Pets Used in Clinical Trials: Application of the Animal Welfare Act

Carol Clarke

PRIM&R Session A-11

PRIM&R's
2016 Institutional Animal Care and Use Committee
Conference • Bellevue, WA March 30-April 2

Disclosure: Dr. Carol Clarke

I have no relevant personal or financial relationships with respect to this educational activity

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Learning Objectives

Veterinarian-Client-Patient-Relationship (VCPR)

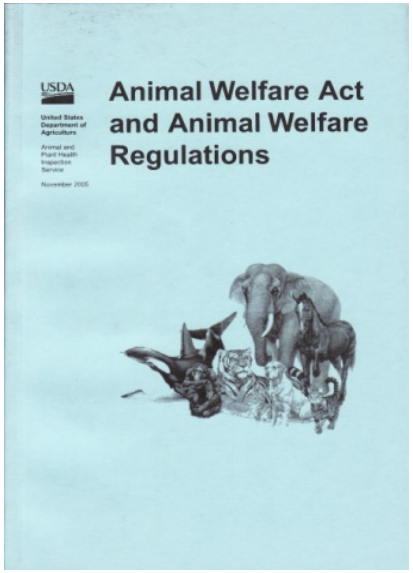
The Animal Welfare Act requirements for animal use in research, testing, and experimentation

The APHIS-Animal Care position regarding use of client owned animals in clinical trials

The Animal Welfare Act (AWA) and Regulations

- The AWA is a law that covers the use of animals in research, testing, teaching, and experimentation.

- The purpose of the Regulations is to describe in greater detail how the USDA should interpret the law



PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Animal

- **AWA § 2132g**: Live or dead, dog, cat, NHP, G. pig, hamster, rabbit used in research, testing, experimentation or exhibition
  - warm blooded animals
- *Excludes*:
  - birds, rats (*Rattus*), mice (*Mus*) bred for research,
  - horses not used for research
  - farm animals used in Ag-research

Veterinarian Client Patient Relationship (VCPR)

AVMA description:

- A VCPR is established only when a veterinarian examines the animal in person, and the relationship is maintained by regular veterinary visits as needed to monitor health.
  - A valid VCPR cannot be established online, via email, or over the phone.
  - A VCPR is no longer valid when it is established but no regular visits occur afterwards.
- A VCPR may be maintained at the vet's discretion between exams via phone or other consultations

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

The USDA's Position

- A pet that receives care pursuant to a valid VCPR and in accordance with a state veterinary practice act is not considered an animal used or intended to be used for research, testing and experimentation
  - Such care includes but is not limited to: routine vaccinations, surgery, and medical treatment
- The collection of data under these circumstances does not make the activity subject to the AWA

The USDA's Position cont.

- **APHIS considers a clinical trial conducted outside of a VCPR to be research, testing, or experimentation i.e.**
  - Administration of a substance for the purpose of research, testing, or experimentation
  - The performance of a procedure or provision of a substance unrelated to improving the animal's well-being
  - The administration of a novel or publically unavailable substance where the beneficial effects are unknown

For AWA Regulated Activities

- Establish an IACUC
  - 3 member minimum: Chair, Veterinarian, Nonaffiliated
- Register the facility with APHIS (except federal)
  - Will undergo Inspections for compliance
- Submit an Annual Report to APHIS.
  - Indicate animals by species, number used, and pain/ distress experienced

Institutional Responsibility

- The Institution conducting or responsible for the clinical trial should:
  - Review each situation on a case-by-case basis to determine whether the activity is AWA regulated

Guidance

- APHIS-Animal Care is available for guidance
  - Fort Collins, CO office 970 494 7478
  - Raleigh, NC office 919 855 7100
  - Riverdale, MD HQ 301 851 3751

Veterinary Clinical Studies Committee

AVMA Policy (*excerpt*):

- "…Animals undergoing standard-of-care treatment within a VCPR that is *not influenced* by their involvement in a *clinical study* may be overseen by **Veterinary Clinical Studies Committees (VCSC**). The VCSC serves to ensure informed consent, and to protect animals from conflict of interest issues.

- When the VCSC determines that the protocol of a clinical research study will influence the management of the animal the VCSC shall refer the proposed work for IACUC review.

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

VSCS cont.

- VCSC should be composed of veterinarians primarily involved in clinical practice, should work closely with the IACUC, and have at least one member who is a member of the IACUC to serve as a conduit between the two entities."
  - *AVMA Council on Research comment:*
    - the people best positioned to determine what is, and what is not, a standard diagnostic (dx) or medical prescription (rx) procedure for a given condition would be veterinarians in clinical practice.

Questions?

Thank you!

Top Noncompliances During USDA Inspections

Dr. Carol Clarke

USDA APHIS-Animal Care

PRIM&R Session B6

PRIM&R's 2016 Institutional Animal Care and Use Committee Conference • Bellevue, WA March 30-April 2

Disclosure: Dr. Carol Clarke

I have no relevant personal or financial relationships with respect to this educational activity

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Learning Objectives

1. Outline the Top 10 noncompliances
2. Discuss the findings on inspections
3. Provide recommendations to achieve compliance

Summary

	Facilities Inspected	Number of Inspections	Total NCI	Direct NCI	Repeat NCI
FY 2015	1296	1350	561	13	56

Data excludes Federal facilities

FY 2015 Top 10 Citations

- IACUC 40%
- Attending Vet /Care 15%
- Miscellaneous 12%
- Sanitation 4%
  - Other species
- Facilities/General 3.5%
  - Other species
- Annual Report 3.4%
- Housing Facilities/General
  - NHP 2.5%
- Housing Facilities/General
  - Dog/Cat 2.3%
- Primary Enclosure
  - NHP 2.0%
- Personnel Qualifications 2.0%
- Sanitation
  - Rabbit 2.0%

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Re-Grouping

- **Top 3 citations**
  - IACUC related
  - Veterinary Care/AV
  - Miscellaneous
- **Annual report**
- **Personnel Qualifications**
- **Housing/Facility/Sanitation/ Enclosure**
  - All species

Top IACUC related NCIs

- Semi-annual Inspection §2.31(c)(2)
- Reports §2.31(c)(3)
- Significant changes to protocol §2.31(c)(7)
- Alternatives §2.31(d)(1)
- Description of activity §2.31(e)(3)

Semiannual Inspection and Report

9 CFR § 2.31

(c)(2)

Inspect, at least once every six months, all of the research facility's animal facilities, including animal study areas…

(c)(3)

- Prepare reports of its evaluations and submit the reports to the Institutional Official of the research facility..

Findings

- No Semiannual inspections performed
- Failure to make a report
- Failure to submit a complete report to IO
  - Failure to distinguish significant deficiencies from minor deficiencies
  - Failure to ensure correction by the date scheduled

The Fix

- Perform inspections and write report
- Verify the report is complete
- Ensure it is submitted to the IO

IACUC: Significant Changes

9 CFR § 2.31(c)(7)

- Review and approve, require modifications to approve, or withhold approval of proposed significant changes regarding the care and use of animals in ongoing activities…

Findings

- Inspectors found no amendment for a significant modification to an on-going activity.
  - Example: Sheep receiving Lutylase but not written in the protocol
  - Examples of Direct NCIs
    - Extra blood collections
    - Additional inoculations.

IACUC: Description of the Activity

9 CFR §2.31(e)(3):

- A proposal to conduct an activity involving animals must contain…A complete description of the proposed use of the animals

Findings

- Inspectors' findings did not support or coincide with what was in the approved protocol
  - Different method of euthanasia
  - Added procedures
    - Example: Spay and neuter not in protocol
  - Changed species

The Fix

Continuous monitoring after approval

- A regulatory requirement

Use an amendment process:

- Full committee or designated member review

  or

- Significant Changes Guidance

  Proposed by NIH-OLAW, accepted by USDA

IACUC: Alternatives

9 CFR 2.31 (d)(1)(ii)

- The PI has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources … used to determine that alternatives were not available;…

Findings

- The search criteria do not correlate to the painful or distressful procedure
- Insufficient information on databases used, search parameters, time frame…
- The search information not in the protocol

The Fix

- Thorough protocol review
  - Pre-review process
- Seek Guidance:
  - Policy 12:Consideration of Alternatives to Painful/ Distressful Procedures
  - Animal Welfare Information Center (AWIC)
    - Offers courses 3X/year https://awic.nal.usda.gov/

Veterinary Care/AV

9 CFR §2.33(a)(1)

- Each research facility shall employ an attending veterinarian under formal arrangements. In the case of a part-time attending veterinarian or consultant arrangements, the formal arrangements shall include a written program of veterinary care and regularly scheduled visits to the research facility;

Findings

- Written Program of Veterinary Care (POVC):
  - Did not exist
  - Not available for review
  - Did not include all of the species

The Fix

- APHIS-Animal Welfare Web
  https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare

  - APHIS Form 7002- Program of Vet Care
  - Policy 3- Veterinary Care
    - Vet visits at least annually, update POVC

Veterinary Care/AV

9 CFR §2.33(b)(2)

- Each research facility shall establish and maintain programs of adequate veterinary care that include…..The use of appropriate methods to prevent, control, diagnose, and treat diseases and injuries, and the availability of emergency, weekend and holiday care

Findings

- Expired drugs
  - Led to a **Direct NCI**: Whole stock was expired
- Overgrown hooves and nails
  - Led to a **Direct NCI** as part of many findings of no oversight
- Not monitoring the progression of weight loss
- No provision for emergency care
- No treatment records
  - Led to a **Direct NCI**: Head tilts, broken legs, and ill animals with no record of vet exam or care

Veterinary Care/ AV

9 CFR §2.33(b)(3)

- Daily observation of all animals to assess their health and well-being…daily observation can be accomplished by someone other than the AV…a mechanism of direct and frequent communication is required…timely and accurate information… is conveyed

Findings

- Failure in communication of the health status of a sick animal in a timely manner to the Attending Veterinarian
  - Examples:
    - No evidence of notification regarding ill animals,
    - No observations of declining status of the animal

The Fix

- Personnel training regarding identification and reporting of sick animals
  - Graph the weight so changes are obvious
- Rounds by the Attending Veterinarian

Miscellaneous

9 CFR §2.38 (b): *Access of records & property*

- During business hours APHIS official allowed to:
  - Enter the business,
  - Examine required records and make copies,
  - Inspect where deemed necessary,
  - Document findings of noncompliance (pictures, other means)

Findings

Fix

- Records not available for inspection
- Person with keys or access not available
- Required documentation not maintained

- Thorough IACUC semi-annual inspections
- Back-up persons
- Education on required documentation

Miscellaneous cont.

- **2.38(f)(1)-Handling**
  - Holding cages too small
  - Broken transport caging
  - Injury due to dropping or improper restraint
  - Escape of NHP due to poor pole/collar method
  - Animal through the cage wash
- **§2.38(g)(1)Identification**
  - Dogs not identified

The Fix

- Proper identification of dogs
- Training on handling
- SOPs on cage inspection before cage wash

Annual Report

9 CFR §2.36

- Each reporting facility shall submit an annual report to the AC Regional Director for the State where the facility is located on or before December 1 of each calendar year. The report shall be signed and certified by the CEO or Institutional Official, and shall cover the previous Federal fiscal year….

Findings

- Not submitted
- Inaccurate reporting of animal locations
- Omission of a species
- Inaccurate animal numbers
- Wrong pain category
  - D animals in C
- Exceptions not documented
  - Changes to feeding and watering

The Fix

Guidance on the Annual Report:

- Inspection Guide- Appendix A
  - https://www.aphis.usda.gov/animal_welfare/downloads/Animal%20Care%20Inspection%20Guide.pdf

- Information provided in the Annual report packets facilities receive

§2.32 Personnel Qualifications

9 CFR §2.32

- (a) It shall be the responsibility of the research facility to ensure that all scientists, research technicians, animal technicians, and other personnel involved in animal care, treatment, and use are qualified to perform their duties …

Findings

- Inadequate training resulted in:
  - No post-op pain med given
  - Improper resting platform set up resulting in injury
  - Poor husbandry practices (long nails)
  - Administrating outdated drugs
  - Poor sexing resulting in unexpected pregnancy with cannibalism
  - Improper use of anesthetic equipment
  - Unfamiliar with disease scoring in protocol

The Fix

- Personnel training:
  - AALAS workshops and wet labs
- Verification of knowledge
  - Tests and other assessments

Facility/Housing/Enclosure

- Small Animal
  - Escapes
    - Ferret- cage improperly closed, death from wedging in between
    - NHP- cage not sturdy, no secondary securing mechanism
  - Exposed wires in caging

- Large Animals:
  - Shelters/enclosures in disrepair
  - Exposed food

Sanitation

- Small Animal
  - Build up of excreta
  - Excessive pests
  - Infrequent sanitation
- Large Animals
  - Dirty treatment areas
  - Pens very soiled
  - Dirt, debris & rust

The Fix

- Know the standards of care for the species
- Thorough semiannual inspections
- Continuous reviews
- Rounds by the Attending Veterinarian

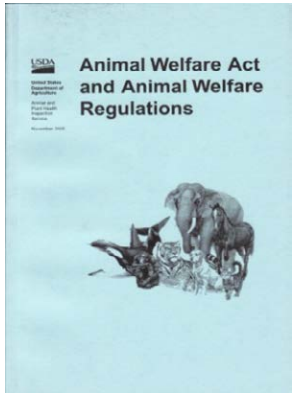
References For Standards

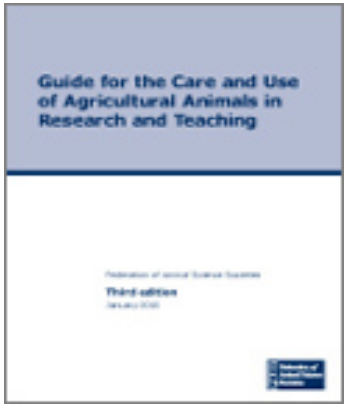
Animal Welfare Act and Regulations

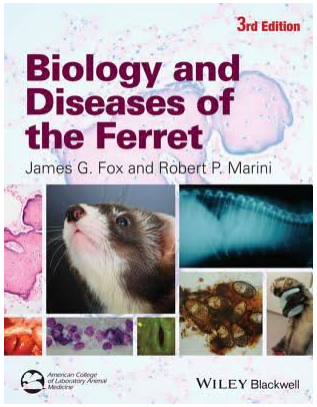
ILAR Guide for the Care & Use of Laboratory Animals

Ag Guide by FASS

Journals and Textbooks







PRIM&R
PUBLIC RESPONSIBILITY IN
MEDICINE AND RESEARCH

Conclusion

- The top 2 noncompliances:
  - IACUC, Veterinary-related
- The top 3rd noncompliance is Miscellaneous
  - lack of access and poor handling
- Noncompliances can be reduced by:
  - training
  - rounds by the attending veterinarian
  - more thorough inspection or continuing review process

Questions?

Thank you!

Client-Owned & CVM-Owned Animals

Helen E. Diggs, MEd, DVM, DACLAM
Laboratory Animal Resources Center
Research Office and
College of Veterinary Medicine
Oregon State University

Te

PRIM&R's 2016 Institutional Animal Care and Use Committee Conference • Bellevue, WA March 30-April 2

Disclosure: Helen E. Diggs

I have no relevant personal/professional/financial relationship(s) with respect to this educational activity

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

OSU College of Veterinary Medicine

- Welcome home!
- A land-sea-space-sun grant university
- Not then AAALAC accredited
- CVM-owned and Client-owned animals fell through the cracks of IACUC oversight
  - ✓ CVM maintained herds for Student Teaching
  - ✓ Client animals for Clinical Studies
    - Examples
    - Oversight was incomplete

Client-owned & CVM-owned Animal Oversight Committee (CAOC)

- Oversees approval of the use of CVM-owned and Client-owned animals in research, testing, teaching, clinical trials
- Smallest Veterinary School in the country
  - Small case load and manageable number of Clinical Trials

CAOC

- Committee: AV (liaison), VTH Director(s), Farm Manager, RVP Herds Clinician, other clinicians as needed.
  - IACUC – AV – CAOC – AV – IACUC
- Approval
  - VTH Herds: 1º purpose is teaching. Only used for studies that cause no more than momentary or slight pain or distress to animals
  - Client Animals: VCPR must exist and Standard of Veterinary Care is expected

Suspension

- If for any reason the IACUC suspends a protocol or the VTH the use of animals, the other must be informed immediately as well as the AV.
- Continued use of the animals is contingent upon the resolution of the situation.

IACUC

- The IACUC is the regulated group ultimately responsible for animal care and use oversight and ethical review.

CAOC Policy

- Also includes information regarding:
  - Client informed consent forms,
  - Funding, resources, space for the study,
  - Acquisition of donated animals for studies,
  - The coordination of the approved study with the VTH Services involved.

Questions?

Thank you!

Issues Confronting Institutions and IACUCs Using and Conducting Clinical Trials in Privately Owned Animals

Elaine Kim, BS, CPIA
Lon Kendall, DVM, PhD, DACLAM
Friday April 1, 2016

Colorado State University

PRIM&R's 2016 Institutional Animal Care and Use Committee Conference • Bellevue, WA March 30-April 2

Disclosure: Elaine Kim

I have no relevant personal/professional/financial relationship(s) with respect to this educational activity

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Learning Objectives:

- What are the applicable regulations to keep in mind? USDA, OLAW, Institutional Policies.
- AVMA and Journal expectations
- CSU: Protocol or not?
- Further discussion points:
  - FDA and Continuing Education
  - Regular Communication with CRB, stakeholders, CRB, and IACUC.
  - Additional administrative burden (CRB and IACUC)

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

FYI: Acronyms

- Colorado State University (CSU)
- Veterinary Teaching Hospital (VTH)
- Clinical Research Review Board OR Clinical Review Board (CRB)
- Food and Drug Administration (FDA)
- Environmental Protection Agency (EPA)
- Investigational New Animal Drug (INAD): Exemption or Waiver
- Quality Assurance (QA)
- Good Laboratory Practices (GLP)
- Good Clinical Practices (GCP): Human vs. Veterinary

Journal Expectations

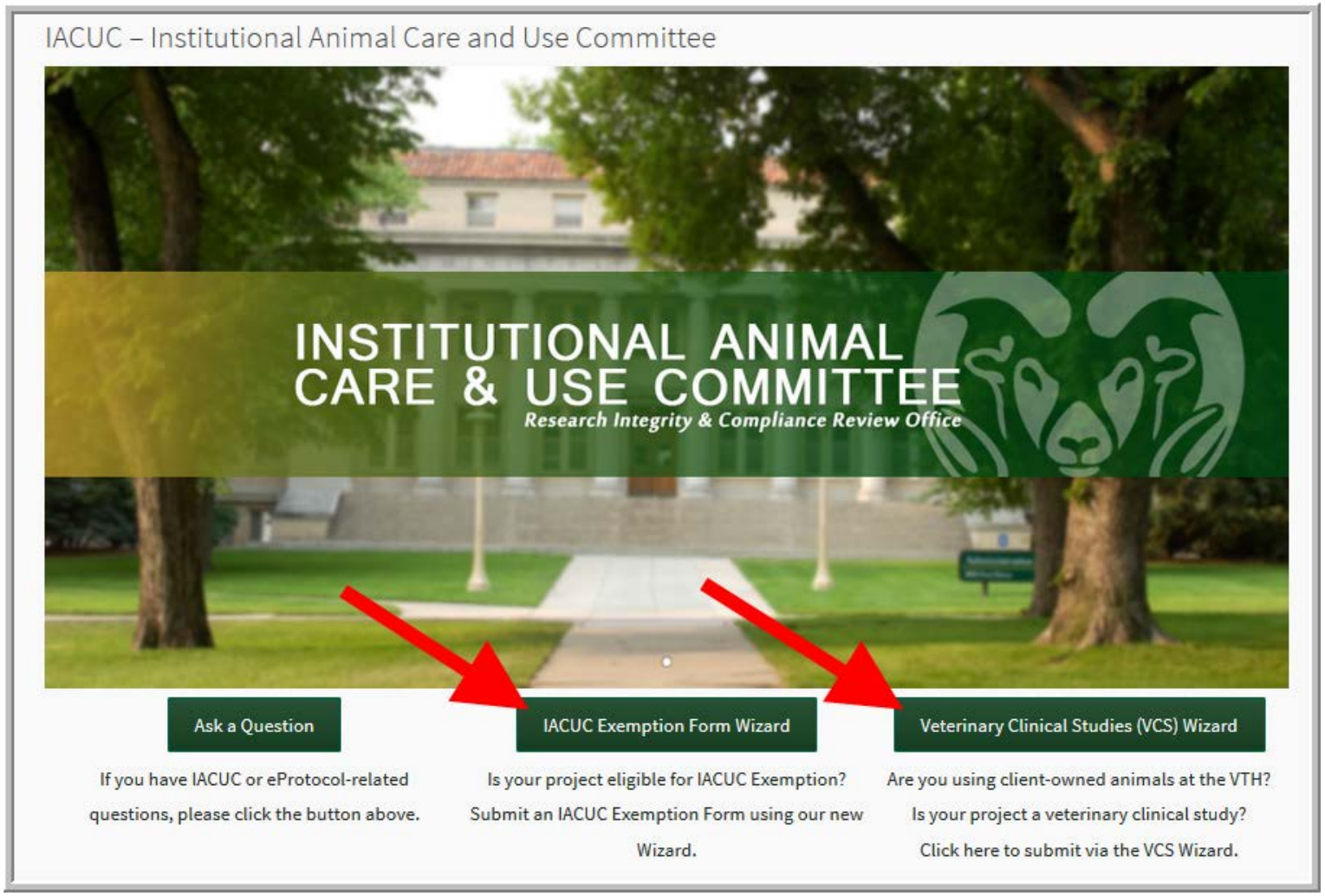
- Journals:
  - JAVMA
    - USDA AWA, PHS Policy, Guide (lab & ag), AVMA Guidelines on Euthanasia
  - AJVR
    - Same as JAVMA
  - JVIM
    - “It is the responsibility of the authors to obtain approval by the appropriate regulatory group…”
    - “The design of the prospective studies involving client-owned animals with spontaneous disease (clinical trials) should be approved by the appropriate regulatory group)…”
  - Veterinary Surgery
    - USDA AWA, PHS Policy, Guide (lab & ag), AVMA Guidelines on Euthanasia
    - Some countries outside of US may have more stringent requirements than the US; others—minimum requirements are US regulations

AVMA Expectations/Policies

- AVMA Policies:
  - Veterinary Clinical Studies Committees (VCSC)
  - Veterinarian-Client-Patient Relationship (VCPR)
  - Comparative Medicine and Translational Research

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

CSU IACUC Website



PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

CSU VCS Wizard Questions

FYI: CRB Review Documents

- Name and employment status (Faculty, Staff, Student, Affiliate, Visiting Scholar)
- Email and Phone #
- Species
- Source of animals
- Reviewed by CRB: Yes/No
- Funding Source
- PHS or NSF-funded: Yes/No
- FDA/EPA question: Yes/No
- If Yes, please indicate regulatory status (GCP, GLP, etc.)
- Who is involved in performing the work—CSU, Non-CSU, Both
- Department or group at CSU
- Are you using biohazardous agents: Yes/No
- If Yes, please provide IBC approval # and/or agent being used. May include but not limited to: infectious agents, recombinant or synthetic nucleic acids, human fluids/cell lines/tissues, generation of transgenic/knockout lines, biological toxins, etc.
- Project Title
- Brief Summary
- Submit → email sent to RICRO Director and Senior IACUC Coordinator

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

The “Wizards”

CSU VCS Wizard: Review

- Reviewed by AV and Senior IACUC Coordinator
  - Clinical treatment, clinical condition/disease, under direction of veterinarian, development of a diagnostic tool to address a clinical condition/disease
  - USDA, OLAW, Institutional Policies
- Memo issued on behalf of the CSU IACUC, assigned a VCS#, and then directed to submit to VTH CRB for client consent form review and approval.
  - PI
  - VTH Director
  - CRB Chair
  - Clinical Sciences Chair
  - IACUC Chair
  - RICRO Director

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

CSU VCS Wizard: Numbers

- 2015: 44 total
  - 6 submissions needed a protocol
  - 38 new VCS#
- Jan-March 2016: 8 so far
  - 6 new VCS#
  - 2 updates from 2015 VCS#
- Turnaround time: Most are 2-3 days, others may take a few weeks. Depends on current workload (AV and myself), project type, etc.
- Total CRB (Jan 2015-Feb 2016) : ~60 studies

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Questions?

Colorado State University

Thank you:
CSU RICRO Staff
CSU VTH

Issues Confronting Institutions & IACUCs Using and Conducting Clinical Trials in Privately Owned Animals

April 1, 2016 – Session (A-11)

PRIM&R's
2016 Institutional Animal Care and Use Committee Conference • Bellevue, WA March 30-April 2

Speaker Disclosure:

I, Venita B. Thornton, DVM, MPH *have no relevant personal/professional/financial relationship(s) with respect to this educational activity*

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Issues Confronting Institutions & IACUCs Using and Conducting Clinical Trials in Privately Owned Animals

Venita B. Thornton, DVM, MPH
CAPT USPHS Commission Corps
Senior Assurance Officer
Office of Laboratory Animal Welfare
National Institutes of Health

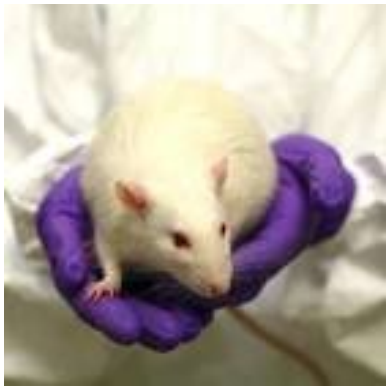
PRIM&R's
2016 Institutional Animal Care and Use Committee
Conference • Bellevue, WA March 30-April 2

Vertebrate Animal Definition

Animal defined as:

"*any live vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes*".

~PHS Policy



PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

Issues Confronting Institutions & IACUCs Using and Conducting Clinical Trials in Privately Owned Animals

- Privately owned animals used in PHS-funded research must be covered on IACUC- approved protocol
- Performance sites must have approved OLAW Animal Welfare Assurance
- Owner's Informed Consent should be obtained prior to start
    - Institution's Legal Counsel involved

Research Activity -or- Veterinary Clinical Care

Research Activities – supported by a grant or contract

- Collection or generation of data – i.e.) Veterinary Clinical trial or Research study

- PHS supported – OLAW Assurance
  IACUC Oversight / Approval

Research Activity -or- Veterinary Clinical Care

Research Activities – (con't)

- Collaboration with private vet clinic/ practice – operational components associated with research covered on Assurance

- Memorandum of Understanding Agreement (MOU)
  - Institution's Legal Counsel involved

Research Activity -or- Veterinary Clinical Care

Research Activities – (con't)

Modification of Assurance for performance site (i.e. private vet clinic / practice)

- Prior Approval on Grant / Contract by Funding Agency
- Processed as needed > Contact OLAW

Research Activity -or- Veterinary Clinical Care

Research Activities – (con't)

- Amendment Request Letter - Assured Institution
  - Institutional Official signs & dates
- Applicability Section of Assurance – Section I.B listing Covered Component(s)
  - For the Purpose of the **designated** Grant / Contract
  - Signature Page of Assurance – Institutional Official signs & dates

Performance site = private vet clinic/ practice = Covered Component

Research Activity -or- Veterinary Clinical Care

Research Activities – (con't)

- Letter of Commitment – Veterinary Clinic
- Veterinary Clinic (i.e. Covered Component) not listed on the OLAW Website as Assured Institution - only in these situations.

Research Activity -or- Veterinary Clinical Care

Veterinary Clinical Care

- Offered as fee-for-service
- Regulated by State Veterinary Licensing Boards
- Not a research activity
- Does not require IACUC approval

Ref: OLAW FAQs- “Applicability of the PHS Policy”- Excerpts

OLAW Web Resources

- **OLAW Webpages:**
  - Significant Changes
  - PHS Policy Tutorial – Good for new members
  - Frequently Asked Questions
  - Topic Index
  - Useful Links – alternatives, ethics, reports, etc.

- **Sample Documents**:
  - Semiannual Facility & Program Review Checklist
  - Semiannual Report to the Institutional Official
  - Animal Study Proposal
  - Animal Welfare Assurances
  - Annual Report

OLAW - Contact Information

- Email: olaw@od.nih.gov
- Phone: 301-496-7163
- Website: http://olaw.nih.gov
- Twitter: @NIH_OLAW
- ListServ or RSS feed: subscribe through OLAW webpage for current announcements, notices, policy interpretations.

Questions?