research: The Key Role of the Investigator" (chapter), in P. Michael Conn (editor), *Animal Models for the Study of Human Disease*, *2d. ed.*, Academic Press, 2017.

IACUC ethical review: Some problems

- The vast majority of IACUC members are not qualified to engage in kinds of scientific merit review that are relevant to ethical review.
- The vast majority of IACUC members do not have extensive knowledge of or background in animal ethics or bioethics.

IACUC ethical review: Some problems

- The ethical principles IACUCs would apply in ethical review are not well-established.
- For example, "harm-benefit analysis", which is often recommended as the central principle for IACUC review, has major problems.
  - It is often impossible to predict what animal experiments will discover, much less that they will discover knowledge that will lead to practical benefits.
  - Harm-benefit analysis would preclude most basic research, because basic research typically is not directly aimed at achieving benefits.

IACUC ethical review: Some problems

- There would be some difficult or contentious issues regarding which there will be major disagreements among IACUCs.
  - Leading to different IACUC decisions and problems this would cause individual researchers and the research community.
- Let's return to the hypothetical monkey emphysema experiment.

The proposed experiment will simulate first-hand cigarette smoking in Rhesus monkeys to examine whether various new potential therapeutic agents can alleviate or reverse resulting emphysema in these animals, and ultimately in humans. Emphysema of different levels of severity will be induced in different monkeys, and selected agents will be administered in various dosages to determine their effectiveness in alleviating or reversing symptoms of the disease.

IACUC #1 regards the goal of the experiment and what will be done to the animals as ethically justified, on the grounds that many people around the world smoke cigarettes, develop emphysema, and need relief.

IACUC #2 rejects precisely this kind of study. It maintains that smoking-related emphysema can most effectively be eliminated or reduced if people simply stop smoking, and believes it is not fair to monkeys to give them the disease to help people who should not have smoked in the first place. However, this IACUC tells the investigator that it will approve a project in which monkeys are subjected to the equivalent of secondhand smoke; this experiment would be ethically justifiable, this IACUC believes, because many people who contract lung disease as a result of smoking by others cannot be held responsible for their illness.

IACUC #3 rejects monkey studies of first or second-hand smoke as unethical, on the grounds that non-human primates should not be used in any kind of tobacco research, but tells the investigator that if the experiment is modified to study first or secondhand smoke in mice, it would be ethically justified and would be approved.

IACUC #4 will approve only studies of secondhand smoke on mice, for the same reason IACUC #2 rejects firsthand smoke studies on monkeys.

Possible solutions?

- APHIS and OLAW regulations that would settle which kinds of animal experiments are ethically justified?
- A standing national body that would promulgate standards and perhaps adjudicate difficult cases?
- A group of academic bioethicists who would provide guidance?
- Something else – including leaving things as they are now?

Take-home messages

- We must be very careful before allowing or requiring IACUCs to engage in full ethical review. Valuable research could be precluded or hindered if problematic ethical standards are imposed.
- Federal agencies must not exceed their statutory authority in addressing this issue.
- Statutory changes – and careful deliberation by Congress – will be crucial if full ethical review is to be allowed or required.

Take-home messages

- All potential benefits and dangers, and a range of different possible approaches, must be carefully considered.
- We cannot allow the understandable and laudable desire to ensure ethical conduct of animal research to threaten research that can improve the health and welfare of humans and animals.

Appendix

HREA §289d

§ 289d. Animals in research

(a) Establishment of guidelines

The Secretary [of HHS], acting through the Director of NIH, shall establish guidelines for the following:

(1) The *proper care of animals* to be used in biomedical and behavioral research.

(2) The *proper treatment of animals* while being used in such research. Guidelines under this paragraph shall require—

(A) the appropriate use of tranquilizers, analgesics, anesthetics, paralytics, and euthanasia for animals in such research; and

(B) appropriate pre-surgical and post-surgical veterinary medical and nursing care for animals in such research.

Such guidelines shall not be construed to prescribe methods of research. …

Italics added

AWA §2143

(a)(6)(A) Nothing in this chapter—

(i) except as provided in paragraph (7) of this subsection, shall be construed as authorizing the Secretary to promulgate rules, regulations, or orders with regard to the design, outlines, or guidelines of actual research or experimentation by a research facility as determined by such research facility;

(ii) except as provided in subparagraphs (A) and (C)(ii) through (v) of paragraph (3) and paragraph (7) of this subsection, shall be construed as authorizing the Secretary to promulgate rules, regulations, or orders with regard to the performance of actual research or experimentation by a research facility as determined by such research facility; … .

[The specified paragraphs and subparagraphs requires number of approaches primarily directed at minimizing animal pain or distress of animal pain and distress.]

US public support: FBR/Echelon

- October 2017 Echelon Insights poll funded by Foundation for Biomedical Research found that 36% of Americans support the "humane use of animals in biomedical research, education, and testing," 42% oppose, 22% are unsure.
- But 57% support the "humane use of animals" where such research "supports the development of medicines prescribed by veterinarians for animals;" 22% oppose, 21% unsure.
- When told that humane use of animals in biomedical research "has significant impact for humans," 48% support, 22 oppose.

US public support: Gallup and Pew

- Polls conducted by the Pew Research Center found that in 2009 52% of US adults "favored," and 43% "opposed," "the use of animals in scientific research." By 2014, those in favor dropped to 47%, and those opposed rose to 50%.
- The annual Gallup Poll on moral attitudes of Americans found that in 2016, 53% of the public believed that "medical testing on animals" is "morally acceptable" and 41% that it is "morally wrong." In 2006, the percentages were 61% and 32% respectively.

EU: Required harm-benefit analysis

"[T]the project evaluation" must include "a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment"

European Union Directive, 2010/63, Art. 38 para. 2(d)).

UK: Required harm-benefit analysis

The Home Office official who must license an animal research procedure shall "carry out a harm-benefit analysis of the programme of work to assess whether the harm that would be caused to protected animals in terms of suffering, pain and distress is justified by the expected outcome, taking into account ethical considerations and the expected benefit to human beings, animals or the environment."

Animals (Scientific Procedures) Act of 1986, as amended 2013 (ASPA), § 5B(3)(d)).

UK: Welfare and ethics committees

- Each licensed research establishment must "establish and maintain a body (to be known as an 'Animal Welfare and Ethical Review Body')." ASPA, Sched 2C, Part 1, para. 6(1).
- The Home Office directs that AWERBs should, among other things (such as assuring implementation of the 3Rs) "provide a forum for discussion and development of ethical advice to the establishment licence holder on all matters related to animal welfare, care and use at their establishment." *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986,* 2014.

Why regulatory overextension

- In enacting the HREA in 1985, Congress prohibited IACUCs from engaging in ethical review and scientific merit review (including scientific merit review that would be a necessary component of ethical review).
- The HREA directed the Secretary of HHS to promulgate and enforce standards applicable to NIH-funded extramural research to effect the animal welfare aims of the statute.
- The NIH adopted as its primary standard for extramural animal research the *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, which it applied to NIH intramural animal research.

Why regulatory overextension

- The *PHS Policy* included authorization of IACUCs to conduct some scientific review.
- The *PHS Policy* also incorporated the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,* which had been adopted by a number of federal agencies including the NIH to apply to their intramural animal research. And Principle II of the *US Principles* does authorize IACUCs to engage in ethical review.

Why regulatory overextension

- And when the Eighth and current edition of the *Guide* adopted a requirement of ethical review at least in certain circumstances, this requirement was made applicable to NIH-funded extramural animal research because the current *PHS Policy* governing such research requires adherence to the *Guide*.

US Principles, Principle II

"Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society."

U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training , 50 Fed. Reg 1985, 20864.