While contributing to the revisal of the AVMA Policy on Veterinary Clinical Study Committees (VCSCs), issued online in 2022, the authors decided to disseminate explanatory comments expanding on the basic concepts of the policy and to propose a structure and charter for the VCSC to facilitate implementation of the policy. Research studies with institutionally owned animals have traditionally been reviewed by IACUCs, and this remains true for research studies involving laboratory animals, whether owned by an institution, governmental agency, or company. The AVMA policy has intentionally linked the VCSC’s activity to that of the IACUC. These 2 committees are different entities, but we build herein off their similarities because of the scientific community’s familiarity with IACUCs and the opportunity to facilitate and enhance governmental funding of veterinary clinical studies, which are important to both veterinary medicine and comparative research. We therefore also propose to maintain the concept of an institutional official (IO), which for privately funded studies is usually the chief executive officer of the sponsoring entity. Similarly to academic institutions, this is the person who will ensure compliance with laws, regulations, and guidelines governing the use of animals. We hope these recommendations will help ensure a more thorough and consistent review of all veterinary clinical studies, regardless of their purpose, funding source, or the context in which they are being conducted.

Definitions

Investigator: “An individual responsible for all aspects of the conduct of a study at a study site. If a study is conducted by a group of individuals at a study site, the investigator is the leader of the group.”

In this definition, a study site is a veterinary hospital or clinic participating in a given study. The investigator is responsible for enrolling patients and following the study protocol, relevant study standard operating procedures, and applicable regulations, as delineated in the investigator agreement the individual signed with the sponsor.
Sponsor: “An individual, company, institution, or organization that takes responsibility for the initiation, management, and financing of a clinical study for the veterinary product under investigation.”¹ The sponsor or other oversight organization designates an IO with delegated responsibilities and functions comparable to those defined for an IO under the Animal Welfare Act,² under the Public Health Service (PHS) Policy,³ and in the Guide for the Care and Use of Laboratory Animals.⁴ In the case of regulated studies performed with the goal of submitting results of the study to the FDA or other applicable authority, this person is responsible for compliance with all pertinent laws, rules, regulations, and guidelines concerning animal use in veterinary clinical research studies.

Veterinary clinical research studies: Studies, often performed in association with veterinary schools or private practices, that include veterinary patients not owned by a research institution or a contracting company but by individuals and referred to in the rest of this document as client-owned animals, with the goal of advancing veterinary medicine and/or biomedical research. Such studies can be clinical trials or more translational in nature.

Serious adverse event or serious adverse drug experience: An adverse event (AE) “that is fatal, or life-threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement.”⁵

Historical Context

The Animal Welfare Act enacted in 1966 and its regulations, enforced by the USDA, provide standards for the care, treatment, and use of certain categories and species of animals, including institutionally owned animals used in biomedical research.² This law and these regulations do not address or provide specific guidance for veterinary clinical studies with client-owned animals enrolled in veterinary clinical or field research studies.

The Health Research Extension Act of 1985, Public Law 99-158 “Animals in Research” (November 20, 1985),⁶ stipulates requirements for the use of animals in federally funded research and does not differentiate between client-owned animals and other animals involved in studies.

In 1986, the PHS published the Policy on Humane Care and Use of Laboratory Animals, administered by the Office of Laboratory Animal Welfare (OLAW), which requires that each institution receiving PHS, NIH, and now also National Science Foundation or Veterans Administration funds obtain a written OLAW assurance prior to conducting research with animals.³ The policy also requires that the institution’s research program comply with the Guide for the Care and Use of Laboratory Animals and maintain an IACUC for scientific and ethical review of research protocols involving vertebrate species and to provide oversight of the animal care and use program.³Regardless of the type of oversight entity (eg, an animal care and use committee but by individuals and referred to in the rest of this document as client-owned animals, with the goal of advancing veterinary medicine and/or biomedical research. Such studies can be clinical trials or more translational in nature.

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While federally funded animal research including clinical research involving client-owned animals must be reviewed and approved by the institution’s IACUC, guidance regarding collaboration with nonfederally funded research involving client-owned animals is less clear.

The Growing Importance of Comparative Medicine and Translational Sciences

Although cross-species comparative research is not a novel idea, it has been playing an increasingly important role in biomedical research over the past few decades as scientists and regulators recognize the similarities between certain diseases observed in humans and other animals.⁷⁻¹⁵ Moreover, our growing understanding of the critical role of the patient’s environment and immune system on disease etiology, progression, and treatment further highlights the benefits of research involving animals with naturally occurring diseases that, in some instances, have shared the same environment as their owners.

What Is Scientific and Ethical Review, and Why Is it Important?

Scientific and ethical review of research is the process whereby a preselected committee of individuals meeting preestablished qualifications reviews the scientific and ethical soundness of a project or protocol. The qualifications and composition of the board will vary depending on the type of board conducting the review: institutional review board for human clinical studies, IACUC for laboratory animal studies, and VCSC for veterinary clinical studies. The purpose of this review is to verify the scientific integrity of the study and ensure that due regard is given to the welfare and safety of the participating humans, animals and their owners, research staff, and the environment. In addition to providing confidence to the research team(s) conducting the study that their plans meet high scientific, ethical, and quality standards, this step also reassures the scientific community, the general public, and—in the case of client-owned animals—owners and any referring veterinarians that the research is valid, safe, ethically sound, and will answer a valid clinical diagnostic or therapeutic question for which an answer is currently not known.

This review process is also often a prerequisite for publication in peer-reviewed journals. Indeed, many journals require a statement from the authors indicating that the research being submitted for publication was approved by a review committee prior to conducting the study. As an example, the JAVMA Editorial Policies state the following: “With the exception of reports of retrospective studies based solely on historical data, manuscripts describing studies that involved the use of animals, including studies that involved the use of privately owned animals (eg, animals owned by clients, staff members, students, or private entities), must include a statement that the study protocol was reviewed and approved by an appropriate oversight entity (eg, an animal care and
use committee or institutional review board) or was performed in compliance with institutional or other (e.g., governmental or international) guidelines for research on animals.”\textsuperscript{16}

**Current Scientific and Ethical Review Processes and Their Limitations**

Several academic institutions and private companies engaged in animal research still rely on an IACUC for scientific and ethical review of all animal studies, including clinical studies involving client-owned animals. We recognize there could be limitations to this approach for the oversight of client-owned animals, as IACUCs were originally established to assure oversight of animal care and use programs at institutions conducting laboratory animal research with institutionally owned animals. The traditional focus of an IACUC is largely on reviewing the scientific and ethical soundness of research performed using purpose-bred laboratory animals, ensuring appropriate housing and care for these animals, inspecting the facilities, and building the necessary administrative framework for the research program. IACUC review does not traditionally take into account considerations of critical importance that are unique to the conduct of a clinical research study involving client-owned animals including, but not limited to, owner consent, proper use of incentives and/or mitigation of undue inducement, the feasibility of the procedures in a clinical setting, good clinical practice standards, biostatistical considerations as they apply to less uniform populations, and owner or patient compliance with the protocol.

**AVMA Policy Regarding Oversight of Veterinary Clinical Studies**

To address the limitations of traditional IACUC review regarding clinical research studies, the AVMA adopted a policy introducing the concept of formation of an oversight committee analogous to an institutional review board to address gaps in the oversight of studies involving client-owned animals. The current version of that policy (updated 2022\textsuperscript{17}; Supplementary Appendix) identifies additional considerations important to the review and approval of clinical research studies by IACUCs and provides guidance for the establishment and use of a VCSC. The policy states that the purpose for review of veterinary clinical research protocols is to ensure that owners understand both the potential risks and benefits prior to providing their consent for enrollment of their animal in the study, as well as to ensure that owners and their animals are protected from conflicts of interest. It also states that a VCSC should include 1 or more veterinarians primarily involved in clinical practice.

While guidance on IACUC composition, review, approval processes, and responsibilities are well-established, uniform guidance for VCSCs is not readily available and not included in the guidance for IACUCs. Later in this manuscript, we suggest best practices for scientific and ethical review of veterinary clinical research studies, regardless of the specific research setting. Therefore, this resource complements the AVMA policy mentioned above by providing additional recommendations on aspects of VCSCs, including considerations we believe to be necessary for the adequate review and oversight of clinical research studies using client-owned animals by VCSCs and IACUCs.

**The Relationship Between the IACUC and the VCSC**

Oversight of veterinary clinical studies using client-owned animals may reflect 1 of 3 different possibilities for the relationship between IACUCs and VCSCs.

First, there may be situations in which an IACUC exists at an institution but there is no plan to form a VCSC. In that scenario, we recommend that the responsibilities and membership of the IACUC be expanded to ensure qualified and complete review that includes aspects unique to veterinary clinical research. For reviews of veterinary clinical research studies, IACUC membership should include veterinary clinicians capable of assessing the clinical validity and feasibility of the study in the species suggested and evaluating the risk-benefit ratio for an animal that might be enrolled into the study. The review must also incorporate a thorough evaluation of the consent document and process, an element not typically reviewed by IACUCs.

Second, there will be instances in which both a VCSC and an IACUC coexist at an institution. In that case, the AVMA policy on VCSCs\textsuperscript{17} (Supplementary Appendix) lays out a clear path whereby the VCSC should work closely with the IACUC to address any gaps in expertise and oversight as described above, relevant to veterinary clinical studies.

Third, some institutions do not have IACUCs, particularly when they do not have vivariums, conduct any laboratory animal research in-house, or house any laboratory animals. Examples include small biotechnology companies that outsource their laboratory animal research studies to contract research organizations; veterinary private practices that may include interns, residents, and clinicians conducting clinical studies with client-owned animals; and private veterinary clinical research organizations that design and run animal studies using client-owned animals and that may recruit private veterinary practices as study sites. In those settings, we suggest the company create an internal VCSC, or contract with an external VCSC, to review and approve proposed veterinary clinical research studies. To provide appropriate scientific and ethical review and given that federally funded animal research requires written OLAW assurance (based on funding) and oversight by an IACUC,\textsuperscript{2} we suggest, for situations in which an institution does not own or house laboratory animals, that the VCSC incorporate the relevant roles and responsibilities of an IACUC. As such, the VCSC would then meet the requirements set forth by PHS for oversight of the studies and OLAW assurance. This committee, mirroring actions of an IACUC, would provide OLAW...
with information on all performance sites (ie, the collaborating private clinical veterinary practices) and the operational components of these performance sites associated with the research activity to facilitate possible coverage of these components under an OLAW assurance “on a case-by-case basis” (PJRB personal communication [email; 13 October 2021] with an OLAW representative).

VCSC Composition

A committee reviewing veterinary clinical studies on client-owned animals should be capable of the following:

1. Fully assessing the scientific and clinical validity of the study.
2. Evaluating the risk-benefit ratio for patients enrolled in the study.
3. Weighing the value of the study’s potential benefit to animal and/or human health.
4. Verifying that the study meets all applicable regulatory requirements (if any).
5. Determining whether the study’s sample size is adequate and that the study design and end points are appropriate for each given study.
6. Ensuring the research is not unnecessarily duplicative, that alternatives to the use of animals have been considered, pain and distress are minimized or avoided, access to appropriate veterinary care is ensured throughout the study, and that all study personnel are appropriately qualified and trained for their roles.
7. Evaluating the adequacy and completeness of the consent process and consent form to be signed by the animal’s owner.

To achieve this goal, we recommend that a VCSC be composed of the following:
1. At least 1 individual with significant IACUC experience, charged with evaluating compliance with all applicable requirements and regulations pertinent to the use of animals in research.
2. At least 1 scientist responsible for assessing the scientific validity of the proposed study.
3. At least 1 veterinary clinician capable of establishing the clinical and ethical validity as well as the feasibility of the study and its value to veterinary medicine more generally.
4. At least 1 representative of the nonscientific/nonmedical community who can provide a layperson perspective on the research and its value to the community and provide input on the readability of any owner-directed materials, including the consent form.
5. At least 1 individual not affiliated with the organization sponsoring the study or the site conducting the study.
6. As needed, ad hoc members, depending on the specific requirements of a given protocol; examples include board-certified clinical specialists, biostatisticians, bioethicists, scientific content experts, or legal experts.

All members of the committee should be properly trained and qualified to fulfill their specific role, and records of their qualifications should be maintained in the review committee’s records. Committee size and composition may vary, as a single individual may fulfill more than one of the above-described roles and/or multiple individuals may be selected for a given role. A minimum of 5 members is recommended to ensure the potential for a diversity of viewpoints and backgrounds. Complete and accurate administrative records for the committee should be maintained as detailed in the next section.

VCSC Responsibilities

The overall responsibility of the VCSC is to perform a scientific and ethical critique of the proposed project, focusing specifically on the protocol and process of consent. To achieve this, the following key elements must be considered in detail.

The VCSC should first and foremost assess the scientific and clinical validity of the project, because it is unreasonable to expect an accurate assessment of a study’s risk or benefit to the patient, the target population, or society without a thorough understanding of whether the proposed study design, hypothesis, objectives, study population, enrollment criteria, end points, and sample size calculations are valid, reasonable, and pertinent. The committee should also review the applicability of and conformance with any pertinent regulatory requirements and should incorporate assessments of conflict-of-interest concerns, data management processes, and biosafety considerations specific to each study or study team.

Once the scientific validity of the study has been confirmed, the committee must assess the risks and benefits of the study from the perspective of the patient and ensure that an appropriate risk to benefit balance is reached and that proper study stopping rules are in place. Each study-specific procedure should be assessed individually for risk and benefit to the patient, and the protocol should describe clear and feasible mitigation strategies to minimize each risk to the greatest extent possible within the context of the study goals and end points. Overall risk of participation in the study should be inferior to the overall potential benefit to the patient, the target population (eg, canine osteosarcoma patients) in the absence of direct benefit to the patient, or society as a whole. Any higher-risk procedures should be carefully evaluated to ensure no alternate approach is possible and, if not, ensure risks are mitigated to the greatest extent possible and balanced with sufficient benefit to the patient.

The VCSC should next determine whether any incentives for study participation described in the protocol or consent form are appropriate or whether they may be considered undue inducement. Study incentives should motivate participation in the study by balancing out the owner’s effort, time, missed work, travel, or expense associated with their animal participating in the study but should never be so generous as to influence the owner to enroll their animal in a study they otherwise would have declined. It is of critical importance that the committee review the process for obtaining owner consent to enroll in great detail, with special attention to the process itself, as well
as the written consent form. The process of obtaining the owner’s consent is multifaceted and encompasses far more than just a signature on a form. The process should incorporate discussions between the owner or responsible party and the study team and may include individuals not directly involved (e.g., the referring veterinarian or family members). The owner should also be given opportunity to thoroughly review the consent form, which should address alternative treatment options for their animal’s condition, study risks and benefits, a description of circumstances that might require removal of their animal’s enrollment from the study, how and why the owner may remove their animal from enrollment from the study for any reason, the required schedule necessary for their animal’s participation, and that they are encouraged to carefully consider the decision to participate. Ultimately, the dated consent form documents the decision with the owner’s signature as well as the signature of the researcher and, sometimes, a witness. The consent form should be reviewed for its reading comprehension level (sixth to eighth grade level), content, clarity, accurate descriptions of investigational procedures, consistency with the protocol, study risks and benefits, alternative treatment options, and compensation. To ensure standardization of consent form completeness and quality, we recommend that a VCSC prepare a consent form checklist to ensure that each consent form contains all the required elements. As the consent form is reviewed, each element should be checked off the list and, upon completion of the review, the checklist should be signed to document that all elements are present. Any missing elements should be brought to the attention of the sponsor when the research is so funded and addressed before an approval is given. The Clinical and Translational Science Award One Health Alliance and others have developed consent form templates that can be useful starting points for consent form development and review.18 The sponsor or veterinary site might elect to seek legal counsel in this process. Regardless of the template used, it should be modified to align with each protocol and investigational product.

All protocol changes should be reviewed by the VCSC prior to implementation. One exception to this rule should be a modification intended to eliminate an immediate hazard to the health of the enrolled patients. Such emergency changes may be put into effect immediately if the VCSC is subsequently notified of the change and the specific circumstances that led to the change.

The VCSC should also be responsible for reviewing safety events, safety management, and medical monitoring processes to include the identification, management, and reporting of AEs associated with a study. These processes should be described within the protocol, with contact information provided in the consent form to ensure the owner knows how to contact the appropriate individual should a safety event happen after the patient leaves the hospital or facility. Serious AEs (SAEs) should be reported as soon as possible to the VCSC with critical information including the protocol number, study patient identification number, date and duration of the event, a description of the event, whether it was expected or unexpected, category of the event, relationship of the event to the study intervention, treatments given, and steps taken as a result of the event. The form should be signed and dated by the investigator. This form should be accompanied by the study medical director’s evaluation of the SAE considering other safety information and trends observed to date across all participating study sites. Indeed, in multisite studies, the single site investigator may not be aware of all AEs, and an event deemed unrelated to the investigational product by a single site investigator may in fact be related to the product if it is found to be unexpectedly occurring across multiple sites, albeit at different levels of severity or seriousness. The VCSC should review the compiled information provided by the sponsor and assess whether the data reveal any significant trends indicating a need for a study stop, updates to the protocol, or changes to the consent form. A new safety finding that represents a risk to enrolled patients should be communicated by the sponsor to all participating investigators and applicable regulatory bodies immediately.

While others have incorporated a review of infrastructure into VCSC responsibilities, it is our opinion that this responsibility should lie primarily in the hands of the sponsor. Each study site should be carefully selected by the sponsor (or clinical research organization on behalf of the sponsor) considering the investigators’ qualifications, expertise, and experience as well as the site’s capabilities (staff and infrastructure), caseload, and competing studies. Typically, this evaluation is performed during a site qualification visit and then further confirmed during the site initiation visit before the site is activated. Sponsors should continue to verify site performance and qualifications throughout the study by conducting site monitoring visits and maintaining consistent site communications and site oversight.

**VCSC-specific Processes**

For each given VCSC, each member should be appointed to the committee for a predetermined number of years (e.g., 2 years), with renewals possible based on performance. This appointment should be documented and training files maintained on each member. These should include curriculum vitae, documentation of specific research oversight training or reading, relevant experience, and contact information. Committee member training should include, at a minimum, Veterinary International Conference on Harmonization Good Clinical Practice1 training; the Guide for the Care and Use of Laboratory Animals4; the Guide for the Care and Use of Agricultural Animals in Research and Teaching (as appropriate)19; applicable elements from the US Government Principles for the Utilization and Care of Vertebrate Animals in Teaching, Research and Training2; relevant state and federal regulations and guidance; and publications focused on current clinical research bioethics concerns. Based on each member’s role on the committee and as appropriate, additional ongoing training and continuing education requirements may be advisable.

The committee should appoint a chairperson who will be responsible for convening the committee on an as-needed basis, documenting meetings through
the drafting of meeting minutes, communicating with the study sponsor regarding submitted protocols and committee decisions, and maintaining VCSC-related records. Critical committee records include committee composition and member appointment records, contact information and training files, meeting minutes from all meetings and reviews, decision letters, communication with the study sponsor and/or investigators, and other relevant records relating to decisions made by the VCSC.

Each study should undergo review on a regular basis (eg, yearly). If no SAEs have been reported and no changes were made to the protocol, an expedited administrative review should be sufficient. Sponsors or investigators should submit the following for the annual review: enrollment status (cases enrolled per year per site to date), a summary of all protocol and consent form amendments made from the time of initial approval or since last renewal, a list of any changes made to the study team, a summary of all protocol deviations per site per year, a summary report of all safety events (AEs and SAEs) or unexpected problems reported per site per year, and a summary of any other findings that could adversely affect the safety of study patients, impact the conduct of the study, or alter VCSC approval to continue the trial. The VCSC will review the submitted information along with the consent form to determine whether any changes need to be made.

Conclusion

The exercise of the veterinary profession is monitored at a state level. Few if any state veterinary medical boards provide guidance on the performance of clinical trials or translational studies. Creating a structured review process provides our profession with a tool to safeguard our patients and their owners, our colleagues and ourselves, and the public at large. Veterinary clinical studies are an important scientific component in the development and enhancement of treatments for animals and humans. Increasing the numbers of these studies is an important goal to achieve and should be accomplished in keeping with quality standards. The proposed methods expand on the AVMA's Policy for VCSCs and present an avenue to achieve that goal.

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5. New animal drug applications. 21 CFR 514

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org