The importance of comparative medicine and the similarities between diseases in humans and animals are concepts fairly easily understood and accepted by all. Publications in this field aimed at a broad audience are generally well received. The importance of scientific advancement in our own veterinary field is an integral part of our daily activities and is spelled out in the American Veterinary Medical Association’s (AVMA) Veterinarian’s Oath (AVMA Policy 1):

Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge.

I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics.

I accept as a lifelong obligation the continual improvement of my professional knowledge and competence (emphasis added by the authors).

As an extension of these concepts, veterinarians work with their human medical counterparts and others in One Health activities, “the integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment” (One Health Initiative, AVMA Policy 2 One Health).

With these perspectives in mind, it will come as no surprise that the performance of clinical studies or trials directly for the benefit of animals and/or indirectly for the benefit of humans elicit positive, supportive responses, as should be. However, as with similar studies in humans, ethical aspects need to be addressed to protect both the study subjects and their owners and the study directors. In that context, we will review the laws and regulations pertaining to this field as well as some definitions and practical aspects influencing these activities.

The terms clinical trial and clinical study are synonymous (ICH). Clinical trials include participants, whether human or animal, who receive specific therapies according to the research protocol developed by the investigators. Clinical trials may involve comparisons between currently recognized therapies (to determine their relative advantages and disadvantages), between a novel investigational treatment and an existing standard of care treatment, or between an investigational treatment and a placebo control. When a new product or approach is studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention).

The principal purpose of any clinical trial is to provide a conclusive resolution to a clinical problem. Biomedical research, clinical studies, and, ultimately, therapy directed at experimentally induced and spontaneously occurring diseases in animals form the basis for animal models of human and animal disease. Comparative medicine may translate basic science knowledge into applied clinical information (AVMA Policy 3, comparative medicine; see also the link at the University of California at Davis, Veterinary Center for Clinical Trials (UC Davis).

The mission of the AVMA includes the improvement of animal and human health; this is one of the fundamental goals of biomedical research. The AVMA has identified the need for companion animal research: research with specifically targeted deliverables for dogs and cats (with horses and other companion species). There has even been a recent endeavor to create an organization to specifically fund this work: the Institute for Companion Animal and Equine Research (AVMA Policy 4 ICAER). Furthermore, the AVMA supports the notion that veterinary medical research is fundamental and encourages academic institutions to have strong veterinary medical research programs (AVMA Policy 5, vet med research). Additionally, the AVMA supports applying knowledge gained from animals with spontaneously occurring disease to enhance the development of new diagnostic tools, vaccines, and therapies for human beings and animals (AVMA Policy 3, comparative medicine). Although this work would be initiated in the realm of basic science, the

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end products or techniques should be evaluated in clinical trials that will serve to enhance animal and human health and welfare and strengthen biomedical research. Translated medical discoveries, taking research from both animal to human and human to animal, improve the practice of veterinary medicine, enhance the value of veterinary care to patients and clients and are fundamental to the continued advancement of our profession and biomedical research (AVMA Policy 6, research priorities).

**Definition of Animal**

The Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals applies to research funded by the National Institutes of Health (NIH; for a list of PHS agencies, see reference GWU). In those cases, the PHS Policy clearly defines an “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes” (PHSP III.A.). Being alive and being a vertebrate are very objective criteria; PHS policy oversight does not include the use of tissues or carcasses, nor does it include invertebrates. The Health Research Extension Act (HREA 1985) defines “research training” as “instruction or training in the humane practice of animal maintenance and experimentation, and the concept, availability, and use of research or testing methods that limit the use of animals or limit animal distress,” that is made available to scientists, animal technicians, and other personnel involved with animal care, treatment, and use by the institution. “Used or intended for use in research” seems quite clear, if we are to assume that the maintenance of breeding colonies and other activities not technically considered “research” would still include animals that are “intended for research.” There is some subjectivity implied in the “or for related purposes statement,” but this would include maintenance of breeding colonies, antibody production colonies, etc. The source of funding, specifically if the PHS is funding the animal research project, is one of the clear determining factors in PHS policy oversight. The PHS policy drills down on that definition even further by stating that the policy is only “applicable to all PHS-conducted or supported activities involving animals…” (PHSP III.A.). This concept applies to not only laboratory animals housed in vivaria at an institution but also animals studied at remote field sites, if that study is funded by the PHS (OLAW FAQ A.6.), as well as privately owned animals in a clinical study funded by the PHS.

The Office of Laboratory Animal Welfare (OLAW), the NIH office overseeing compliance with the PHS Policy, offers additional clarification for privately owned animals, specifically what should be covered by Institutional Animal Care and Use Committee (IACUC) oversight (NRC 2011) and what is specifically subject to compliance with the PHS Policy (OLAW FAQ A.8.). Each research institution has an IACUC, that is, a committee responsible for oversight and evaluation of the entire program of animal care and use at that institution, including review and approval of proposed animal use protocols, inspection of animal housing and use facilities and areas, ongoing assessment of animal care and use, and establishment of a system for receipt and review of concerns regarding the program. If the study is PHS funded, the institution must have an OLAW-approved Animal Welfare Assurance (an assurance by the institution setting forth its compliance with PHS Policy) covering all performance sites and is subject to compliance with the PHS Policy. Although standardization of institutional practices is encouraged, institutions may define animal areas that are programmatically and functionally separate and that do not support PHS-funded animal activities (OLAW FAQ A.1.).

It is important to note that veterinary clinical care of a privately owned animal (standard of care, provided in a competent and humane manner consistent with current veterinary medical practice in the state) is not a research activity and does not require IACUC approval or compliance with the PHS policy. In this latter case and in accordance with common veterinary practice, a veterinarian-client-patient relationship (VCPR) needs to exist (AVMA VCPR).

The Animal Welfare Act (AWA 2012) and Regulations (CFR Title 9 2013) enforced by the United States Department of Agriculture (USDA) similarly apply to all species covered as stipulated by that department’s secretary. The AWA is not so clear in its definition of animal, in that there may be differing interpretations of some language in the Act and Regulations. As stated in this document, “The term ‘animal’ means any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, as the Secretary may determine is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet; but such term excludes (1) birds, rats of the genus Rattus, and mice of the genus Mus, bred for use in research, (2) horses not used for research purposes, and (3) other farm animals, such as but not limited to livestock or poultry, used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs including those used for hunting, security, or breeding purposes” (AWA 2012).

Some guidance was provided in commentary from the USDA in a case scenario involving research using privately owned animals (Lab Animal 2010). The distinction is made between research activities using tissue obtained from medically justified procedures (standard care) versus those procedures that may be considered “experimental”—specifically, the live animals’ roles in those activities, that is, patient or research subject. Oversight by the USDA may not extend to those animals with a documented VCPR. As part of this relationship, if the animal undergoes procedures that are
medically justified, that is, standard of care, even if the results are used for research purposes (e.g. biopsy sample, blood chemistry values, etc.), the privately owned animals are not subject to USDA oversight. Conversely, if the research project includes procedures that extend beyond the boundaries of standard veterinary care (e.g. an experimental surgery, evaluating the efficacy of a new drug), then the animals would be subject to USDA regulations if a covered species, and IACUC review and approval would be required.

The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International, a private not-for-profit organization that accredits programs of animal care and use) has a straightforward definition of an “animal.” AAALAC International defines “laboratory animals” as any live vertebrate animal (and any other animal designated by applicable legislation) used or intended for use in research, testing, or teaching. AAALAC has had a long-standing policy of following animal ownership as a mechanism for determining inclusion in the accredited animal care and use program. When privately owned animals are brought into a research institution for clinical care, the animals are not owned by the institution, and therefore AAALAC does not consider them as part of the accredited program (AAALAC FAQ C.10.).

Review of Protocols

In the United Kingdom, the Royal College of Veterinary Surgeons (RCVS) and the British Veterinary Association published a report of their joint working party on the Ethical Review for Practice-based Research (RCVS 2013). This report makes a case for including ethical review of as many studies and scientific data acquisitions as possible to prevent potential disputes at a later time, as well as to ensure the public and the profession of the solid moral and ethical basis of the veterinarian’s work. However, surplus tissues collected during standard treatment may be used for research purposes without review or a special license. Veterinary diagnostic or therapeutic interventions for the benefit of the animal when a VCPR exists are exempt from review. In the United States, these latter interventions are veterinary activities regulated by state veterinary medical boards.

The review of studies with privately owned animals in the United States has been the subject of debate, including at the AVMA, who supports a third party review of all research and teaching activities in these cases (AVMA Policy 7, Use of animals in research, testing, and education). The benefit of a review is accepted by all parties, not only for peer review of the study design and the science but also for the legal and ethical protection provided. However, the manner and efficiency in which this review are performed are important factors, because they will influence the strength and quality of the support provided to the researchers. Review of animal research at research facilities, both private and public, is already performed by IACUCs who have the task to apply the existing laws and regulations. Studies with privately owned animals in private clinics or hospitals, similar to those with human patients in private practices, are not regulated unless funded by NIH or other federal agencies; however, publication of the results of that research is subject to acceptance by journal editors who, in most instances, require formal review of the research protocols and documentation of the oversight of the welfare of research subjects.

IACUCs primarily handle the more traditional laboratory animal protocols. Protocols for clinical studies are sufficiently different from these laboratory animal protocols to warrant protocols specifically focused on diagnostic and therapeutic interventions on veterinary patients, such as questionnaires and documentation one would find in veterinary clinics or hospitals. Creating clinical veterinary medical research committees to review these clinical protocols provides an efficient mechanism to critically review and validate the proposed clinical studies and informed consent of the clients. At the same time, these committees can provide a supportive infrastructure to the clinicians performing the studies, including assistance with financial aspects of the research, drafting informed consent letters, Good Clinical Practices documentation and structures when needed, intellectual property protection, patient recruitment, and statistical design and data analysis (e.g. UC Davis Clinical Investigator). It is advisable to include a varied membership in the clinical veterinary medical research committees, perhaps including clinicians experienced with an Institutional Review Board (IRB), client communications, bioethics, and representation from the institution’s general counsel.

It is important, though, to ensure connectivity of the clinical research committee with the IACUC. The IACUC is a legally required committee, and its functions are spelled out in regulations and guidelines. Creating a second independent committee performing essentially the same functions, but in the absence of regulations, could lead to disparate or even opposite conclusions within the same research unit. The links between the two committees can vary, but including clinicians on the IACUC and the attending and laboratory animal veterinarians on the clinical research committee are ways to ensure a holistic approach and an efficient use of resources.

The review process developed at Cornell University in Ithaca, NY is as depicted in the following flowchart with legend (Figure 1):

CVM, College of Veterinary Medicine; CVMRC, Clinical Veterinary Medical Research Committee; PI, principal investigator. Note that funding sources are not taken into account in this flowchart.

At the Ohio State University (OSU), the link between the IACUC and the Clinical Research & Teaching Advisory Committee is similarly accomplished by appointing at least one standing member of the IACUC to the clinical research review committee. The joint appointee is familiar with IACUC procedures and able to advise the local committee on potential concerns that the IACUC may have; s/he is also
able to report back to the IACUC and speak to the integrity of the review process performed by the clinical research committee. A formal agreement (effectively a memorandum of understanding) has been approved, through which the Chair of the IACUC grants the Chair of the Clinical Research & Teaching Advisory Committee the right to recommend a waiver of formal IACUC review for protocols that involve privately owned animals and procedures that are consistent with standard of care for veterinary medicine. Under this arrangement, when approving an “exempt” protocol, the Chair of the local committee forwards a request for a waiver to the IACUC office (OSU VTH process). The IACUC retains absolute authority in requesting additional documentation and, if deemed necessary, the right to decline the waiver request and insist on the submission of an IACUC protocol for review by either designated members or full committee.

At the University of Pennsylvania (UPenn), the Privately-Owned Animal Protocol includes a description of any research that is conducted with the purpose of generating new knowledge and is reviewed by both the IACUC and a Privately-Owned Animal Protocol Review Committee (PRC) in the veterinary school. The description of “standard” animal care is not included in a regular IACUC protocol and is not considered in the IACUC review. The PRC consists of clinicians with IRB experience and expertise in oncology and client communications. In addition to reviewing the animal care associated with the study (including standard care), it also reviews the informed consent form and any materials that will be viewed by the general public. Because many journals require documentation of an institutional review, all UPenn-conducted animal studies and clinical trials that yield data and results that will be presented at meetings, submitted as abstract/posters, or published in a journal are considered research that requires IACUC approval. The fact that a research study involves “no risk” or “low risk” does not exempt it from IACUC and PRC review. Outside of the ethical review by the IACUC and the PRC, the Matthew J. Ryan Veterinary Hospital of UPenn also conducts a hospital impact analysis of any research project involving privately owned animals and focuses on assessing the impact that a study will have on hospital resources to ensure that adequate resources are available or can be made available. Most clinical studies are coordinated through the Veterinary Clinical Investigations Center (UPenn VCIC). Additionally, it is important to remember that if the clinical study involves the collection of information about humans for research purposes (e.g., questionnaires that ask about a person’s household habits, medical conditions, beliefs regarding end-of-life care, etc.), this requires either approval or exemption by the IRB.
Informed Consent

Informed consent is an issue at the forefront of everyday veterinary practice, not just clinical research studies involving privately owned animals (AVMA Policy 8, Owner consent). “Owner consent” should be granted only following the veterinarian explaining the diagnostic and treatment options available, the risks and benefits of such choices, a prognosis, and an estimate of the cost for any service. Such explanations should avoid complex medical jargon and be put in lay terms. Documentation of owner understanding and consent is recommended and may be included in the written medical record. In fact, several states have statutes outlining informed consent, a few of which even require this in writing (Flemming and Scott 2004).

Though many general concepts of biomedical research using privately owned animals are at least similar to research using laboratory animals, one difference is the requirement for informed consent. From a research perspective, the principles of informed consent of owners of animal research subjects have their roots in Ethical Principles and Guidelines for the Protection of Human Subjects of Research (NCPHS 1979). Institutions conducting clinical studies using privately owned animals should consider the general principles of respect for the person (the client/owner has the ability to make informed choices), beneficence (animal subjects should be protected and their well-being secured), and justice (study participants should be included based only on reasons directly related to the problem being studied). Complete and unbiased information must be appropriately communicated to and understood by the owners; client vulnerability should be considered, particularly because they are likely to be desperate to solve the pet’s medical problems (Hampshire 2003).

Owner consent may include consideration of the following topics:

- Emphasis on the fact that participation of one’s pet in a clinical research study is voluntary
- Declination of participation will not result in the loss of benefits the pet would otherwise be entitled to
- Information on other treatment options not directly related to the study
- Discussion with other family members and the primary care veterinarian is encouraged
- Clarifications of any medical terms will be provided by the study veterinarian
- Purpose of the study (e.g. investigating a new device, drug or therapeutic plan)
- Amount of time the pet will be on study
- Number of other pets that may be included may aid in the owner’s decision to enroll if the pet will be one of only a few or one of many other patients
- Description of the test/procedures that the pet may undergo, including the number of times the test may be performed
- Clarification on which tests/procedures are standard care (routine procedures or therapies normally used for the disease being treated and studied) and which are “experimental” (procedures or therapies that are being studied but are not routinely practiced)
- Complete explanation of any risks or discomfort the pet may experience
- Explanation of the possible benefits of the study and a clarification that there may not be any benefit to an individual pet if the experimental therapy is not effective or the pet receives the placebo
- New information discovered (e.g. unexpected side effects) during the course of the study will be relayed to the client, as this information may alter the agreement of consent
- Description of any waiver of costs or the provision of monetary compensation
- How adverse reactions/events will be managed and who will be financially responsible for the management of an adverse event
- Postmortem evaluation may be expected for animals if they die while on study
- The client may withdraw the pet from the study at any time; full financial compensation may or may not be contingent on completion of the study
- Explanation of privacy, for example, who else may see the pet’s clinical and study records.

Because the details of informed consent can be quite subjective (e.g. setting risk stratification, privacy, etc.), institutions are strongly encouraged to involve their legal departments or general counsel when establishing informed consent policies for veterinary clinical trials.

Private Clinical Practices

In the United States, there are no regulations or guidelines that specifically apply to private practices that wish to conduct research. When a VCPR exists, it can be difficult to decide when the treatment is classified as “research” versus “standard of care.” In some instances, the private practice may collaborate with a research institution such as a veterinary college or a contract research organization. These entities can have IACUCs that provide protocol review and oversight functions. If the study is funded by the PHS, per OLAW FAQ A-8: “The institution must have an OLAW-approved Animal Welfare Assurance covering all performance sites and IACUC approval for the research activity. If the study is being conducted in collaboration with a private clinical veterinary practice, the operational components of the practice associated with the research activity should be a covered component of an Assured institution. When doing research on a pet, the institution is responsible for obtaining informed consent for
the research activity. If the research activity is being conducted in collaboration with a private veterinary practice, the institution should consider the use of a memorandum of understanding agreement. The institutional legal counsel may be involved in the development of the document.”

The RCVS considers that “Any collection of clinical data where the intention is to communicate information about the clinical practice may be described as clinical research” (RCVS Report, section 5.1). It further states that “conducting research without an intention to publicise the results more widely is difficult to justify ethically” (RCVS Report, section 5.6). The RCVS recommends ethical review for “clinical research.” They also suggest four methods of providing ethical review (RCVS Report, section 8): (1) collaboration with colleagues in research institutions that already have ethical review committees; (2) purchase of ethical review services from institutions that have ethical review committees and are prepared to provide these services; (3) the establishment, under the auspices of the RCVS, of a national independent body available to practitioners for ethical review of veterinary practice based research; and (4) setting up an ad hoc ethical review process.

These are timely comments, and the concerns and potential solutions are shared by the AVMA as pointed out in their Comparative Medicine and Translational Research section: “Therefore, the AVMA supports applying knowledge gained from animals with spontaneously occurring disease to enhance the development of new diagnostic tools, vaccines, and therapies for human beings and animals. This will require development of a national research infrastructure to support comparative animal research, including enhanced funding sources for domestic animal research, development of domestic animal disease databases, development of consortia to perform clinical trials, and implementation of strategies to increase the number of veterinarians with expertise to support comparative animal research, including enhancement of consortia to perform clinical trials, and implementation of strategies to enhance the development of new diagnostic tools, vaccines, and therapies for human beings and animals. This will require development of a national research infrastructure to support comparative animal research, including enhanced funding sources for domestic animal research, development of domestic animal disease databases, development of consortia to perform clinical trials, and implementation of strategies to increase the number of veterinarians with laboratory animal medicine focus.” (AVMA Policy 3; emphasis by the authors). A practical application of this research infrastructure could include proposals for providing review of clinical studies in private veterinary practices.

**Special Conditions**

**Medical Waste**

Although the use of biologic material that would otherwise be discarded represents a reasonable and logical request, one has to be careful about how the materials are derived. For example, at the authors’ institutions, it has been commonplace to freeze and retain excess serum from samples collected for routine serum chemistry analysis. When retained in a deidentified manner, the use of these waste materials for research should not pose any dilemma, although any data collected from such samples may be of limited value without access to pertinent demographic and/or medical history. The situation becomes more complex, however, when considering prospective rather than retrospective sample collection. If an investigator wants to use 1 mL of serum taken in excess of the clinical requirement, should this be allowable? Our universities’ approach to this has been to ask whether research or clinical practice is driving the collection process. In other words, if the clinical sample does not yield sufficient excess material for a research specimen, will additional sampling be performed to collect the sample for research? In most cases, the answer is yes and, under those circumstances, one would consider this to be a research sample and handle it exactly as one would any other experimental procedure, that is, with IACUC oversight. However, standard of care is likely to evolve, and it is already within reach today to include a blood or tissue sample large enough to also perform genetic analyses and bank a sample for future reference.

**Use of Tissues from Cadavers**

Although there are distinctions between PHS policy, AWA regulations, and AAALAC guidelines regarding the definitions of what represents an “animal” as well as whether oversight extends to both living and dead animals, the common feature in all cases is that the oversight is for animals that are intended for use in research, teaching, or testing. A clear distinction must therefore be made between a tissue sample that may be procured entirely for the purposes of research, and the privately owned animal whose purpose is most likely as a companion animal or production animal. OSU and UPenn have incorporated consent language into the large animal euthanasia and necropsy documentation to permit the collection of research samples from privately owned large animals that are to be euthanized for reasons unrelated to research, teaching, or testing. A similar approach is currently under discussion for small animals. The consent language, fairly broad in terms of the types of specimens that can be collected and the uses to which they can be put, is consistent with that used in the local human cancer hospital. It should be noted that ownership of the tissue and any derivative biologic specimens is transferred to the institution under this consent document. This seemingly insignificant consideration deserves some emphasis, because it allows for the generation, use, and potential sale or transfer of cell lines or other biological material (protein, DNA, etc.) derived from clinical specimens. With increasing interest in the use of allogeneic biologic materials for tissue repair and regeneration, there is great interest in collecting source biologic materials for use as either a cellular source (e.g. bone marrow) or a matrix scaffold (e.g. bone graft, decellularized cartilage). The inclusion of language covering the collection, processing, storage, and use of these materials is therefore recommended for consent documents dealing with the collection of biologic specimens from live or dead animals.
Satellite Practices

Although the complexity of the referral caseload to secondary and tertiary referral centers offers a tremendous opportunity for clinical research and clinical trials activities, there are many situations in which it is helpful for researchers to access cases seen in a primary care setting. A good example of this would be a study on medical management of osteoarthritis in dogs. At referral centers, dogs with osteoarthritis are typically presented for surgical rather than medical management. The ideal population of dogs with moderate to severe osteoarthritis is seen in a primary care setting. Issues that need to be addressed include the need for appropriate ethical review, oversight of the clinical protocol, the use of financial inducements to encourage owner enrollment and reimburse practitioners for lost income, and oversight of employee health and safety issues. One option would be to create a network of approved clinical trial centers, perhaps with inclusion of key practitioners as adjunct clinical faculty. Staff at the centers would receive training from the central institution to ensure that the study procedures are consistent across all of the satellite facilities. Oversight of the research activities would fall to the Clinical Research Committee at the referral center that is coordinating the study. Some contract research organizations have already set up such organized research programs (e.g., VetPharm). The situation becomes more complicated when IACUC oversight is required for a particular study, as this necessitates site visits by the IACUC, something that may not be practical or desirable within a clinical practice in which clinical research represents a tiny percentage of the staff activity.

Survey Instruments

Owner surveys or questionnaires provide a relatively straightforward and very useful approach to deriving qualitative and quantitative data relating to perceptions of treatment outcome and owner satisfaction. When the goal of a telephone inquiry or e-mail is simply to determine how an individual animal is progressing and to determine whether there is a need for ongoing veterinary care, there is no requirement for ethical review. However, if there is any possibility that the information will be presented or published, either on its own or as part of a larger collated series of data, ethical review is recommended. Wherever possible, validated clinical survey tools (or instruments) should be used in clinical practice. If these instruments are not available, the advice of someone with experience and expertise in survey design should be sought. If personal information regarding the owner or family is being sought (e.g., household income), consultation with the IRB may be required to determine the need for additional ethical review. Another way to view this is as follows: If the human is the logical information pathway to the animal subject (i.e. asking directive questions about the animal), then there is no need for IRB review, as this would not be considered research involving human subjects. If the human is being asked her/his opinion about issues related to the animal and not just to report facts on behalf of the animal, then this would generally be interpreted as involving human subjects and thus would require an IRB review.

Use of Healthy Controls for Reference Values

Whenever possible, it is ideal to be able to collect normal reference samples from healthy dogs that are already under an IACUC-approved protocol. However, for truly randomized studies or for studies that look at age- or breed-specific conditions, it is often impractical to make comparisons against data collected from the animals that are typically available within a laboratory animal setting (often young Beagles or Hounds). With appropriate justification, it should be possible to collect samples from appropriate control populations as long as the procedures used for sample collection have been reviewed and approved by both the IACUC and the clinical research committee. The IACUC review focuses on the justification for using animals at all, whereas the clinical research committee review focuses on whether the risks associated with the procedures are appropriate for privately owned animals. For example, short-duration anesthesia is entirely reasonable for a clinical procedure in dogs, but its use in healthy, privately owned animals for the purposes of baseline sample collection may be unreasonable.

Use of a Placebo/Control Group

Although scientifically robust, use of an untreated or placebo-treated control group can be very controversial. For example, withholding chemotherapy in a dog or cat with cancer or withholding analgesics in animals that have undergone surgery is ethically unacceptable unless the study design incorporates measures to allow for rescue of animals that experience pain, distress, or suffering as a consequence of the omission of a clinically effective treatment modality. Whenever possible, it is preferable to compare new treatments against a predicate treatment that already has a history of clinical effectiveness. If this is not possible, the outcome measures selected for the study should be sensitive enough to provide a rapid read-out of clinical effectiveness and safety. For example, it may be feasible to use a pharmacodynamic end point (e.g., serum or intra-tumoral biomarker) to assess a new chemotherapeutic agent or an objective functional test (e.g. force plate analysis, or von Frey algometry) to assess a new analgesic agent.

Evaluation of Novel Devices, Drugs, and Biologics

There is no legal obstacle to a veterinarian prescribing off-label use of a licensed veterinary drug, or use of an unlicensed
drug, device, or biologic, as long as the procedure is performed as part of standard veterinary care. Veterinarians are therefore granted tremendous latitude with regards to treatment options in the clinic, and these accommodations extend into the clinical research arena. In the oncology space, clinical trials on a new chemotherapeutic agent can be performed without IACUC oversight as long as (1) the prescribing veterinarian believes that the new treatment is a reasonable alternative to established therapies, and (2) the treatment and posttreatment follow-up involve procedures that are standard of care for nonstudy participants with the same diagnosis. Two cautionary notes should be sounded, however. First, the prescribing veterinarian needs to consider the background data available on the safety of the drug, device, or biologic. If preclinical toxicology data are available from other species or, even better, from the intended target species, this can be very helpful in supporting the clinical evaluation of a new agent. If data from clinical studies in humans are available, these may lend further support to evaluating the treatment agent. If data from clinical studies in humans are available, this can be very helpful in supporting the clinical evaluation of a new agent. If data from clinical studies in humans are available, these may lend further support to evaluating the treatment in animals. If no preclinical safety data are available, evaluation in clinical patients within a veterinary setting seems premature, and the clinical research committee or IACUC would be justified in asking for these data ahead of approving a clinical study. The second cautionary note relates to the definition of “standard of care” procedures when evaluating new drugs, devices, and biologics. Although many of the procedures that are used in determining biologic safety and efficacy are clinically applicable (e.g. blood collection, tissue biopsy, imaging studies), clinical trial protocols may involve the use of these procedures in a manner that is not consistent with standard of care, that is, both a series and a number of sampling procedures that are similar to those used in clinical patients with the same diagnosis and not enrolled in a study. Collection of a blood sample for complete blood count each week after administration of chemotherapy may therefore be consistent with standard of care, but (repeated) lymph node biopsy for the purposes of evaluating response to therapy will likely fall outside standard of care and require IACUC review.

It is important to differentiate “off-label” use of a drug and the initiation of a clinical trial for a condition using that drug or evaluation of a new drug in the pet population following laboratory research. New drug development generally follows a 3-step sequence: (1) investigating the drug in in vitro or rodent studies, (2) evaluating the drug in research dogs and cats, and (3) performing clinical trials in small or large animal populations. Prior to this final step, the preliminary work in laboratory animals must be summarized for the FDA’s Center for Veterinary Medicine (Hampshire 2003). The Federal Food, Drug and Cosmetic Act requires that investigational new animal drugs or new animal drug applications be approved by the FDA Center for Veterinary Medicine (FDA CVM).

Finally, with the many computerized veterinary management software programs available, private practitioners can now access data to perform retrospective studies on various treatment modalities and outcomes (e.g. feline sarcomas and correlation with vaccine sites). Such information is a valuable resource and should be shared with other practitioners, either by publishing or presenting the information (formally or informally) at continuing education opportunities. Owner and client confidentiality must always be considered.

Recommendations

1. Clinical studies are needed, and those conducting them should receive support in performing them.
2. Institutions offering clinical trials should establish a local clinical research committee (or similar title) to evaluate study design and consent documentation as well as to assist investigators with patient recruitment, data collection, and data handling. The oversight process should be coordinated with the local IACUC to ensure consistency of the review as well as clear demarcation between clinical activities and research activities.
3. Privately owned animals that are recruited for clinical studies (not PHS funded) do not need to be subjected to IACUC oversight as long as their involvement includes only procedures that are consistent with the standard of care provided to patients with the same diagnosis that are not included in the clinical study. Oversight of these studies should fall to the local IACUC. If additional, nonstandard interventions are envisaged, these may require IACUC oversight, and a formal IACUC review should be recommended.
4. If there is ever disagreement within the committee as to whether IACUC oversight is required, the protocol should be submitted for IACUC review.
5. The classification of what represents "an animal" is variable across the various regulatory agencies, and the classification of a covered species can depend on funding source. In the interests of standardization, we recommend that institutions consider any privately owned animal, irrespective of species, in their local oversight process. The source of funding, intramural or extramural, should not influence the oversight of clinical research activities.
6. Consent language should cover planned and potential future use of the research samples that are collected. Whenever possible, we would recommend that institutions request transfer of ownership of all biologic materials (and their derivatives) to the institution to reduce the risk of subsequent legal jeopardy.
7. A two-tiered approach to informed consent might provide the needed freedom to operate; concomitant consent forms could support such an approach. The first tier would inform all clients/owners that during the provision of standard-of-care diagnostic evaluation and treatment at the clinic, excess (i.e. unused, normally discarded) sample
could be used to provide data to further our knowledge of disease processes. The second tier, when applicable, consists of enlisting a patient in a clinical study and requires a full-fledged informed consent form as described above.

8. Clinical trials performed by private practitioners in veterinary clinics and hospitals should get easy access to ethical review, either to confirm none is needed or to provide it efficiently when required. Expansion of the present provision of review through institutional committees needs to be addressed by governmental, national and/or regional professional organizations.

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References


