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How to Write a Protocol the IACUC Will Approve

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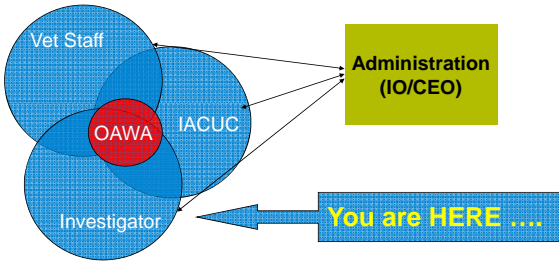
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A Successful Protocol Approval Process Requires You Know Where You Are ... And Where You Need To Go



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Foundation of the Duke Animal Care and Use Program



Vet Staff


OAWA

IACUC


Investigator


Administration (IO/CEO)


You are HERE

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Background References for Protocol Review

USDA - Animal Welfare Act 


OLAW / NIH - PHS Policy 

NRC - Guide for the Care and Use of Laboratory Animals 

ILAR - Occupational Health and Safety in the Care & Use of Research Animals


AVMA - Panel on Euthanasia 


All of these are available on the [Duke animal program web site!](#)

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IACUC Goals for Protocol Review


- ✓ Apply regulations / guidelines / policies consistently
- ✓ Full consideration of animal care and use concerns
- ✓ Appropriate expertise used to evaluate protocols
- ✓ Protocol evaluated objectively



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Protocol Process

Before	After
<ul style="list-style-type: none">• Online training• Health review form• Confirm facilities• Veterinary review• OESO approval• Submit protocol• Address concerns	<ul style="list-style-type: none">• Order animals• Personnel training• Follow protocol• File amendments• Maintain records• Annual review and progress report


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Common Problem
Lacks Contact Information (Section Admin.)

ISSUE: 'After-hours contact information is required.

SOLUTION: A contact person / number must be provided.


- This is ANIMAL emergency, not HUMAN emergency
- Should include 'work' contact number and 'off work' contact
- May (or may not) be Principal Investigator. NEED TO BE SOMEONE WHO WILL RESPOND ON ANIMAL EMERGENCY ISSUES!

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Common Problem
Too Much Scientific Jargon (Section Admin.)

ISSUE: The federal guidance requires 'an informed decision by ALL IACUC members.' Scientific jargon is not always easy to understand.


SOLUTION: Write the protocol in 'newspaper' language. Remember, that the IACUC's community members are intelligent but not usually scientifically oriented.

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Common Problem
Pain/Distress Not Identified (Section Admin.)

ISSUE: Pain / distress must be categorized to assist in oversight and reporting.


SOLUTION: Clearly describe the anticipated pain or distress and assign the numbers of animals to each category.

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Common Problem
Pain/Distress Not Identified (Section Admin.)

CATEGORIES:

- Experiments which involve no pain, distress or use of pain relieving drugs.
Ex: Observations (no handling).
- Experiments which involve momentary or slight pain or distress. Ex: Handling of wild animals, euthanasia w/o research, chemical restraint drugs.
- Experiments involving accompanying pain or distress to animals and which appropriate anesthetic, analgesic, or tranquilizing drugs are used. Ex: If anesthesia is used, then this is a MINIMUM category.
- Experiments involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would adversely affect the procedures, results, or interpretation of the experiments.
Ex: Inflammation studies, no post-operative analgesia


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Common Problem
Missing Justification for Species / Strain (Section IV)

- **Issue:** Federal guidance requires justification of model selection.

– **Bad Example:** 'We require mice because they are cheap and we can breed many in a short period of time.'

– **Good Example:** 'Mice are necessary because we will be able to directly reference a large database of prior work using mice, especially for the development of the tumor types we are studying.'

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Common Problem
Literature Search Not Complete (Section IV)

- **Issue:** Federal guidance requires confirmation that a literature search was performed.

– **Bad Examples:**

- 'The PI is the expert in this area of research'
- 'The laboratory performs routine searches each month.'


– **Good Example:** 'Include the date, of the search <M, D, Y>; the range of the search <1980 – present>; keywords used'

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Common Problem
Poor Justification for No. Animals (Section IV)

- **Issue:** All animals use must be clearly and scientifically justified as necessary to achieve the desired outcome.


- **Bad Example:** 'We can use up to 1000 mice per year for our studies.'
- **Good Example:** 'Experiment 1: Based upon a S/delta 0.67, alpha value of 0.05, and beta value of 0.20, we will need 6 mice per experiment. We must replicate each experiment 3 times for statistical validation and will evaluate 6 time points to assure sufficient data capture. (6 X 3 X 6 = 108 mice for Experiment 1).'

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Common Problem
Poor Justification for No. Animals (Section IV)

- **Issue:** All animals use must be clearly and scientifically justified as necessary to achieve the desired outcome.


- **Bad Example:** 'We need to capture as many animals as we can to assure we have maximized our statistical assurance.'
- **Good Example:** Experiment 2: 'Based on our prior work where we captured 237 animals, a colony expansion of 20% would provide positive evidence of reintroduction of the species. Therefore we are requesting 285 animals for this study. (237 X 0.2 = 285 for Experiment 2)'

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Common Problem
Alternatives Not Considered (Section IV)

- **The 4 'Rs' of Research:**
 - **Replacement** with non-animal models
 - **Reduction** in the numbers of animal used
 - **Refinement** of techniques to eliminate unnecessary pain or distress in animals
 - **Responsibility** of the animals and their care

KEY: Do not overlook reduction / refinement strategies or responsibility of the animal use.

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Reduction / Refinement Strategies

- **Pilot studies:**
 - Determine earliest endpoints where valid data can be collected
 - Investigate scientific validity using less invasive alternatives
- **Pain-relieving drugs:**
 - Sedation, analgesia, or anesthesia
 - Plan developed with consultation of a veterinarian
- **New diagnostic and therapeutic techniques:**
 - Sophisticated imaging equipment to reduce invasiveness of data collection and ease therapeutic monitoring
 - Advanced blood and tissue sampling techniques and processing methods permit easier collection and smaller sample sizes

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Resources for Finding Alternatives

- USDA, Animal Welfare Information Center
 - <http://www.nal.usda.gov/awic/>
- ALTWEB
 - <http://altweb.ihsph.edu>
- University of California, Center for Animal Alternatives
 - http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm


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Common Problem

Environmental Enrichment Not Included (Section V)


- **ISSUE:** All animals must participate in an environment enrichment (E.E) program, or be scientifically exempted from E.E. participation.
- **SOLUTION:** Always include E.E. or provide clear scientific reasons why E.E. is not appropriate.

Note: EE is necessary for ALL species!

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Common Problem
Exemptions Are Not Justified (Section VII)

- **ISSUE:** Include all exceptions to the Guide, and applicable regulations / policies / guidelines.
- Examples of exemptions requiring specific approval:
 - Decreased sanitation frequency (biocontainment, pheromone studies)
 - Increased housing density (breeding colonies, stress studies)
 - Unusual light:dark cycles
 - Single housing of social animals (metabolic cages, infectious disease studies)

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Common Problem
Sedation / Anesthesia / Analgesia Not Clear (Sec. VII)


- **ISSUE:** Procedures that MAY cause pain or distress (if performed in humans) must be performed with appropriate sedation, analgesia, or anesthesia
- **NOT ACCEPTABLE:**
 - ‘Analgesics will (or may) interfere with the study’ is not considered sufficient justification
 - ‘Animals do not appear to show any pain, therefore analgesics are not required’ is not appropriate justification.

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Common Problem
Sedation / Anesthesia / Analgesia Not Clear (Sec. VII)


REMEMBER:

- It is not the IACUC's obligation to prove analgesics will not interfere with the data outcome.
- It is a federal requirement that analgesics be provided unless there are SCIENTIFIC REASONS for not using analgesics.
- Withholding relief must be justified for scientific reasons, in writing, and approved by the IACUC!

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Common Problem
Procedure Detail is Not Sufficient (Sec. VII)


- **ISSUE (Agency Funding):** A funding grant and an animal protocol are parallel but SEPRATE review documents with different purposes and outcomes!!!! Grants = 5 years & funds; Protocol = 3 years and procedures!
- **CRITICAL ISSUES:**
 - All animal procedures described in the grant MUST be described in the protocol. (More procedures can be listed in the protocol that are not in the grant).
 - All animal protocol procedures must describe specific steps.

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Common Problem
Procedure Detail is Not Sufficient (Sec. VII)


- **ISSUE:** Enough detail MUST be provided to allow all IACUC members sufficient information to make an informed decision!
- **SOLUTION:**
 - Details of the procedure (e.g. approach, activity, AND closure)
 - Pre- and post-operative patient care
 - Intra-operative monitoring of patient
 - Aseptic technique (species specific? Or not ...)
 - Qualification of the personnel involved




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Common Problem
Procedure Detail is Not Sufficient (Sec. VII)


- **Bad Procedure Example:** 'Briefly, we will perform a surgery and place a catheter in internal carotid. After a week, the animals will be evaluated'
- **Good Procedure Example:** 'Animals will be held of feed for <r> hours. Water will be provided up until anesthesia. The animals will be anesthetized with <x> at a dose of <y>. The fur will be removed by <z>. Ophthalmic ointment will be placed on the eyes, and initial analgesia will be given using <k>. Skin prep will consist of a 3 cycle scrub using <q> and <r>.'




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Common Problem
Procedure Detail is Not Sufficient (Sec. VII)


- **Bad Procedure Example:** 'Procedure will be performed according to the publication of Smith et al; 1999: 203-209.'
- **Good Procedure Example:** 'The procedures are described as follows:'
 - <description of procedure>
 - <attach ONLY the procedure description from the literature>




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Common Problem
Procedure Detail is Not Sufficient (Sec. VII)


- **Bad Post-op Example:** 'Briefly, we will perform a surgery and place a catheter in internal carotid, then recover the animals. After a week, the animals will be evaluated'
- **Good Post-op Example:** 'The skin will be blotted free of blood and the animal placed over toweling on warming tray monitored to 37 C. Animals will be provided with 3 cc of warmed saline SC during recovery. Sutures will be checked daily and removed by 14 days post procedure'



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Common Problem
Monitoring Plan is Not Sufficient (Sec. VII)

- **ISSUE:** Clear indices and methods to be used to monitor the level of anesthesia and conditions during surgery must be included in the proposal.
- **SOLUTION:** Include ATLEAST 3 parameters to assess condition (Respiratory rate, Reflexes, Heart rate, Capillary refill time, Mucous membrane color, Blood pressure, Body temperature, Oxygen saturation, EKG, Other (list))


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Common Problem
Anesthesia Plan is Not Sufficient (Sec. VII)

• **ISSUE:** Appropriate measures to prevent pain / distress are required. Prior experiences of 'no pain' is not sufficient argument!

Best Practices:

- Everyone receives analgesia
- Pre-emptive use is preferred
- Selected according to procedure invasiveness
- Not based solely on signs of pain (anthropomorphic)
- Choose an effective route of administration

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Common Problem
Humane Endpoints Not Clearly Described (Sec. VII)

• **ISSUE:** Animals must not experience unnecessary pain or distress.

• **SOLUTION:** A detailed (and common sense) plan for use of humane endpoints must be included in the protocol

- Select endpoints as early in the study as possible
- Remove an animal from a study if 'x' occurs
- Treat an animal for pain or distress
- Euthanasia


NOTE: Frequent and appropriate monitoring of animal health is essential to allow for the proper intervention with humane endpoints.

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Common Problem
Humane Endpoints Not Clearly Described (Sec. VII)


• **Bad Example:** 'We will euthanize animals before they experience pain or distress.'

• **Good Example:** 'Animal condition will be monitored daily, and then twice a day during those periods of time where pain or distress might be possible. We will use behavior, feeding behavior, drinking behavior, nesting behavior as indicators of well being.'

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Common Problem
Euthanasia Not Described (Sec. X)


- **ISSUE:** The method used must be consistent with the recommendations of the AVMA Panel on Euthanasia (unless scientific justification for alternative methods of euthanasia is approved by IACUC)
- **SOLUTION:** The choice of a method for euthanasia depends on many factors:
 - Species
 - Age
 - Availability of restraint
 - Skill of the person performing euthanasia
 - Must be consistent with the goals of the research

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Common Problem
Euthanasia Not Described (Sec. X)

- **Bad Example:** 'At the conclusion of the study, animals will be sacrificed.'
- **Good Example:** 'At the conclusion of this experiment, these animals will be euthanized using barbiturate dosed at 250 mg/kg IV.'

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Common Problem
Safety Concerns Not Addressed (Sec. All) 

- **ISSUE:** The protocol does not describe (or provide protections for) the use of materials that are hazardous to the animals and humans involved, giving special attention to the use of:
- **SOLUTION:** Contact OESO during protocol preparation if:
 - Radioactive substances
 - Infectious microorganisms
 - Biological toxins
 - Hazardous chemicals
 - Recombinant DNA

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'Best Practice' Suggestions

1. Review program policies / guidelines on the web site
2. Download the most current protocol template
3. Submit the application AS EARLY AS POSSIBLE!
4. Do not cut and paste the grant into the protocol
(Do send the grant if required by funding agency)
5. Do respond to OESO / EH / OAWA ---- ASAP
6. Email if you have a question
7. Pre-submission review if it is new or complex
(simple is good)

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Questions?

