IACUC 101 PLUS
Virtual

PROTOCOL REVIEW

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Objective

Describe the role of the IACUC and the application of PHS and USDA protocol approval criteria in order to both ethically and scientifically justify the use of animals in research.

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ROLE OF THE IACUC

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The IACUC

The responsible advancement of science and medicine depends upon the use of animals in humane and scientifically important research reviewed and approved by IACUCs that work in a facilitated partnership with investigators to ensure the use of animals is justified while operating in an institutional culture that stresses both quality science and animal welfare.

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PROTOCOL REVIEW RECOMMENDATIONS

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IACUC Review Recommendations

- Base IACUC reviews on SOPs, the PHS Policy, the Guide, and USDA regulations, as applicable.
- Practice the concept of reasonable protocol flexibility.
- Ensure IACUC reviews are consistent for each PI and across PIs.
- Engage in constructive dialogue with the PI throughout the review process.

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IACUC Review Recommendations *cont'd*

- Ensure IACUC review letters are succinct, understandable and diplomatic.
- Issue IACUC review letters ASAP.
- Make protocol review a facilitative and educational process for the PI.
- Consider the position and pressures of being a PI.

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IACUC PROTOCOL APPROVAL CRITERIA

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Elements of Protocol Review

- Rationale and purpose of proposed use of animals
- Clear, concise, sequential description of procedures
- Availability of alternatives
- Justification for species and number of animals requested
- Unnecessary duplication
- Unusual housing and husbandry requirements
- Impact of proposed procedures on animal wellbeing
- Appropriate sedation, analgesia, anesthesia
- Surgical procedures
- Post-procedural care
- Description and rationale for selected endpoints
- Criteria for humane intervention
- Euthanasia/ disposition of long-lived species
- Adequacy of training/experience of personnel
- Personnel safety (hazards)
- Experimental & humane endpoints
- Unexpected outcomes
- Physical restraint
- Weigh objectives against welfare concerns
- Multiple survival surgeries
- Food and fluid restriction
- Non-pharmaceutical grade substances
- Avoid or minimize discomfort, distress & pain
- Alternatives (for procedures that cause more then momentary or slight pain or distress (*written narrative*)
- Assurance of no unnecessary duplication
- Procedures that may cause more than momentary or slight pain or distress
- Appropriate pain relief
- Humane euthanasia for animals that experience severe or chronic pain
- Living conditions appropriate for the species
- Medical care available and provided by a qualified veterinarian
- Personnel conducting procedures are appropriately trained/ qualified
- Surgery
- No more than one major operative procedure with recovery
- Methods of euthanasia must adhere to the AWR definition of euthanasia

John Bradfield, DVM, PhD

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SECTION I
Scientific Aims

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IACUC Approval Criteria

- The goal of the research is supported by key background information (published and unpublished).
- The specific aims of the research are clear, and their achievement is judged to be feasible.

PHS Policy IV.D.b.;
The Guide, p. 25;
9 CFR 2.31(e)(2)

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SECTION II
Animal Subjects

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IACUC Approval Criteria

- The specific aims of the research cannot be achieved using non-animal models (*replacement*).
- The required animal subjects:
  - are a scientifically appropriate species and strain
  - possess the required biological characteristics:
    - sex, age, weight
    - health status, genetic background, source
- The selected species is the least sentient that is scientifically suitable

PHS Policy IV.D; USGP III; 9 CFR 2.31(d)(e)(1,2); The Guide, pp. 5, 12, 25-26; NOT-OD-16-006, October 13, 2015

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SECTION III
The Study Design

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The Study Design

The study design constitutes a scientific framework or "roadmap" used to collect and analyze data to achieve the specific aims of the research.

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Question

Should an IACUC evaluate the study design for scientific soundness regardless of whether there was prior peer review?

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GUIDANCE

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PHS Policy

"Procedures with animals will avoid or minimize discomfort, distress, and pain to the animals, consistent with sound research design."

PHS Policy IV. C. 1. a.

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NIH OLAW Guidance

"The PHS Policy and The Guide expect the IACUC to consider whether the research design is sound."

Lab Animal Vol. 49: 29-31, 2020

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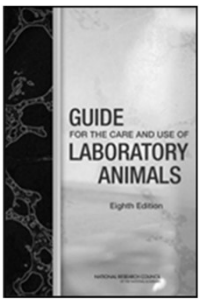
The Guide

"…the IACUC … should evaluate scientific elements of the protocol…. For example, hypothesis testing, sample size, group numbers and adequacy of controls…."

The Guide, p. 26



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AAALAC Guidance

"Scientific rigor and experimental reproducibility directly impact the welfare and number of animals used in research …. The IACUC review should confirm [*based on an initial review by a grants panel or as an assigned responsibility to the committee*] that the protocol contains pertinent study design elements … including randomization, blinding and controls."

AAALAC FAQ on Scientific Reproducibility, 2021

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IACUC Approval Criteria

- The study design incorporates the necessary scientific elements that fit the protocol:
  - a testable hypothesis
  - experimental and control groups are specified
  - statistically/scientifically justified animal numbers per group
  - procedures are concisely and sequentially described, including flow charts as necessary
  - procedures are clearly linked with the specific aims
  - minimization of bias using randomization and blinding
  - appropriate statistical analysis of resultant data leading to valid conclusions

PHS Policy IV.D.1.d.; USGP III; The Guide, pp. 25-27; 9 CFR 2.31(e)(3)

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SECTION IV
Animal Pain, Distress, Discomfort (AEs)

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Painful Procedures

"Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals."

USGP IV

"Any procedure that would reasonably be expected to cause more than slight or momentary pain or distress in a human being to which that procedure is applied…."

9 CFR 1.1

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Distress

"An aversive state in which an animal fails to cope or adjust to various stressors with which it is presented."

The Guide, p. 121

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IACUC Approval Criteria

- The PI has provided a written narrative describing the methods and sources used to determine that no alternatives to procedures that may cause more than momentary or slight pain or distress were scientifically feasible (*AWAR requirement*):
  - Literature database(s) searched (usually at least 2), including the date of search, years covered, and key words
  - Other sources consulted (e.g., named expert)
  - Consideration of reduction, replacement and refinement

9 CFR 2.31(d)(1);
"AWIC" htpp://www.nal.usda.gov/awic

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IACUC Approval Criteria Cont'd

- The PI has provided an explanation why any alternatives described in the relevant peer reviewed scientific literature cannot be used to achieve the specific aims of the research.

PHS Policy IV.D.1;
USGP III, IV; 9 CFR 2.31(d)(1);
The Guide, pp. 5, 12, 25-26

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IACUC Approval Criteria *Cont'd*

- Procedures will be used that have the <u>least amount</u> of potential PDDMM (AEs) in consideration of any justifiable scientific constraints.

PHS Policy IV.D.1;
USGP III, IV; 9 CFR 2.31(d)(1);
The Guide, pp. 5, 12, 25-26

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IACUC Approval Criteria *Cont'd*

- The nature, magnitude, and duration of any anticipated AEs are adequately described *and* consistent with known effects of the procedures applied to the species involved in the research. AEs are:
  - more than momentary or slight pain or distress
  - more than minor discomfort
  - cumulative AEs
  - other
- The assigned USDA pain categories (B, C, D, E), as applicable, fit the protocol.

9 CFR 2.31(d)(IV);
The Guide, pp. 120-121

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IACUC Approval Criteria *Cont'd*

- The regimen to treat anticipated pain, discomfort or distress involves use of appropriate state of the art sedation, analgesics, and anesthesia administered pre-operative, intra-operative and post-operative, as necessary.
- Any withholding of pain-relieving agents or use of neuromuscular blockers is clearly justified for compelling scientific reasons.

PHS Policy IV.C.1.b; USGP IV; The Guide, pp. 26, 121-123; 9 CFR 2.31(d)(1);
Recognition and Alleviation of Pain in Laboratory Animals (NRC 2009a)

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IACUC Approval Criteria *Cont'd*

- The humane endpoint is the earliest possible point at which pain and distress are prevented, terminated or relieved.
- The experiment is designed so that the experimental and humane endpoints are closely linked.
- The species-specific humane endpoint assessment criteria are appropriate.
- The action(s) to be taken upon reaching the humane endpoint is acceptable.

USGP VI; The Guide, pp. 27-28;
9 CFR 2.31(d)(1)(v)

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SECTION V
Post-Procedure Monitoring

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Monitoring

Careful clinically and scientifically based monitoring of animal subjects with timely attention given to any problems should they occur.

The Guide, pp.119-120

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IACUC Approval Criteria

- The monitoring plan, including frequency of evaluation, use of pain scales, assessment of health status, and humane endpoint criteria, is appropriate based upon:
  - The nature of the intervention(s)
  - The species
  - The magnitude of anticipated pain, discomfort, or distress
  - The duration of anticipated pain, discomfort, or distress
  - Possible complications

PHS Policy; 9 CFR 2.33(b)(3)(5); The Guide, pp. 27-28, 119-120

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SECTION VI
Altered Living Conditions

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IACUC Approval Criteria

- Any departure from species-appropriate living conditions, as set forth in The Guide, applicable USDA Regulations, or that are medically necessary, must:
  - Be fully justified
  - Provide animals with as much choice and control over their environment as possible
  - Provide as much environmental enrichment as possible

The Guide, pp. 41-103; PHS Policy IV.C.d; USGP VII; 9 CFR SUB A-F

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SECTION VII
Euthanasia

37

IACUC Approval Criteria

- The method(s) of euthanasia complies with current AVMA Guidelines, based upon:
  - The specific aims of the research
  - The species, size and age of the animal
  - A minimum of pain and distress associated with the method
  - Ability to quickly produce a loss of consciousness
  - Legitimate logistical considerations
  - Safety of personnel
- Deviations from the AVMA Guidelines are scientifically justified
- The method to confirm death is appropriate

PHS Policy IV.C.1.g; 9 CFR 2.31(e)(5);
The Guide, pp. 123-124; AVMA Guidelines 2020

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SECTION VIII
Scientific Merit

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Scientific Merit

Scientific merit can be defined as a scientifically valuable, important, relevant, and beneficial contribution to knowledge about the biology and behavior of living systems derived from research conducted with scientific rigor.

Based on NIH Grants Policy, October 24, 2021

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Question

Should the IACUC evaluate scientific merit of the research regardless of whether there was prior peer review?

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GUIDANCE

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PHS Policy

A description of procedures for "… the conduct of scientifically valuable research …."

PHS Policy IV. D.1.d.

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USGP 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."

USGP II, PHS Policy, p 4

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OPRR-AWD Guidance

"The primary focus of the SRG is scientific merit whereas the primary focus of the IACUC is animal welfare. It is evident, however, that there is… overlap of function between the two bodies… The IACUC is expected to… consider in its review the general scientific relevance of the proposal."

ILAR News 33 (4): 68-70 (1991); USGP II

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NIH Guidance

"The primary role of SRGs is addressing scientific merit while IACUCs focus on evaluating animal welfare … These functions are not mutually exclusive because it is not entirely possible to separate scientific value from animal welfare …."

NOT-OD-22-005, October 18, 2021

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NIH Guidance *Cont'd*

- "… peer review by SRGs is not intended to supersede or substitute for IACUC review and approval …."

NOT-OD-22-005, October 18, 2021

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USDA

"A proposal … must contain … a description of procedures … for the conduct of scientifically valuable research."

9 CFR 2.31(e)(4)

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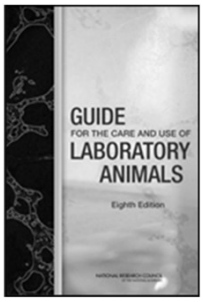
The Guide

"Using animals in research is a *privilege* granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being."

The Guide, p. 4.



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IACUC Approval Criteria

- The research is judged to be scientifically valuable and will *potentially* provide:
  - A significant advancement of knowledge
  - Improvement in human or animal health and well-being
  - A contribution to the good of society

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SECTION IX
Ethical Cost–Benefit Analysis

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Question

Should the IACUC assess whether the potential benefit of the research justifies the ethical cost, regardless of whether there was prior peer review?

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Ethical Cost Benefit Analysis

A *nonempirical* analysis of the ethical cost of the research versus the potential benefits in order to determine if the costs experienced by the animals are justified by the possible benefits.

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Ethical Cost

- PDDM (adverse effects) constitute an ethical cost or "price" which is involuntarily incurred by the animal subjects when there is no prospect of direct benefit to the animals.
- The magnitude of the ethical cost is dependent upon the nature and procedural elements of the research.

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Ethical Cost *Cont'd*

- The ethical cost increases or decreases depending upon:
  - the species involved
  - nature of the research
  - number of animals used
  - amount of animal pain, discomfort or distress
  - the potential value (importance) of the research
- The higher the ethical cost, the greater the need for a higher potential value.
- There are ethically based limits beyond which research should not be approved.

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GUIDANCE

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The Guide - AAALAC

- "…the IACUC is expected to weigh the objectives of the study against potential animal welfare concerns"

The Guide, p. 27

- AAALAC International expects the IACUC (or comparable oversight body), as part of the review process, "will weigh the potential adverse effects of the study against the potential benefits that are likely to accrue as a result of the research … This analysis should be a primary consideration in a review process."

AAALAC FAQs on Harm/Benefit Analysis, 2021

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CIOMS-ICLAS IGP

- "…a system of animal use oversight … should promote a harm-benefit analysis … balancing the benefits derived from research … with the potential pain and/or distress experienced by the animal."

CIOMS-ICLAS IGP X (2012)

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Ethics from the 1990s

- "Because a living creature serves as the experimental model, it is ultimately necessary to justify the use of animals in terms of an ethical cost-benefit assessment."

Prentice ED, Crouse DA, and Mann MD.
Scientific Merit Review: The Role of the IACUC.
ILAR vol 34, 1-2, p. 18, 1992

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IACUC Approval Criteria

- The ethical cost is minimized to the greatest extent possible.
- The research is judged as scientifically valuable.
- There is a *reasonable expectation (possibility/likelihood)* that the resultant data will be of *sufficient* potential benefit related to:
  - improved human health and well-being
  - improved animal health and well-being
  - provision of significant new knowledge
  - contribution to the good of society
- It is reasonable to conclude that the potential benefit (short and/or long term) justifies the ethical cost.

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Path to Success

Your Dedication
⇩
Teamwork
⇩
Animal Welfare
⇩
Progress
⇩
Benefit

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Conclusion

- The use of animals in research is a privilege, not a right.
- Society expects animal use to be justified, humane and ethical.
- Ethical research is characterized by 7Rs:
  - Replacement
  - Reduction
  - Refinement
  - Rigor
  - Reporting
  - Reproducibility

  and Respect

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Addendum
METHODS OF IACUC REVIEW

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Designated Member Review (DMR)

- The protocol is deemed eligible for DMR in accordance with IACUC policy.
- All IACUC members are given (at least) a list of protocols with written descriptions available.
- DMR begins only after all IACUC members have had an *opportunity* to review the protocol and call for FCR.
- At least one qualified IACUC member, without a COI, serves as the designated reviewer (DR).
- The DR is appointed by the IACUC Chair.

PHS Policy IV.C.2; 9 CFR 2.31(d)(2); NOT-OD-035

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DMR *Cont'd*

- IACUC members do not vote in DMR.
- If DMR involves more than one reviewer, consensus must be achieved.
- Possible actions by the DR:
  - Approve the protocol.
  - Require modifications (to secure approval).
  - Refer the protocol to FCR.
- Recognize the need to maintain review consistency across DRs

PHS Policy IV.C.2; 9 CFR 2.31(d)(2)

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Full Committee Review (FCR)

- A convened face-to-face meeting is preferable for complex, invasive protocols.
- Ensure presence of a quorum (*simple majority*).
- Reiterate the review findings for clarity
- Possible actions by the FC:
  - Approval
  - Require modification (*to secure approval*)
  - Withhold approval
- Recognize the need to maintain review consistency across FCR meetings

PHS Policy IV.C.2; 9 CFR 2.31(d)(2)

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Review of a Modified Protocol after Initial FCR

- Re-review at a subsequent FCR meeting
- Re-review by DMR using either of the following methods:
  - IACUC members present at the FCR *unanimously* agree to allow DMR, subsequent to FCR, of the revised protocol, in accordance with an IACUC policy.
  - If all IACUC members are present at the FCR, the committee may require modifications (to secure approval) and have the revised protocol reviewed by DMR.

NOT-OD-09-035, January 8, 2009

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Use of DMR vs. FCR

Consider having a policy specifying research procedures, pain levels and species which require FCR or are eligible for DMR, based upon the anticipated impact of procedures on animal well-being.

DMR	FCR
▪ Non-survival surgery	▪ Major Survival surgery
▪ Tissue collection	▪ Radiation sickness
▪ Antibody production	▪ Tumor inducement
▪ Telemetry	▪ Toxicology
▪ Animal behavior obs.	▪ Infectious disease
▪ ….	▪ ….

Note: The PHS Policy and USDA Regulations do not prescribe research categories which require FCR.

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Significant Changes

"Significant changes include changes that have, or have the potential to have, a negative impact on animal welfare. In addition, some activities that may not have a direct impact on animal welfare…are also considered significant."

NOT-OD-14-126

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IACUC Review of Significant Changes

- Changes per the PHS Policy/AWAR which require review and approval by either DMR or FCR (classic methods)
- Changes which are eligible for administrative handling (AH) in accordance with an IACUC policy
- Changes which are eligible for Veterinary Verification and Consultation (VVC) in accordance with an IACUC policy

NOT-OD-14-126 August 26, 2014
OLAW Guidance on Significant Changes, April 20, 2021

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Classic Methods vs. VVC

Requires FCR or DMR	Eligible for VVC	Eligible for AH
Nonsurvival to survival surgery	Changes in anesthesia, analgesia, sedation, experimental substances	Increase in previously approved number of animals
Increase in pain, distress, or invasiveness	Change in AVMA-approved methods of euthanasia	Change in personnel (other than the PI)
Change in study objectives	Change in duration, frequency, type or number of procedures	Correction of typographical and grammatical errors
Change in Principal Investigator		Contact information updates
Change which impacts personnel safety		
Change in housing or use of animals in a location not overseen by the IACUC		
Change in species		

PHS Policy IV.C.2; NOT-OD-14-126, August 26, 2014

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Why VVC?

- Allows implementation of changes more quickly
- Avoids delays which could compromise research progress
- Reduces PI frustration with the IACUC
- Decreases the workload of the IACUC
- Helps reduce noncompliance

Note: VVC cannot be used to add a new procedure (e.g., blood draw). However, if the blood draw is already an IACUC-approved procedure, the frequency of the blood draws may be increased under VVC.

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The VVC Policy

- Describe the VVC process and procedures
- Specify significant changes eligible for VVC
- Include approved drug formularies which can be used for VVC
- Designate the veterinarian(s) authorized by the IACUC to conduct VVC
  - Knowledgeable and experienced in laboratory animal medicine
  - Understands the IACUC-approved VVC policy
  - Not necessarily the AV or an IACUC member
- Review and approve the VVC policy at least every 3 years

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The Role of the Veterinarian in VVC

- Veterinary Verification
  - Ensure the change does not require FCR or DMR
  - Verify the change is supported by the VVC policy
  - Determine if the change is appropriate under the specific circumstances
    - Species-specific
    - Circumstances-specific
- Veterinary Consultation
  - Recommend revision to the change if within the scope of the policy and is appropriate
  - Document the consultation
- Authority to Defer
  - Defer to FCR or DMR if necessary

NOTE: The veterinarian is not conducting DMR. VVC is a verification process, not an approval process.

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VVC Documentation

- Ensure documentation of changes allowed under VVC are in the protocol file and the IACUC is notified.
- If the change extends to all animals under the protocol, ensure that the protocol is revised accordingly.
- If a change is not eligible for VVC and is referred for FCR or DMR, document the reasons for the referral.

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Administrative Handling (AH) of Animal Number Increases

Increases in animal numbers may be handled administratively without additional consultation or IACUC notification in accordance with the following:

- The IACUC policy designates an authorized individual(s) to perform the administrative handling of the request.
- The IACUC policy specifies allowable increases in the number of animals.
- The original rationale for the number of animals is supportive of the increase in number or a revised rationale is provided.
- The IACUC policy may be written broadly for all species or specifically by species or genus.

NOTE: The use of fewer animals than approved does not require IACUC-approval, notification, consultation, or administrative handling.

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Continuing Review Procedures

- Obtain an up-to-date protocol for review and a Continuing Review Form with a *progress report* that includes:
  - the status of the research
  - unanticipated problems (technical, AEs, mortality)
  - a list of publications and presentations derived from the research
- Consider using DMR for protocols subject to continuing review without animal welfare issues or other problems.

Note on the OLAW Website:
"Model for Performing … Continuing Review",
Contemporary Topics 35(5):53-56, 1996*;*
The Guide, p. 34;

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Continuing Review Deadlines

- PHS Policy: Complete (de novo) re-review of the project *no less* often than once every 3 years.
- USDA: Complete (de novo) re-review of the project *no less* often than once every 3 years.

PHS Policy IV.C.5; 9 CFR 2.31(d)(5);
Amended AWAR, effective 12/27/21, 86 FR 66919 (11/24/21)

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