

Perspective

Perspective J Vet Intern Med 2016;30:527–535

Conduct, Oversight, and Ethical Considerations of Clinical Trials in Companion Animals with Cancer: Report of a Workshop on Best Practice Recommendations

R. Page, P. Baneux, D. Vail, L. Duda, P. Olson, L. Anestidou, N. Dybdal, G. Golab, W. Shelton, M. Salgaller, and C. Hardy

Development of effective and safe treatments for companion animals with cancer requires the collaboration of numerous animal health professionals and the full engagement of animal owners. Establishing 'Best Practice Recommendations' for clinical trials in veterinary oncology represents an important step toward meeting the goal of rigorous clinical trial design and conduct that is required to establish valid evidence. Likewise, optimizing patient welfare and owner education and advocacy is crucial to meet the unique ethical obligations to both owners and animals enrolled in these clinical trials and to ensure trust in the team conducting the research. To date, 'Best Practice Recommendations' for clinical trial conduct have not been reported for veterinary oncology. This document summarizes the consensus of a workshop held in November, 2014 to identify relevant ethical principles and to ensure responsible conduct of clinical research in companion animals with cancer. It is intended as a working document that will be updated as advances in science and ethical considerations require. To the extent possible, existing guidelines for the conduct and oversight of clinical trials in humans have been adapted for veterinary trials to avoid duplicative effort and to facilitate integration of clinical trials such that translational research with benefits for both companion animals and humans are encouraged.

Key words: Ethics; Oncology; Patient welfare; Treatments.

Clinical trials involving companion animals with naturally occurring cancers have been conducted for over 50 years with the intent of improving both animal and human health.^{1–4} The National Cancer Institute (NCI) formally recognized the potential to advance the study of cancer in companion animals by establishing the Comparative Oncology Program (COP) in 2003. The COP has conducted numerous clinical trials through the Comparative Oncology Trials Consortium (COTC) of 20 veterinary academic institutions. In June 2015, the National Cancer Policy Forum of the Institute of Medicine (now National Academy of Medicine) conducted a workshop to determine the current status and future needs of comparative oncology as it relates to the drug

From the Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO (Page, Hardy); Cornell University, Ithaca, NY (Baneux); School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI (Vail); School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA (Duda); Olson Consulting, Animal Health and Welfare, Fort Collins, CO (Olson); Institute for Laboratory Animal Research, National Academy of Sciences, Washington, DC (Anestidou); Genentech, Inc., South San Francisco, CA (Dybdal); American Veterinary Medical Association, Schaumburg, IL (Golab); Virtual Beast Consulting, San Mateo, CA (Shelton); The Conafay Group, Washington, DC (Salgaller).

Corresponding author: R. Page, Flint Animal Cancer Center, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523-1601; e-mail: Rodney.page@colostate.edu.

Submitted September 25, 2015; Revised December 7, 2015; Accepted February 2, 2016.

Copyright © 2016 The Authors. Journal of Veterinary Internal Medicine published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1111/jvim.13916

Abbreviations:

NIH	National Institutes of Health
NCI	National Cancer Institute
COP	Comparative Oncology Program
COTC	Comparative Oncology Trials Consortium
AVMA	American Veterinary Medical Association
IACUC	Institutional Animal Care and Use Committee
CONSORT	Consolidated Standards of Reporting Trials
BSC	best supportive care
RECIST	response evaluation criteria in solid tumors
VCOG-CTCAE	Veterinary Cooperative Oncology Group – Common Terminology Criteria for Adverse Event
GCP	good clinical practice
FDA	Food and Drug Administration
CRO	contract research organization
VCSC	veterinary clinical studies committee
CRB	clinical review board
IRB	Institutional Review Board
ICF	informed consent form
COI	conflict of interest
IOM	Institute of Medicine

development process for humans with cancer.⁵ The workshop helped generate a series of recommendations designed to facilitate and improve cooperation between the fields of human and companion animal clinical oncology.

Standard guidelines for clinical trial conduct are well-established⁶ and periodically revised for human clinical trials.^{7–10} A consensus for similar guidelines for trials in companion animals has not been developed. Although clear and established policy guidelines for the use and care of laboratory animals in research exist, many of these guidelines are limited in their direct applicability to client-owned animals included in clinical trials. The ethical conduct and oversight of clinical research involving client-owned companion animals require the proper

management of concerns and expectations that may differ from both laboratory animal research oversight and clinical trial conduct in humans. To address these issues, it is necessary to consider how clinical trial guidelines initially could be developed, and how they should be reviewed and updated as science and technology progress, the role of companion animals in society evolves, standards of care become better established, and palliative and supportive treatments improve and become more widely available.

A workshop bringing together a diverse group of stakeholders was convened at the American Veterinary Medical Association (AVMA) headquarters in Washington, DC in November 2014 to confirm guiding ethical principles (Table 1) and develop 'Best Practice Recommendations' for clinical trial conduct and oversight in veterinary oncology. Workshop participants included: (1) professionals experienced in conduct and oversight of laboratory animal research from government, academic and industry settings; (2) clinical oncologists with expertise in trial conduct; (3) animal welfare and ethics experts from academia and the AVMA; and (4) consultants in biomedical research. The agenda included development of guiding ethical and operational principles for clinical trial conduct in animal patients and their owners, review of the various clinical trial approval policies and their relative strengths and challenges, the structure and operation of clinical trial programs already in existence for companion animals with cancer and identification of ethical issues at each phase of the process. Particular attention was focused on creating a consensus around the institutional approval for use of companion animals in clinical trials and on the extent to which ethical requirements of informed consent used in clinical trials in humans may be relevant to the owners of companion animals enrolled in veterinary trials. The recommendations described below are not intended to be regulations or mandates; rather, they should be interpreted as a template for implementing

changes that improve clinical trial conduct and oversight.

Study Design – Best Practices and Ethics Recommendations

The integrity and feasibility of all clinical trials should be assured through scientific review of proposals or protocols by a panel of subject experts. Such a review includes assessment of particular features relevant to the research proposal, the team, and environment associated with the proposed research, project design, preliminary data, likely relevance of the anticipated outcomes of the research, and budget appropriateness. This process establishes accountability of the study process in terms of commitment of the time, resources, and effort of all parties engaged in clinical trials. Although the majority of clinical trials undergo formal review, this is not always the case. Commercially sponsored trials, donor-sponsored trials, and hospital-subsidized trials may not receive a scientific peer review separate from an evaluation by the Institutional Animal Care and Use Committee (IACUC), the mandate of which does not always include such scientific merit review. Although IACUC approval currently is mandatory for all research involving animals that are conducted by institutions that receive federal funding, it is primarily designed to protect the welfare of laboratory animals, not privately owned pets.¹¹ The IACUC review process may face challenges in addressing some scientific and ethical concerns that are unique to client-owned animals involved in clinical research. For this type of animal research, particular attention to and critical evaluation of clinical merit are warranted. This evaluation has similarities to that performed by Institutional Review Boards (IRBs) charged with evaluating clinical trials involving humans. In addition, postapproval monitoring and research oversight should be an integral component of all veterinary clinical trials, including standardized clinical endpoint assessments, the need for interim evaluations, accrual targets, and adherence to patient enrollment criteria. A more thorough discussion of postapproval monitoring is included below. A rigorous scientific and ethical review of all veterinary clinical trials is warranted to ensure the validity of the research and protection of animal patient welfare, and to maximize translational potential.

The adoption of innovative trial designs that decrease the number of patients needed for meaningful results should be vigorously encouraged. Conduct of trials so designed is also compatible with the tenets for appropriate use of animals in research: Replace, Reduce, and Refine.¹² Several recent reports describe standard and modified novel trial designs currently used for veterinary clinical studies in companion animals with cancer.^{13–15} Two examples of these include (1) adaptive or Bayesian designs for phase I–III trials in which a dynamic assessment of data is used to continuously update the probability of outcomes such as safety, efficacy, or both, at the same time in order to decrease early phase patient enrollment^{16,17}; and (2) enrichment

Table 1. Guiding ethical principles

Clinical trials must preserve patient well-being and provide for best supportive care, and the relief of pain and other distressing clinical signs.
Before implementation all clinical trials should be peer-reviewed for scientific and therapeutic merit, feasibility, sound design, and absence of redundancy.
The consent process must be honest, thorough, and well-communicated and the pet owner must have adequate time to consider participation without real or perceived coercion or conflict of interest from any member of the investigative team.
Accountability and oversight of research conduct by all those involved (institutional officials, researchers, sponsors, participants) must be maintained. The Office of Research Integrity at the (NIH) describes in detail the elements of responsible conduct of research. ⁴³
Results from all trials should be published to ensure reproducibility and avoid redundancy.
Continued improvement of and education in clinical trial conduct and oversight is critical to both animal health and appropriate translation of collected data to human health.

of the study population to insure the new product will be studied in the correct subset of patients capable of responding appropriately to a specific targeted therapeutic agent and the use of validated biological endpoints that regulate downstream response.¹⁸ The continuous evaluation of innovative trial designs should improve risk:benefit evaluation and result in fewer patients at risk and fewer patients needed to make a 'go/no go' decision to the next level of investigation.

The assessment of goals, risks and cost are critical determinants of an owner's decision to enroll in a study. Table 2 compares the risk-benefit relationship between the human patient and the study team for phase 0 and phase I trials which represent those with the most controversial ethical concerns in the clinical trials continuum. Phase 0 trials are those in which minor procedures are conducted on a patient, and involve minimal clinical impact of either toxicity or efficacy.^{19,20} Such trials may include fine-needle aspirates of a patient's tumor to assess a biological process or target modulation or microdosing of a compound to define prelimi-

nary pharmacokinetics without risk of systemic effects. Phase 0 and phase I trials often are conducted in both human and animal patients with poor to grave prognoses that have already progressed through multiple conventional or investigational treatment regimens or both. In both phase 0 and phase I studies, there may be minimal to no benefit to the patient. As explained further in the section on informed consent recommendations it is important for the clinical trials team to thoroughly understand and clearly articulate the purpose and potential risks and benefits of the study.

In animal patients, other ethical scenarios arise because standards of care do not exist for many cancers in companion animals. As a result, phase 0, phase I, and some phase II trials may be offered early in the treatment course. In addition, even when conventional treatment options are available, these treatments may be delayed while short-term study interventions (such as drug microdosing or tumor sampling) are conducted in exchange for a therapeutic incentive provided by the study sponsor to support subsequent conventional treatment. A potential ethical conflict occurs when an animal is placed at risk, real or perceived, in return for a therapeutic incentive. The owner is placed in a financially vulnerable position when study completion is required before receiving reimbursement for veterinary care.

The conduct of randomized clinical trials with a control group (either a true placebo or a no-treatment group) may be necessary in some situations when there is no known effective conventional treatment for comparison with the investigational product. Such trials may be necessary for evaluation of a new animal health product, but placebo or no-treatment control groups are only needed rarely for animal patient studies focused on, product development for humans, (ie, comparative oncology trials). Trials involving a placebo group should be minimized in patients with cancer and careful evaluation of the risk of tumor progression during placebo treatment period must be considered.²¹⁻²³

All patients enrolled in clinical trials, whether studied with or without a control group, must receive best supportive care. "Best supportive care" (BSC) is defined as treatment focusing on relieving symptoms (eg, pain, inappetence) in order to maintain or improve quality of life, but does not include treatment directed specifically at the cancer. Best supportive care may include analgesics, appetite stimulants, antibiotics, and anti-emetics as needed to maintain or improve quality of life. As an example, a randomized placebo-controlled trial could divide patients into an investigational new treatment plus BSC group versus a placebo treatment plus BSC group. Consequently, because of financial support for enrollment in a clinical study that provides frequent monitoring and BSC management, study participants conceivably could receive improved care regardless of study group assignment. Nonetheless, full disclosure of the trial design, study purpose, and all contingencies must be clearly communicated to the owner.

In addition to providing BSC for all study patients, strict criteria for release from the study or offer of res-

Table 2. Ethical Issues for Phase 0 versus. Phase I trials in human patients.²⁰ Similar issues and concerns seemingly apply to animal patients

	Phase 0	Phase I
Patient Motivation		
Benefit	NA	+/-
Altruism	+	+
QOL/Performance Score	Neutral	Neutral
Risk	Low	14% Gr IV Tox; 0.5% Death
Informed Consent		
Study Goal Recall	No data	<50% understand trial goals
Voluntariness	Low potential for pressure	7-9% feel pressured and potentially vulnerable because of physician status and conflict of interest. Most feel empowered to make their own decisions.
Vulnerability	Not considered a problem because of advanced patient status with appropriate safeguards and minimal invasiveness.	Ph I patients in low socio-economic status categories are considered vulnerable.

Phase 0: Microdosing, target modulation detection with biopsy, biomarkers. Limited drug exposure studies in a late-stage, often terminal, patient. Focus: Patient assists the physician-scientist with their work without personal benefit.

Phase I: Dose escalation trials to determine maximally tolerated dose. Some toxicity and perhaps some benefit may result from study. Focus: Physician-Scientist assists the patient with their medical needs.

cue treatment must be in place if progressive tumor growth occurs or if the patient experiences substantial adverse clinical signs. Recommended criteria exist in veterinary oncology including Response Evaluation Criteria in Solid Tumors (RECIST) measurements, Response Evaluation Criteria for Peripheral Nodal Lymphoma (RECPNL), and the Veterinary Cooperative Oncology Group – Common Terminology Criteria for Adverse Event (VCOG-CTCAE) reporting.^{24–26} It also is recommended that trials incorporate a quality of life scoring system and performance scores throughout the enrollment period and the conduct of the trial to characterize the impact of treatment on these indicators of response.^{27,28} Biomarkers and imaging assessments also provide evidence of cancer progression and such outcomes routinely are included in trials. Cross-over trial designs to the investigational treatment, exit to a distinct therapeutic cohort or management with a non-investigational, conventional treatment option at rescue should be considered in all placebo group trials. Finally, weighted randomization (eg, 2:1 investigational compound:placebo accrual ratio) frequently is used to compare a smaller group of patients in the placebo group to an investigational product group if determined to be acceptable by a formal statistical assessment of outcome expectations.

The selection and evaluation of meaningful and measurable endpoints for each study must be clearly described in the protocol. Biological endpoints often are evaluated to interpret and predict clinical endpoints. For example, pharmacologic measurements, target-drug interactions, and genetic determinants of treatment outcomes frequently are assessed in personalized therapeutic trials. Toxicity endpoints are quantified by the use of VCOG-CTCAE criteria and are standardized for acute adverse event reporting.²⁴ Chronic or delayed toxicity may be subject to reporting bias if follow-up is not consistent or timed appropriately.

Reporting bias of efficacy endpoints can occur from imprecise or incomplete collection of clinical data or from interindividual interpretation variability in endpoints such as pathologic assessments or imaging interpretation. Efficacy endpoint evaluations after a clinical study should be conducted on a defined schedule (eg, thoracic radiographs every 2 months) and any variance from this schedule should be reported. Otherwise, the progression-free interval may be subject to significant error as tumor progression or metastasis may be only intermittently evaluated creating a large margin of error. The interpretation of imaging data or pathologic samples also is subject to variability, and adjudication procedures should be described and followed in the protocol. Multiple, independent reviews of clinical endpoint assessments by qualified specialists should be considered best practice for clinical trials.^{29,30}

Overall survival is a relatively poor efficacy endpoint because of multiple, potentially competing, and confounding issues. Owner acceptance of palliative or hospice care of their pets is variable, multiple interventions that are challenging to account for may be attempted to achieve responses after tumor progression and censoring

rules for death may not be accurately interpreted. In addition, euthanasia is a well-known confounder for determination of overall survival in animal patients enrolled in clinical trials.³¹ Elective euthanasia, when a patient in a self-supportive, clinically stable status is euthanized at the owner's request, must be considered carefully when examining outcome data from clinical trials. Euthanasia because of imminent death is less problematic from a data-reporting perspective. Reporting of overall survival should be carefully interpreted and thoroughly explained. Complete financial support for necropsy procedures, cremation, and return of animal remains may minimize concerns about endpoint misinterpretation and optimize owner participation.

When clinical trials are conducted for purposes of registration of results for approval of a new therapeutic entity with the Center for Veterinary Medicine of the Federal Drug Administration (FDA), a separate standard of oversight and documentation are required. Multiple data recorders and monitors, data audit requirements, sample custody issues, and secondary biorepository sites to insure sample security are some of the additional responsibilities. The specific requirements and execution for these trials often are managed by professional contract research organizations (CRO).

Clinical Trial Approval Policies – Best Practice Recommendations

A recent review assessed the coordination of the approval of clinical trials in companion animals between the institutional IACUC committee and an advisory committee that is comprised of veterinary clinical specialists.³² Several institutions have adopted the model of a clinical review board (CRB) to evaluate the merit, feasibility, and compliance with ethical standards for clinical trials in client-owned animals. These boards or committees may be granted the ability to recommend a waiver of full review from the IACUC when appropriate. The IACUC may support the review from the clinical review board or choose to implement a full review. The AVMA also has recently addressed clinical trial management and approved a policy entitled "Establishment and Use of Veterinary Clinical Studies Committees".³³ According to this policy, the VCSC would evaluate clinical research that conforms to general standards of care but requires additional bio-materials that would be in excess of residual portions of samples taken only for routine health screening under a client-veterinarian relationship. Similar to the function of the CRB, the VCSC serves to ensure informed consent and to protect animals from conflict of interest issues. The AVMA recommends that when the VCSC determines that the protocol of a clinical research study will influence the management of the animal patient, the veterinary clinical studies committee should refer the proposed work for IACUC review.

Broad representation of clinical expertise is needed for a clinical review board and should include at least 1 member of the IACUC committee as a liaison for communication and clarification. Someone with expertise in

animal welfare should be included on the IACUC, CRB, or both. Currently, expertise in veterinary clinical research ethics is frequently not available, but expanding this resource is desirable. Specific training for CRB members has not been established but should be developed in the future. Resources developed to aid clinical IRB members for trials involving humans to evaluate the scientific merit of a study, Informed Consent Forms (ICFs), and the consenting process can be readily adapted for veterinary clinical trials.³⁴

The usual responsibilities of the VCSC or CRB include consideration of study merit, study feasibility, and the informed consent process. A review of the clinical study design by a peer group is particularly useful for those trials that have not undergone a formal scientific review. Complex trials may require an expert ad hoc assessment by those best qualified to evaluate the project. The CRB may request review by such ad hoc experts. The CRB also may be tasked with other responsibilities such as evaluation of conflict of interest, coordination of postapproval monitoring and insuring adverse event reporting for all study participants. Adequate resources are required to accomplish all of these responsibilities. Administrative support, educational support for the members of the CRB and clinical investigators, and data capture management systems are recommended as best practices.

Several specific considerations for veterinary cancer clinical trials involving new drugs and devices have been emphasized.³² For example, careful consideration of preliminary data on toxicity in the target animal species is critical before to initiating a clinical study. Insufficient information about product safety may result in failure of the clinical trial to be approved under the full review and oversight of the IACUC.

Oversight of the clinical trial approval process in nonacademic or private veterinary practices also must be addressed and should evolve as such facilities are asked to participate in multisite clinical studies. Several issues that may be of concern include oversight of animal welfare assurance and sufficient training for veterinarians and staff. Several models for conducting research at nonacademic institutions may be considered. If a study is being conducted under the assurance of an institution with a formal IACUC, that institution is responsible for completion of all requirements for compliance such as the informed consent process and its documentation, communication of adverse events with all other sites involved, and postapproval monitoring procedures. Another option is to contract with a professional IACUC associated with a contract research organization (CRO) that is charged with ensuring that similar responsibilities are met at the nonacademic site.

Consenting Process – Best Practices And Ethics Recommendations

Informed consent provides the ethical assurance of patient welfare, owner understanding, and study compliance throughout clinical research. The optimal process of informed consent for humans enrolling in

clinical trials has been challenging to achieve effectively. Guidelines have been continually revised.^{35–38} The guiding principle stated in Table 1 [*The consent process must be honest, thorough, well-communicated, and the owner must have adequate time to consider participation without real or perceived coercion*] fulfills the intention of the informed consent process from the owner's perspective and should drive communications relevant to enrollment of an animal patient in clinical oncology trials. Recently, the National Cancer Institute (NCI) reviewed and simplified its standard informed consent document for human patients in order to ensure better comprehension, and we recommend that veterinary cancer clinical trials adopt a similar template.³⁹

Full disclosure of the study purpose, associated risks and benefits, study design and interventions required, funding source for the study, incentives to the owner, and conflict of interest (COI) statements from the study staff and investigators are required elements to address during the consent process. The recommended best practice for the consenting process is that it be managed by a neutral individual (nurse, nonsponsor supported veterinarian) with a witness present. Examples of the intended purpose of a study include whether the study seeks to improve clinical signs associated with cancer or its treatment, if a study represents a safety or efficacy study and whether the study is intended to ultimately benefit animal health, human health, or both. Animal patients participating in clinical trials without an efficacy intent must receive extraordinary protection. All potential scenarios of risk should be explained, particularly for phase I trials that are designed to identify a "safe" or "maximally tolerated dose" when direct patient benefit may not be achieved. The source of funding for each study should be disclosed because it often indicates whether or not any potential COI exists.^{40–42} Conflict of interest concerns should be disclosed and, if necessary, managed in a manner consistent with the Office of Research Integrity guidelines from the Department of Health and Human Services.⁴³

All financial subsidies or incentives should be carefully and fully described. A description of what is not subsidized is equally important. As mentioned previously, a standard of care does not formally exist in veterinary oncology for many types of cancer. Therefore, the enrollment of animal patients, when conventional treatment offers little likelihood of response or success, requires very careful discussion regarding study goals and expectations. Even more critical is the communication with pet owners who may be unable to afford an effective, conventional treatment option, and are inclined to enroll their pets into a preliminary clinical trial to receive a subsidy for the conventional treatment. The ethical issues of considering the enrollment of animal patients into clinical trials under these circumstances should be clearly understood by the study team and discussed honestly with the owner.

A primary advocate for the owner of an animal patient being considered for enrollment into a clinical trial should be identified. Currently, the principal investigator or member of the clinical team such as the study

coordinator or study nurse often is considered the primary advocate if no conflict of interest exists in the study (or if it is disclosed and managed). Careful oversight of whether study personnel are in a position of conflict is vital to the trust required of owners to enroll their pets in clinical trials. In addition, there should be a *de facto* advocate assigned whom the owner can contact if he or she does not feel comfortable communicating concerns with the PI. For example, a designated ombudsman, counselor, or a clinical trial hotline for anonymous communication could be made available. The primary care or referring specialist veterinarian also may serve as a patient advocate. A copy of the informed consent document should be provided for review and consultation with the owner and the identified patient advocate. If needed, independent psychological, social, and grief counseling support should be identified and utilized for discussions related to clinical study advocacy during the consenting process.

The informed consent document should describe the aspects of the study in simple, concise, and easy-to-understand language. An evaluation of the quality of patient comprehension after a standard informed consent process identified several features that were statistically associated with high patient recall of study goals and requirements.⁴⁴ These include the use of the NCI template, the extent of the patient's education, high English language proficiency, and involvement of a nurse familiar with the study and thorough reading of the consent form with adequate time to consider the study consent issues outside of the examination room.

Postapproval Monitoring – Best Practices Recommendations

Oversight and surveillance of clinical trials after approval and during conduct of the study often are negligible in companion animals but should be rigorously applied to ensure accurate interpretation of results. Postapproval monitoring commonly applies to more traditional studies employing laboratory animals as a formal policy to observe and ensure good welfare practices and adverse event (eg, pain) management. Such postapproval monitoring procedures are designed to provide close observation when there is a "required action" (eg, addendum to the protocol) or when a protocol breach is suspected. The postapproval monitoring of clinical trials also should manage animal welfare issues, trial protocol adherence, and owner concerns. In addition, postapproval monitoring should include oversight of data relevant to endpoint assessment, adjudication, and adverse event communication.

Indications for a postapproval audit may include any concerns regarding study participant eligibility, use of proper informed consent procedures, protocol compliance, and adverse event or compliance reporting. A confidential mechanism for communication of concerns identified by anyone engaged in clinical studies including owners, staff or students should be available. Routine or random postapproval monitoring efforts including audits of clinical trial procedures may be rec-

ommended to provide ongoing quality assurance and accountability. Postapproval monitoring procedures and audits for conventional laboratory animal studies often are conducted by the university veterinarian or delegate, and include a mechanism for study coordinators to respond to or appeal the audit. The process for clinical study postapproval monitoring also could be managed, as with more routine situations, by the institutional veterinarian or could be the responsibility of the clinical review board, IACUC, or the Research Integrity and Compliance Review Committee at the institutional level or through a CRO. The NCI has developed audit guidelines that are readily adaptable to veterinary clinical trials.⁴⁵

The role of the academic hospital administration and facilities in the conduct of clinical research also is a critical component of a clinical trials program in veterinary medicine. The hospital may be the repository for study documents (eg, consent forms), provide trained personnel and facilities to execute sampling and data gathering, offer financial support for animal care, and provide counseling and emotional support for owners. These activities should be coordinated with those responsible for conducting the trials.

Reporting And Publication – Best Practice Recommendations

The use of Consolidated Standards of Reporting Trials (CONSORT) guidelines offers a well-accepted and standardized method to assess design for clinical trials in humans.^{46,47} Many journals now require such reporting guidelines compliance for publication of clinical trials. Until an equivalent set of guidelines is developed for companion animal trial reporting, the itemized listing of trial reporting requirements is sufficient, and should ideally be broadly implemented.

Registration of clinical trials in a searchable database offers several important advantages. It provides a catalog of initiated trials that is accessible by clinical investigators and owners considering enrollment in a clinical trial. A clinical trials registry for human participants was initiated in 2000 and is managed through the National Library of Medicine.⁴⁸ Registration of a clinical trial is required for future publication of trial results. This registry ensures public access to trial information and permits assessment of unnecessary duplication of trials.

A comprehensive clinical study registry for animal patients does not currently exist. The Veterinary Cancer Society has developed a voluntary listing of active clinical trials for pets with cancer.⁴⁹ However, resource limitations preclude archival data collection, data retrieval, and a mechanism for reporting trial results. Individual institutions list currently available clinical trials as resources allow. A comprehensive clinical trial registry system should be considered as an essential component of clinical trials best practices.

Effective data sharing is considered vital to the success of multi-institutional clinical trial conduct and was the subject of an IOM Workshop.⁵⁰ The scientific and

ethical considerations of data sharing are summarized in the following excerpts from that report:

“The moral and ethical arguments for data sharing center on fulfilling obligations to research participants, minimizing safety risks, and honoring the nature of medical research as a public good.

The practical and scientific arguments for data sharing include improving the accuracy of research, informing risk/benefit analysis of treatment options, strengthening collaborations, accelerating biomedical research, and restoring trust in the clinical research enterprise”.

Implicit in the concept of data sharing is open access to data, which provides greater transparency of study protocols, study reports, and adverse event documentation. Several data management systems have been developed for data sharing, and an effort should be made to develop a usable, cost-effective platform that would integrate multi-institutional trial data, and ideally integrate with data management platforms used in clinical studies in humans.

As mentioned previously, publication of results should follow accepted guidelines that describe the design, conduct and analysis of clinical trials. The publication of all trial results, whether associated with a positive or a negative outcome, in a searchable database would address the ‘Three Rs’ of animal welfare in research: Replace, Reduce, and Refine. A recent editorial from the editors of the British Journal of Pharmacology details a policy of reporting transparency of research involving animals including increased accountability for animal use and ‘open access’ to all primary data including negative studies.⁵¹ Such reporting guidelines are likely to be adopted by numerous journals. To fully realize such guidelines, a publication strategy would need to be established for negative study reporting and the release of embargoed data from contract-sponsored research after a suitable period.

Commitment to Improvement of the Clinical Trial Process

An overarching purpose of the workshop and this document is to encourage continued research and education on clinical trial improvement by outreach to scientists, veterinarians, and the pet-owning public. Biomedical researchers should be educated about the value of translational research in naturally occurring diseases in companion animals and the various resources and opportunities available to do so. Veterinary schools need to be informed of the resources available so as to encourage and facilitate the responsible conduct of clinical research and bio-ethics by their students, faculty, and employees.^{43,52} Veterinary specialists need to be aware of research opportunities and how to incorporate them into their practices. General veterinary practitioners need to be educated in the value of clinical trials for their patients and owners. The ability to

improve owner comprehension regarding clinical trials is an essential component of this concept. Owners need to clearly understand how knowledge gained by enrollment in clinical trials might help companion animals and humans in the future even though trials may not be designed to help their individual pet. Equally important is facilitating the continued debate regarding unique ethical considerations of clinical research in companion animals. Finally, the value of translational clinical research into cancer care linking animals and humans should be better defined and promoted to all stakeholders.

It is implicit in “Best Practice Recommendations” that regular review and revision will occur as required by the development of resources, regulations, and ethical priorities. Such revisions will be driven by both quantitative and qualitative research concerning communication with, and comprehension of, companion animal owners, improved trial design, and compliance. As with the evolution of clinical trial conduct in human oncology, we suspect that owner participation in data gathering and outcome assessment will become better integrated in trial management. The role of social media methods to support trial completion and to educate the public regarding the critical role of studies to improve animal health inevitably will grow.

It will likewise be critical to review and adopt best practices as they emerge from other disciplines, institutions, and countries engaged in discussion on the ethical and proper conduct of clinical studies. We anticipate that additional workshops will be forthcoming to determine more best practice recommendations or deepen discussions on current issues and will include multidisciplinary perspectives within oncology and affiliated specialties. When properly addressed by adherence to sound scientific principles, ethical conduct of research, and respect for patients and their owners, better health may result in the future for all members of the family—animals and people.

Acknowledgments

This workshop was supported by the Shipley Foundation – Boston, Massachusetts and The Flint Animal Cancer Center at the College of Veterinary Medicine and Biomedical Sciences and Colorado State University, Fort Collins, Colorado and was held at the AVMA offices in Washington, DC.

Conflict of Interest Declaration Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Prier JE, Brodey RS. Canine Neoplasia: a prototype for human cancer study. Bull WHO 1963;29:331–344.
2. Paoloni M, Khanna C. Translation of new cancer treatments from pet dogs to humans. Nat Rev Cancer 2008;8:147–156.
3. Khanna C, London C, Vail D, et al. Guiding the optimal translation of new cancer treatments from canine to human cancer patients. Clin Cancer Res 2009;15:5671–5677.

4. Gordon I, Paoloni M, Mazcko C, Khanna C. The Comparative Oncology Trials Consortium: using spontaneously occurring cancers in dogs to inform the cancer drug development pathway. *PLoS Med* 2009;6:e1000161.
5. IOM (Institute of Medicine) Workshop: The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research. Available at: <https://iom.nationalacademies.org/Activities/Disease/NCPF/2015-JUN-08.aspx> Accessed February 15, 2016.
6. Guidance for Industry – E6 Good Clinical Practice. US Dept of Health and Human Services, Food and Drug Administration 1996. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>. Accessed February 15, 2016.
7. American society of clinical oncology policy statement: oversight of clinical research. *J Clin Oncol*, 2003;21:2377–2386.
8. Report of the Clinical Trials Working Group of the National Cancer Advisory Board. Restructuring the National Cancer Clinical Trials Enterprise. June 2005. Available at: <http://www.cancer.gov/about-nci/organization/ccct/about/ctwg-report.pdf>. Accessed February 15, 2016.
9. Zon R, Meropol NJ, Catalano RB, Schilsky RL. American Society of Clinical Oncology statement on minimum standards and exemplary attributes of clinical trial sites. *J Clin Oncol*. 2008;26:2562–2567.
10. IOM (Institute of Medicine). Implementing a National Cancer Clinical Trials System for the 21st Century: Second Workshop Summary. Washington, DC: The National Academies Press; 2013.
11. NRC [National Research Council]. Guide for the Care and Use of Laboratory Animals. Washington, DC: National Academy Press; 2011. Available at: <http://grants.nih.gov/grants/olaw/Guide-for-the-care-and-use-of-laboratory-animals; Key Concepts. The Three Rs pp4-5>.
12. Russell WMS, Burch RL. The Principles of Experimental Technique. London: Methuen and Co; 1959. [Reissued: 1992, Universities federation for Animal Welfare, Herts, UK]. Available at: http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc.
13. Thamm DH, Vail DM. Veterinary oncology clinical trials: design and implementation. *Vet J* 2015;205:226–232 doi:10.1016/j.tvjl.2014.12.013.
14. Marconato L, Buracco P, Aresu L. Perspectives on the design of clinical trials for targeted therapies and immunotherapy in veterinary oncology. *Vet J* 2015;205:238–243 doi: 10.1016/j.tvjl.2015.02.020.
15. Burton J, Khanna C. The role of clinical trials in veterinary oncology. *Vet Clin North Am Small Anim Pract* 2014;44:977–987.
16. Cook N, Hansen AR, Siu LL, Abdul RA. Early phase clinical trials to identify optimal dosing and safety. *Mol Oncol* 2015;9:997–1007.
17. Catenacci DV. Next-generation clinical trials: novel strategies to address the challenge of tumor molecular heterogeneity. *Mol Oncol* 2015;9:967–996.
18. Dienstmann R1, Rodon J, Tabernero J. Biomarker-driven patient selection for early clinical trials. *J Curr Opin Oncol* 2013;25:305–312.
19. Takimoto CH. Phase 0 clinical trials in oncology: a paradigm shift for early drug development. *Can Chemother Pharmacol* 2009;63:703–709.
20. Abdoler E, Taylor H, Wendler D. The ethics of phase 0 trials. *Clin Cancer Res* 2008;14:3692–3597.
21. Daugherty CK, Ratain MJ, Emanuel EJ, et al. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. *J Clin Oncol* 2008;26:1371–1378.
22. Kossowsky J, Donado C, Berde CB. Immediate rescue designs in pediatric analgesic trials: a systematic review and meta-analysis. *Anesthesiology* 2014;122:150–171.
23. Sanderson C, Hardy J, Spruyt O, Currow DC. Placebo and nocebo effect in randomized controlled trials: the implications for research and practice. *J Pain Symptom Manage* 2013;46:722–730.
24. Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol* 2013;13:176–183. doi: 10.1111/vco.12032.
25. Vail DM, Michels GM, Khanna C, et al. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)—a veterinary cooperative oncology group (VCOG) consensus document. *Vet Comp Oncol*. 2009;8:28–37.
26. Veterinary cooperative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol* 2011; Article first published online: 20 JUL 2011, DOI: 10.1111/j.1476-5829.2011.00283.x.
27. Lynch S, Savary-Bataille K, Leeuw B, Argyle DJ. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Comp Oncol*. 2011;9:172–182.
28. Modified ECOG Perf Scores. Available at: <http://ecog-acri-n.org/resources/ecog-performance-status> Accessed February 15, 2016.
29. Wilson MK, Collyar D, Chingos DT, et al. Outcomes and endpoints in cancer trials: bridging the divide. *Lancet Oncol* 2015;16:e43–e52.
30. Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. *Lancet Oncol* 2015;16:e32–e42.
31. Hosgood G, Scholl DT. The effect of different methods of accounting for observations from euthanized animals in survival analysis. *Prev Vet Med* 2001;48:143–154.
32. Baneux PJR, Martin ME, Allen MJ, Hallman TM. Issues related to institutional animal care and use committees and clinical trials using privately owned animals. *ILAR J* 2014;55:200–209.
33. AVMA Policy - Establishment and Use of Veterinary Clinical Studies Committees. Available at: <https://www.avma.org/KB/Policies/Pages/Establishment-and-Use-of-Veterinary-Clinical-Studies-Committees.aspx>. 2015. Accessed February 15, 2016.
34. Amdur RJ, Bankert EA. Institutional Review Board Member Handbook, 3rd ed. Sudbury, MA: Jones and Bartlett Publishing; 2011.
35. FDA proposal: Document 2014-16492, Draft Informed Consent Information Sheet: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors (79 Federal Register 41291).
36. FDA draft Guidance for consent process. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf> Accessed February 15, 2016.
37. PRIM&R response to FDA proposal. Available at: <http://www.primr.org/publicpolicy/>. Accessed February 15, 2016.
38. IOM (Institute of Medicine). Contemporary Issues for Protecting Patients in Cancer Research: Workshop Summary. Washington, DC: The National Academies Press; 2014.
39. NCI Informed Consent Template. Available at: http://ctep.cancer.gov/protocolDevelopment/informed_consent.htm. Accessed February 15, 2016.
40. Lo B, Wolf LE, Berkley A. Conflict of Interest for Investigators in Clinical Trials. *N Engl J Med* 2000;343:1616–1620.
41. Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection 2004. Available at: <http://www.hhs.gov/ohrp/policy/fguid.pdf>. Accessed February 15, 2016.
42. Shekelle PG, Ruelaz A, Miake-Lye IM, et al. Maintaining Research Integrity: A Systematic Review of the Role of the Institutional Review Board in Managing Conflict of Interest, VA-ESP Project #05-226; 2012.

43. US Department of Health and Human Service Office of Research Integrity. Introduction to Responsible Conduct of Research. Available at: <https://ori.hhs.gov/sites/default/files/rcrintro.pdf>. Accessed February 15, 2016.
44. Joffe S, Cook EF, Cleary PD, et al. Quality of informed consent in cancer clinical trials: a cross sectional survey. *Lancet* 2001;358:1772–1777.
45. NCTN Audit Guidelines. Available at: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm. Accessed February 15, 2016.
46. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *Open Med* 2010;4:e60–e68 Epub 2010 Mar 24.
47. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;63:e1–e37.
48. Clinical Trials.Gov. Available at: <https://clinicaltrials.gov/>. Accessed February 15, 2016.
49. Veterinary Cancer Society Clinical Trial Registry. Available at: <http://www.vetcancersociety.org/members/clinical-trials/>. Accessed February 15, 2016.
50. IOM (Institute of Medicine). *Sharing Clinical Research Data: Workshop Summary*. Washington, DC: The National Academies Press; 2013.
51. McGrath JC, McLachlan EM, Zeller R. Transparency in Research involving Animals: The Basel Declaration and the new principles for reporting research in BJP manuscripts. *Br J Pharmacol* 2015;172:2427–2432.
52. NIH Department of Bioethics. Available at: <http://bioethics.nih.gov/courses/index.shtml>. Accessed February 15, 2016.