



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

May 12, 2014

TO: Office of Laboratory Animal Welfare

FROM: Deputy Director for Intramural Research and Intramural Research Program Institutional Official, NIH

SUBJECT: NIH IRP Response to the OD Notice: *Invitation to Comment on Proposed Guidance Regarding Significant Changes to Ongoing Animal Activities*

The NIH Intramural Research Program appreciates the opportunity to provide input on this potential change in guidance from the Office of Laboratory Animal Welfare regarding how our Institutional Animal Care and Use Committees (IACUCs) acknowledge and process significant changes to our Animal Study Proposals. Some aspects of the proposed changes are commendable as they focus on pain, distress, and animal welfare. However, too many of the proposed changes seem unnecessarily prescriptive and ambiguous, and also place constraints on the discretion and authority of the IACUC.

The PHS *Policy on Humane Care and Use of Laboratory Animals (PHS Policy)*, under section IV.C.: "Review of PHS-Conducted or Supported Research Projects", is generally comprehensive and provides sufficient detail to direct IACUC activities in regard to this topic. We believe that the suggested changes to your guidance will diminish the discretion allowed by the IACUC, will hinder the responsiveness of the review/approval process, and will remove needed flexibility and authority from the IACUC. The duly-constituted IACUC is ultimately the best entity to judge the information presented by the investigators and then make appropriate decisions on the disposition of the proposed change to the activity.

The NIH IRP Scientific Directors, IACUC Chairpersons, Animal Research Advisory Committee members, and Animal Program Directors strongly endorse and prefer that OLAW maintain the language presented in PHS Policy and keep this guidance as simple as possible, as we have outlined as the preferred option in our response. Ultimately, if OLAW chooses not to take this approach, the NIH IRP has provided additional suggested changes to address specific concerns identified in the proposed guidance.

Please direct questions or comments regarding the intent or contents of this memorandum to me or to the Director, Office of Animal Care and Use, telephone: 301-496-5424.

A handwritten signature in black ink, appearing to read "Michael M. Gottesman".

Michael M. Gottesman, M.D.

NIH IRP Response to the OD Notice: Invitation to Comment on Proposed Guidance Regarding Significant Changes to Ongoing Animal Activities [5-14-2014]

The NIH Intramural Research Program (IRP) Animal Research Program wishes to commend the Office of Laboratory Animal Welfare on some of the recommended changes, e.g.:

The proposed change from:

“Examples of changes considered to be significant include ... [those] resulting in greater discomfort or in a greater degree of invasiveness” to:

“Significant changes are those ... that have the potential to increase the level of pain or distress of the animal” is valuable.

The definition of a significant change by the potential for reduced animal welfare is extremely important, and should be the basis by which most proposals are judged to be significant changes (with the few exceptions of technical amendments such as change in PI and addition of new animal holding locations to an animal program).

Preamble:

The NIH IRP Animal Research Program is concerned that some of the proposed changes are too prescriptive and specification-based, rather than performance-based. The description of significant changes as provided in the PHS *Policy on Humane Care and Use of Laboratory Animals (PHS Policy)* under section IV.C. “Review of PHS-Conducted or Supported Research Projects” is generally comprehensive and provides sufficient detail to direct IACUC activities in regard to this topic. We perceive that the suggested changes to your guidance will diminish the discretion allowed by the IACUC, will hinder the responsiveness of the review/approval process, and will remove needed flexibility and authority from the IACUC. The IACUC is ultimately the best entity to judge the information presented by the investigators and then make appropriate decisions on the disposition of the proposed change to the activity.

With these concepts in mind, the NIH IRP has formulated the following two options that OLAW should strongly consider as modifications of the proposed guidance changes.

Option A (preferred option):

The NIH IRP finds your current position statement on “[Cost](#)” useful: “Animal welfare and the integrity of research findings ... should be the primary factors in decisions related to assuring compliance with the recommendations in the Guide in PHS-funded research ... OLAW believes compliance can be best accomplished using teamwork, professional judgment, and experience ... OLAW recognizes that there are many ways to achieve humane animal care and use. An institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy as determined by OLAW. In many instances, institutions and IACUCs elect to exceed the standards. This is not required and can add expense to the program. OLAW does not discourage or encourage institutions from exceeding the standards.”

With the OLAW “[Cost](#)” position statement in mind, the NIH IRP endorses and strongly prefers the following simplified language. This language focuses on the PHS *Policy on Humane Care and Use of Laboratory Animals* concerning significant changes:

Significant changes must be approved by one of the valid IACUC approval methods described in the PHS Policy IV.C.2., full committee review or designated member review.

The IACUC has discretion to define what it considers a significant change, or to establish a mechanism for determining significance on a case-by-case basis, while remaining consistent with PHS Policy, Animal Welfare Regulations and the U.S. Government Principles. It is the responsibility of the IACUC to clearly define and communicate to investigators its policy for determining significance.

As stated in PHS Policy IV.C.3. “Review of PHS-Conducted or Supported Research Projects”, at a minimum, the following circumstances warrant review as a significant change:

- *Procedures with animals will avoid or minimize discomfort, distress, and pain to the animals, consistent with sound research design.*
- *Procedures that may cause more than momentary or slight pain or distress to the animals will be performed with appropriate sedation, analgesia, or anesthesia, unless the procedure is justified for scientific reasons in writing by the investigator.*
- *Animals that would otherwise experience severe or chronic pain or distress that cannot be relieved will be painlessly killed at the end of the procedure or, if appropriate, during the procedure.*

- *Personnel conducting procedures on the species being maintained or studied will be appropriately qualified and trained in those procedures.*
- *Methods of euthanasia used will be consistent with the recommendations of the **American Veterinary Medical Association (AVMA) Panel on Euthanasia** (PDF), unless a deviation is justified for scientific reasons in writing by the investigator.¹⁰*

Based on these criteria and the other referenced regulatory standards, significant changes are viewed as those that have or may have a direct impact on animal welfare, human safety or data integrity.

Changes that are not significant may be handled by the IACUC staff without IACUC review and approval. However, the IACUC is to be informed of changes handled by the IACUC staff. This information may be provided after the change has been reviewed and initiated.

Option B:

If OLAW does not accept the above short, simplified version, the NIH IRP supplies the following concerns and specific rectifying modifications:

1. Concern about OLAW's proposed change: The proposed change from: "The IACUC has discretion to establish a mechanism for determining significance on a case-by-case basis" to "The IACUC has discretion to add to the following sections A. and B. or to establish a mechanism for determining significance on a case-by-case basis while remaining consistent with A. and B" is too prescriptive, and contradicts OLAW's definition of FAQ and Notice guidance: '*should be viewed as recommendations in that an institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy*'.

IRP's suggested modification – change the 'new' language to: "The IACUC has discretion to define what it considers a significant change, or to establish a mechanism for determining significance on a case-by-case basis, while remaining consistent with PHS Policy, Animal Welfare Regulations and the U.S. Government Principles."

2. Concern about OLAW's proposed change: "If the investigator chooses to use a single value rather than a range, he or she is required to adhere to that standard" is too restrictive, as scientific research can be unpredictable, and establishing ranges, in some cases, can lead to unintended consequences.

IRP's suggested modification – change the 'new' language to: "If the investigator chooses to use a single value rather than a range, he or she is required to adhere to that standard unless a change in that value results in less pain and/or distress or invasiveness." Furthermore, this specific guidance example would be better placed at the end of the guidance (i.e., after section C).

3. Concern about OLAW's proposed changes that in many instances seem ambiguous or vague, and thus create difficulty and uncertainty for interpretation and implementation. They include:

- a. "Significant changes ... *include all changes that involve* anesthesia, analgesia, sedation, or euthanasia" is problematic, because 'involve' is indefinite. For example, it is difficult to perceive limits on 'involvement' of sedation for defining an amendment proposal as a significant change. Almost all procedures on large NHPs require sedation, thus the proposed guidance might be interpreted to require all that involve sedation must now be handled as significant changes. Moreover, it is not clear that 'all changes' excludes those made for non-experimental, veterinary-care purposes.

IRP's suggested modification – change the 'new' language to: experimental changes in compound class/type or method of anesthesia, analgesia, sedation, or euthanasia.

- b. "Significant changes are those changes ... in frequency, *interval, type, number, or anatomical location* of procedures ...'. The addition of 'interval' seems unnecessary when 'frequency' is provided. The term 'type of procedure' is very vague and has no statutory or regulatory definition. Without definition of 'type of procedure', this addition is confounding. The addition of 'anatomical location' is also confusing. It is not clear how specific an anatomical location is supposed to be identified, nor what kind of change in anatomical location should be considered significant. Perhaps 'route' would be a better term here. The omission of 'duration' in the proposed revisions (from the current FAQ PR #9) is perplexing, and was perhaps unintentional. Clearly some changes in the duration of procedures should be considered significant.

IRP's suggested modification – change the 'new' language to: "changes in duration, frequency, type, number, or

anatomical location/route of procedures” and provide further input for or a definition of ‘type’.

- c. “Significant changes are those changes ... in frequency...type...of *substances delivered to the animal*”. The term ‘type of substance’ is very vague and has no statutory or regulatory definition. Without definition of ‘type of substance’, this addition has potentially enormous transactional costs, as amendments of additional non-injurious substances can be a significant proportion of amendments.

IRP’s suggested modification – change the ‘new’ language to: “changes in compound class/type of experimental substances delivered to the animal”.

- d. The proposed change from “Examples of changes considered to be significant include ... [changes] in the species or in approximate number of animals used” to “Some activities that may not have a direct impact on animal welfare are also significant ... [including changes] in animal numbers or species” is problematic, and appears to conflict with the non-significant change in number (total increase in animal number for animals not regulated by USDA that does not exceed 10% of the number reviewed and approved by the IACUC) cited in C. Notably, PHS Policy IV.D.1.a states “approximate number of animals to be used”.

IRP’s suggested modification – change the ‘new’ language to: “in approximate animal numbers (depending on species and other factors; see Section C, below)”

- e. The proposed change from “Examples of changes considered to be significant include ... [changes] in the objectives of a study” to “Some activities that may not have a direct impact on animal welfare are also significant ... [including changes] in the scope of an approved animal activity” introduces ambiguity. The terms ‘scope’ and ‘activity’ are indefinite. The linked document (NIH Grants Policy Statement Part 2 8.1.2.5.; Terms and Conditions of NIH Grant Awards / Administrative Requirements / Changes in Project and Budget / Prior Approval Requirements / Change in Scope) states: “A change in scope is a change in the direction, aims, objectives, purposes, or type of research training, identified in the approved project”, attributes most of which are specified in the Study Objectives section of an Animal Study Proposal. It is not clear how ‘scope’ applies to an ‘animal activity’. The current guidance is clear and unambiguous.

IRP’s suggested modification – change the ‘new’ language back to: “in the study objectives” versus “scope of an approved animal activity”.

- f. The addition of section C (Changes that are not significant may be handled by the IACUC staff without IACUC review and approval ...) represents unnecessary specification and prescription, and opens the door to confusion in interpretation, as exemplified by the apparent contradiction between section B and section C regarding changes in animal numbers.

The inclusion here of “changes that would result in less discomfort or invasiveness to the animal, except the changes described in section A” is concerning. Changes that would result in less discomfort or invasiveness should be implemented as quickly as possible – to delay so would be negligent of animal welfare and counter to the goals and responsibilities of the IACUC.

Additionally, by omitting the additions of non-injurious substances (regardless whether of the same or similar ‘type’ as substances previously approved), if the non-injurious substances are consistent with Study Objectives (along with the absence of a definition of ‘type of substance’ in section A), would have tremendous consequences on the work necessitated should the proposed guidance revisions be adopted unchanged.

IRP’s Suggested modification – delete these examples, or, if they will be kept make the following changes:

- i. “Change that would result in less pain or distress to the animal, including changes for veterinary care purposes, and which do not impact human safety, animal welfare or data integrity.”
- ii. “Addition of non-injurious members of already-approved compound classes/types of experimental substances delivered to the animal.”