Clinical Trials in Veterinary Medicine: A New Era Brings New Challenges

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Randomized clinical trials (RCTs) are among the most rigorous ways to determine the causal relationship between an intervention and important clinical outcome. Their use in veterinary medicine has become increasingly common, and as is often the case, with progress comes new challenges. Randomized clinical trials yield important answers, but results from these studies can be unhelpful or even misleading unless the study design and reporting are carried out with care. Herein, we offer some perspective on several emerging challenges associated with RCTs, including use of composite endpoints, the reporting of different forms of risk, analysis in the presence of missing data, and issues of reporting and safety assessment. These topics are explored in the context of previously reported veterinary internal medicine studies as well as through illustrative examples with hypothetical data sets. Moreover, many insights germane to RCTs in veterinary internal medicine can be drawn from the wealth of experience with RCTs in the human medical field. A better understanding of the issues presented here can help improve the design, interpretation, and reporting of veterinary RCTs.

Key words: Competing risk; Endpoints; Epidemiology; Study design.

A glance through recent issues of the Journal of Veterinary Internal Medicine identifies prospective randomized clinical trials (RCTs) involving dogs, cats, cows, and horses that cover the fields of neurology, oncology, cardiology, and internal medicine. Collectively, these findings suggest that we have entered into an era of prospective veterinary RCTs. Without question, this is an achievement worth celebrating, but as is often the case, with progress comes new challenges. Randomized clinical trials yield important answers, but results from these studies can be difficult to interpret, incomplete, unhelpful, or even misleading unless the study design, execution, reporting, and interpretation are carried out with care. The methodology of well-designed and reported veterinary RCTs has been the subject of several previous publications. In a very simple sense, the best RCTs foster better everyday clinical decisions made at the patient’s side. This review addresses emerging challenges associated with RCTs, including use of composite endpoints; the reporting of different forms of risk; including baseline, relative, and absolute risk; analysis in the presence of missing data; and, issues of reporting and safety assessment. These topics are explored in the context of previously reported internal medicine studies as well as through illustrative examples with hypothetical data sets. Additionally, many insights can be drawn from the wealth of experience with RCTs in the human medical field. A better understanding of the issues presented here can help improve the design, interpretation, and reporting of veterinary RCTs.

Composite Endpoints

A critical choice when designing RCTs is the choice of the study outcomes or endpoints. The primary endpoint is the main event that the treatment being evaluated is intended to beneficially affect. Additional, or secondary, endpoints also are commonly examined to gather related evidence that supports the primary outcome. Endpoints and any expected treatment benefit must be sufficiently important to the animal and owner with respect to morbidity, mortality, quality of life, or some combination of these. Many endpoints involve a dichotomous (i.e., yes versus no) event such as death, tumor relapse, or hospitalization for worsening disease. In RCTs in human medicine,22 and increasingly in veterinary RCTs, multiple clinical endpoints are combined into a single “composite” endpoint, defined as the occurrence or time to first of any of the component outcomes, or more simply, time-to-event (TTE). Ideally, the selected components should all be related to the primary outcome, expected to respond to the treatment under study, and occur with similar frequency.27,28

Abbreviations:
- CHF: congestive heart failure
- DSMB: data and safety monitoring board
- HR: hazard ratio
- ITT: intention-to-treat
- PP: per-protocol
- RCTs: randomized clinical trials
- TTE: time-to-event
For example, studies in human medicine of coronary artery disease commonly combine several major adverse clinical events into a composite endpoint. Such events typically include cardiovascular death, reinfarction, stroke, or need for coronary vessel revascularization; the TTE analysis takes the timing of whichever event occurs first as the endpoint. An example of a composite endpoint in veterinary medicine is the use of time to either onset of congestive heart failure (CHF) or sudden death of dogs with dilated cardiomyopathy. A dog was considered to have experienced the endpoint either by developing CHF or by dying suddenly, whichever came first. Similarly, in a study evaluating whether an intervention prevented tumor recurrence or death due to mammary cancer in dogs, the time to the first of either event was regarded as an endpoint.

Investigators utilize a composite endpoint primarily for efficiency. For TTE outcomes, the number of events drives study power, which is the probability the study will detect a true underlying difference between treatment and control groups. In these studies, the number of events can be increased by enriching the sample size or by extending the duration of follow-up. Use of a composite TTE outcome can markedly decrease the sample size (and cost) of a study by increasing the number of expected events. For example, consider planning for a hypothetical study to detect a hazard ratio of 0.65 at a significance level of 0.05. For this endpoint, 90% of the control group are expected to experience the event, 406 subjects are required (i.e., 203 in the control group and 203 in the treatment group), but if 80% of control subjects reach the endpoint, only 242 subjects (i.e., 121 in each group) are needed. By enriching the number of expected events by using a composite endpoint, what might have been an unrealistic veterinary study in terms of patient numbers suddenly becomes feasible.

Another advantage of composite endpoints relates to the issue of multiplicity. Having multiple primary endpoints instead of a single composite endpoint increases the probability that 1 of those endpoints will be significantly different between groups merely by chance. For example, if rather than combining 3 separate clinical events into a single composite endpoint, an investigator chooses to evaluate each component separately, the possibility that the treatment comparisons for 1 of these 3 outcomes will be significant merely by chance is 14.3% (1 − [1 − 0.05]3), assuming independence of the endpoints and the typical 0.05 significance level. This problem rapidly grows such that in a study with 14 primary outcomes, the chance of 1 being significant by chance is >50%, again assuming independence. Typically, the outcome of raising a composite endpoint by approximately 70% compared to placebo. Yet, when looking at each endpoint separately, neither of the individual components, namely time-to-first onset of CHF or sudden cardiac death, was significant on its own. On the surface, this might seem like a dubious result in which pimobendan prevented neither CHF nor sudden death. The driving motivation behind use of the composite endpoint however was to decrease the necessary number of patients, and thus any evaluation of the individual components would likely be underpowered. In this particular instance, veterinarians should find it reassuring that the composite endpoint was significant, both trended strongly in the direction that was favorable to the active treatment. Although a trial with a composite endpoint offers less evidence for benefit on the individual endpoints than 1 powered for that individual endpoint, a reasonable inference is that given a larger number of patients, both composite endpoints and the individual components was significant, both trended strongly in the direction that was favorable to the active treatment. Although a trial with a composite endpoint offers less evidence for benefit on the individual endpoints than 1 powered for that individual endpoint, a reasonable inference is that given a larger number of patients, both composite endpoints and the individual components was significant, both trended strongly in the direction that was favorable to the active treatment.

A more difficult scenario arises when the overall composite is positive but ≥1 individual components are decidedly neutral or even trend in the opposite direction. This problem is magnified if there are considerable differences in the clinical severity of the individual components (e.g., if both nonfatal and fatal components are used simultaneously). Examples from both the human and veterinary literature help illustrate this point. One study evaluated human patients with diabetes at risk for heart disease with a composite endpoint of new onset of heart failure or sudden death, and found that treatment significantly lowered the risk of nonfatal infarction by 24%, but the rate of coronary-related death tended to increase in patients receiving treatment. Another example from human medicine is a study that reported that treatment with an insulin sensitizer significantly decreased risk of a composite endpoint consisting of new onset of diabetes or death by 50%, but the rate of coronary-related death tended to increase in patients receiving treatment. Another example from human medicine is a study that reported that treatment with an insulin sensitizer significantly decreased risk of a composite endpoint consisting of new onset of diabetes or death by 50%, but the rate of coronary-related death tended to increase in patients receiving treatment. Another example from human medicine is a study that reported that treatment with an insulin sensitizer significantly decreased risk of a composite endpoint consisting of new onset of diabetes or death by 50%, but the rate of coronary-related death tended to increase in patients receiving treatment. Another example from human medicine is a study that reported that treatment with an insulin sensitizer significantly decreased risk of a composite endpoint consisting of new onset of diabetes or death by 50%, but the rate of coronary-related death tended to increase in patients receiving treatment. Another example from human medicine is a study that reported that treatment with an insulin sensitizer significantly decreased risk of a composite endpoint consisting of new onset of diabetes or death by 50%, but the rate of coronary-related death tended to increase in patients receiving treatment.
groups is based on death for any reason. In studies...chemotherapy? For these reasons, weighting has not...deniably arbitrary. Is death really 3 times as bad as...These examples highlight the difficulty in examining...surgery? How much better or worse is surgery than...endpoint of first onset of CHF or sudden cardiac...is not protected by randomization because. For instance, in a study utilizing a composite endpoint of first onset...of CHF or cardiovascular death in dogs with preclinical mitral valve disease, a relative risk of cardiovascular death resulting in a treatment-related risk reduction of 4% with extremely wide 95% CI ranging from a 55% decrease in risk to a 210% increase in risk specific to this component. Difficulties such as those described in these examples are particularly common in studies with a mixture of fatal and nonfatal endpoint components. Mortality is obviously an important clinical event, but in trials of particularly short but practical duration, the majority of participants experience the less severe or nonfatal clinical endpoints, which then subsequently drives the analysis. Over one-third of medical trials in humans utilizing composite endpoints involving mortality components demonstrated a significant overall result that did not include a detectable contribution by the mortality component. This situation is most problematic if the effect on the most severe but less frequent endpoint, such as mortality, is in the opposite direction of the effect on the remaining components of the composite. There are no universally accepted solutions to the problems inherent in use of composite endpoints, but a number of approaches have been proposed. One potential way to balance the importance of different components is to weight them according to their severity or whether they are fatal or nonfatal. For instance, in a hypothetical study of patients with neoplasia, an endpoint of death due to metastatic disease could be weighted 3 times greater than an endpoint of surgery for tumor reoccurrence, and need for surgery could be weighted 1.2 times greater than the need for additional chemotherapy. In practice, weighting of different outcomes is a difficult task. Despite methodology that tries to account for patient preference, the weights are undeniably arbitrary. Is death really 3 times as bad as surgery? How much better or worse is surgery than chemotherapy? For these reasons, weighting has not been widely used. Another strategy is the careful selection of secondary endpoints for analysis, such as all-cause mortality, for which the overall survival between groups is based on death for any reason. In studies with low rates of cause-specific mortality, the finding that patients receiving treatment survived longer no matter what the cause of death is reassuring. In summary, use of composite endpoints attempts to strike a balance between feasibility of a trial and results devoid of ambiguity around the individual components. In practice, constructing composite endpoints that meet these criteria can be very challenging.

Analysis of Patient Populations with Missing Outcome Data

The ability of RCTs to produce an unbiased estimate of effect between 2 treatment groups is threatened when outcome data are missing. If a study involving 200 randomized patients ultimately collects outcome data on only 120 individuals, the comparability of the treatment groups is no longer protected by randomization because those with missing data might be systematically different from those who provide data. Missing data can arise from a variety of causes. Investigators might remove randomized individuals from study analysis for reasons such as failure to comply with the study protocol or concurrent use of prohibited medications. Missing data also occurs when patients are lost to follow-up or when the animal was withdrawn early from the study. Investigators tend to ignore the problem of missing data by assuming that withdrawals and losses between groups are due to random chance (i.e., are independent from the treatment or outcome) and can therefore be ignored. Many studies then exclusively analyze the subset of patients that successfully completed the protocol, have outcome data, and complied with the study protocol (i.e., “per-protocol” [PP]), while ignoring that fact that missing data might not be missing completely at random and that treatment comparisons subsequently might be biased.

The only reliable way to produce a truly unbiased estimate in the face of missing data is to perform an “intent-to-treat” (ITT) analysis, in which every subject that was randomized regardless of subject compliance with the protocol is included. An important implication of ITT analysis is that studies should gather outcome data on every randomized study patient, regardless of whether or not the patient fully or properly completed the study. Although this is not always possible, the closer one comes to including outcome data on all subjects, the less concern there will be about biased comparisons. Where outcome data due to withdrawals and losses are missing, these cases still can contribute to the ITT analysis by providing valuable information either up until the time they were withdrawn or lost by methods to compensate for the missing data, such as multiple imputation or inverse probability weighting, use of best/worse case scenarios, or other sensitivity analyses. Intent-to-treat analysis provides a conservative estimate of effect because of potential dilution from early withdrawals from study treatment and decreases the likelihood of a type I (i.e., false positive) error. Intent-to-treat analysis also tends to mimic the interventions effectiveness in the real...
clinical world wherein these types of withdrawals and losses occur. 41

Similarly, there are certain advantages and disadvantages associated with PP analysis. By excluding any individual that did not wholly and completely adhere to the treatment protocol, the PP analysis, in principle, should closely reflect the treatment effect and the underlying scientific basis for its effect. However, a major disadvantage of the PP analysis is that the reason(s) for the missing data might be related to the intervention, or outcome. If so, we might find, for example, a difference between groups that is largely due to removing those with the poorest prognosis from 1 of the groups. A classic RCT that demonstrates the potential for this bias is Coronary Drug Project, 45 which examined the efficacy of clofibrate on survival in human patients at high risk of dying from heart disease. After adjusting for known risk factors, the mortality rate in those with poor adherence to the study protocol was higher regardless of whether they were receiving active treatment or placebo, setting up a situation in which censoring for protocol violations was no longer completely at random. In trials designed to show the superiority of 1 intervention over another or over placebo, the more conservative ITT analysis is usually the primary analysis and PP, if considered, is a secondary analysis. 41 When both the ITT and PP analyses lead to the same conclusion, “the confidence in the trial results is increased, bearing in mind, however, that the need to exclude a substantial proportion of subjects from the (PP) analysis throws some doubt on the overall validity of the trial.” 41

The use and reporting of ITT and PP methods in both the human and veterinary medical literature varies widely. In many studies, key pieces of information, including original number of patients recruited and randomized, how missing data was treated, and exactly which analysis methods and data sets were used, are lacking. 48,49 Readers are dependent on such data to exactly which analysis methods and data sets were used, and randomized, how missing data was treated, and the descriptions of both the patient ITT and PP analysis sets in a so-called CONSORT diagram. Studies involving livestock and food safety issues are encouraged to follow analogous standards specific to these types of studies as set forth by the Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety (REFLECT) guidelines. 51

Risk: Baseline, Relative, and Absolute

Randomized clinical trials provide a group estimate of effect, but the clinician and animal owner want to make clinical decisions relative to an individual animal. Thus, one needs to test characteristics of the patient population in which the trial established benefit and whether the found treatment effects apply equally across different patient types and individuals. Important baseline variables can affect a patient’s prognosis and whether or not a patient will experience treatment benefit. High baseline risk opens the opportunity for a favorable risk-benefit ratio, 52 whereas the patients with low risk might gain little or no treatment benefit. 53 In the case of treatments that are associated with a risk of adverse effects, the benefit-harm ratio might even be reversed for low-risk patients. 54 In addition to baseline risk, 2 distinct types of risk comparisons should be considered. The first of these is a relative risk comparison. The hazard ratio, a potential summary of relative risk, has been mentioned previously. The hazard is a somewhat esoteric mathematical quantity that assesses the instantaneous risk of having the event in the next small time interval, among those still at risk. The commonly used log-rank test and Cox proportional hazards regression model estimate the hazard ratio between groups and assume this ratio is constant throughout the study. 55,56 A more intuitive measure of relative risk is the risk ratio (i.e., the ratio of probabilities of event occurrence between 2 groups at a given time [p1/p2]). 57

The second type of risk comparison involves examining the absolute difference in the probability of event occurrence between groups of individuals over a specified amount of time (i.e., p1-p2). 57 The distinction between these different forms of risk assessment, relative versus absolute, is important because individual treatment benefit is critically dependent not only on the relative risk, but also on the magnitude of the baseline risk and the absolute risk reduction anticipated from treatment. 58 Consider, for example, a hypothetical treatment for cancer that is associated with a 15% relative risk reduction in mortality compared to no treatment that is uniform across all patient subgroups (Table 1). Consider next that patients are stratified by their baseline risk of mortality at the outset of the study into low- and high-risk groups. Such an exercise indicates that the overall absolute treatment benefit is driven almost entirely by the subgroup of patients at highest risk. The absolute risk reduction in patients with low risk at baseline is exceedingly small simply because their risk of dying was low at the outset. Another way to consider absolute risk reduction is to calculate the number of patients needing to undergo treatment in order to have 1 patient benefit. Numerically, the number needed to treat is the inverse of the absolute risk
Table 1. Comparison of the relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT) in a hypothetical study that reduces risk of death by 15% in patients receiving treatment.

| Patients          | Control Death Rate (%) | Treatment Death Rate (%) | RRR (%) | ARR (%) | NNT |
|-------------------|------------------------|--------------------------|---------|---------|-----|
| High-risk patients| 50                     | 42.5                     | 0.85    | 7.5     | 13  |
| Low-risk patients | 10                     | 8.5                      | 0.85    | 1.5     | 67  |

Patients have been stratified into those with low and high baseline risk for death at the study outset. While treatment is associated with a lower risk for death in both groups, the ARR for death (i.e., the difference between the control and treatment death rates) in the low-risk patients is extremely small, primarily because these patients were at low risk for death to begin with. NNT is the inverse of the ARR and represents the number of patients needing to be treated in order for 1 patient to gain benefit and is substantially higher in the low- versus high-risk group. Moreover, if the hypothetical treatment happens to be associated with adverse effects in more than 1.5% of patients treated, the net absolute effect of treatment might be harm to the low-risk patient group.

In human medicine, baseline risk scores based on specific demographic and disease characteristics can be derived from large observational data sets. For instance, the Gail Breast Cancer Risk Assessment Score was developed from a database of nearly 6,000 women and estimates the risk of developing breast cancer over specific periods of time. The score includes influential variables such as family history, race and ethnicity, presence or absence of certain genetic mutations, and age. Another example is the Framingham Heart Study, which utilized 12-year follow-up of >8,400 individuals to predict future cardiovascular disease based on age, smoking status, cholesterol, presence or absence of diabetes, and blood pressure. Predictive data such as these are increasingly available in veterinary patients across a variety of disease conditions, including neoplasia, cardiovascular disease, and various diseases in horses and cows. Incorporation of baseline risk in RCTs potentially can help estimate treatment effects in heterogeneous patient populations with greater accuracy and help clinicians select individuals that are most likely to experience treatment benefit.

In the previous example of low- and high-risk patients, we assumed that the decrease in relative risk would be uniform across the entire cohort of patients regardless of baseline risk. Different patient subgroups however may experience different levels of relative risk reduction. In principle, this “heterogeneity of treatment effect” across subgroups can be statistically evaluated by assessing treatment by subgroup interactions, which involves testing whether the observed differences across subgroups are more than would be expected by chance. In many instances, power to detect interaction effects will be low in trials with sample size calculated for the overall treatment effect. This is not to say such analyses should be avoided; exploratory analyses can be valuable in suggesting need for further study, but results of such analyses need to be interpreted very conservatively. In the absence of a prespecified and well-powered interaction effect, the overall treatment effect generally will be the most reliable estimate of efficacy.

To frame the concepts of baseline, relative, and absolute risk in a clinical scenario, consider a hypothetical statement presented to a dog owner who is contemplating adjunctive chemotherapy for a geriatric dog after surgical resection of a tumor. Which statement is more helpful to the owner? The first statement, based solely on relative risk, is as follows: “Chemotherapy will, on average, decrease the risk of tumor recurrence by 50% compared to not giving chemotherapy.” This sounds very promising, but only if the risk of tumor recurrence is high, associated adverse effects are tolerable or of low risk, cost of chemotherapy is reasonable, and if the risk of dying in the interim from some unrelated cause is low. Consider next a statement that takes all 3 risk types into consideration as follows: “In dogs with similar baseline risk as your dog, the probability of tumor recurrence in the next 24 months is 8%, and treatment will, on average, decrease this probability to 4%. There is a 3% chance of serious adverse effects from the treatment, and in the interim, there is a 50% chance that your dog will die from its concurrent renal disease rather than the tumor.” This second statement provides a much clearer basis for decision-making. If the baseline absolute risk for an event is low, likelihood of an unrelated competing risk event is high, and if there exists even a small risk for treatment-related harm, treatment is unlikely to be beneficial (and in the worse case could actually be harmful) regardless of the reported group effect.

Other Issues in Clinical Trials in Veterinary Patients

The benefits of well-designed RCTs are self-evident, whereas harm from poorly designed RCTs is more insidious. Poor RCTs waste valuable resources, complicate future research, provide false hope to owners, and potentially could jeopardize patient safety. One of the easiest ways for investigators to insure good design is to carefully predefine their endpoints and statistical plan, preferably with the input of a biostatistician. The International Committee of Medical Journals Editors (ICMJE) requires registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. For United States journals, this means investigators leading RCTs in humans are required to make their study endpoints and statistical plan public before the start of the study by registering the study on a
publicly accessible website. This practice protects the investigator from charges of posthoc data dredging and protects the consumer from being misled by poor analytical practices. The website also tracks the results of trials regardless of whether the end result was confirmatory or null, thereby avoiding the bias that can occur when journals only accept or authors only submit positive trials for publication. Veterinary journals adopting a set of requirements for the publication of RCTs, as put forth by ICMJE, could further strengthen the quality of research. Organizations such as the American Veterinary Medical Association and VetAllTrials consortium recently have launched voluntary public registries for veterinary clinical trials that include description of the trial objectives, potential benefits and risk, and criteria for enrollment.

The number and size of veterinary RCTs relative to the human medical field is small, which presents a number of unique challenges in the veterinary field. For example, the number of patients and duration of follow-up may be fewer due to the small number of animals available to participate in trials. Veterinary investigators should seek to replicate findings from human RCTs, but the small number of patients and duration of follow-up in veterinary trials mean that findings are more likely to be valid. If findings from human RCTs are inconclusive or unexpected, the standard recommendation is to “collect more substantial evidence on the issue,” which usually means additional RCTs. Clinical practice guidelines in human medicine typically rely on confirmatory findings from multiple RCTs, often involving many hundreds or thousands of subjects. Veterinary investigators should seek to replicate findings from human RCTs, but the small number of patients and duration of follow-up in veterinary trials mean that findings are more likely to be valid despite the relatively constrained resources available within the veterinary profession. In our opinion, of this study, many veterinarians and animal owners are fully willing to participate in clinical trials, and thus, the limiting factor is 1 of resources and infrastructure. In instances where concerns over repeating a study that showed a new treatment had great benefit or low incidence of disease limit patient enrollment, the veterinary profession might look to studies of cancer or rare or “orphan” human diseases (i.e., those typically affecting <200,000 humans in the United States) for ideas on how to deal with the inability to perform repeated clinical trials. In this respect, the Food and Drug Administration (FDA) offers some general considerations for obtaining “adequate and well-controlled” evidence from single studies and to increase the amount of supporting evidence in the form of consistency across closely related diseases. The FDA stresses that proper study design and planning are even more critical in these situations than for more common diseases. Aspects of study design that might be particularly suited to relatively small RCTs have been previously reviewed.

Issues involving design of RCTs do not necessarily stop once a trial is underway. Independent data and safety monitoring boards (DSMBs) are utilized in many RCTs in human medicine. They comprise clinicians and statisticians not directly involved in the planning or execution of the trial or product being studied. The primary purpose of DSMBs is to oversee patient safety, primarily with respect to adverse events. In many cases, another important component of this oversight is the review of prescheduled interim analyses of unblinded outcome data to determine whether there is sufficient evidence to terminate the study before its scheduled completion of accrual and follow-up, thereby either accelerating the use of superior treatments in the population or decreasing patient exposure to an ineffective or unsafe drug. The analysis of unblinded data necessitates a reviewing body such as a DSMB that is independent of the daily operations of the trial and who can maintain the confidentiality of interim results. If early stopping is considered (and it need not be except in trials where the primary outcome is death or another serious event or those that involve a considerable number of patients and duration of follow-up), the statistical thresholds guiding this decision should be prespecified and based on the need to maintain the desired overall type 1 error rate (typically 5%). However, just because these guidelines are met does not mean a trial is automatically stopped. Particularly if the number of patients experiencing the endpoint is few. Additionally, a DSMB may recommend that a study continue even if the stopping boundary is crossed, if questions regarding the effects of treatment on important subgroups or secondary endpoints involving either efficacy or toxicity still remain. A DSMB’s recommendation to the investigators and sponsor to stop a trial for patient safety or efficacy is a difficult advisory decision that relies on the independence and impartiality of a DSMB. Some large veterinary RCTs have recently utilized DSMBs, interim analysis, or both including a trial that was prematurely halted due to safety concerns, a trial in which interim analysis deemed it best to continue to its scheduled (and ultimately positive) endpoint, and a trial that was prematurely halted for benefit after meeting stringent prespecified criteria.

Finally, in addition to sound study design and analysis, independent reviewers of scientific journals are important arbiters of quality. Peer review should inject a healthy dose of skepticism into the scientific process and help offset the potential bias of investigators toward their own results. To be fair, there is always an asymmetry in how closely any potentially negative or discrepant result is scrutinized. The mere suggestion of ineffectiveness or harm elicits intense scrutiny, whereas similar levels of evidence pointing toward benefit often are ignored. In general, reviewers should ensure that the benefits and risks of an intervention are clearly discussed, supported by the presented data, and are primarily derived from prespecified analysis and criteria.

**Conclusion**

The age of prospective RCTs in veterinary medicine is fully upon us. There is an acute need to ensure the valid design and accurate reporting of RCTs and to maximally leverage the limited resources we have in the veterinary profession. Close attention to study endpoints, different forms of risk analysis, and issues of planning, monitoring, and reporting are needed. Many
insights can be drawn from the wealth of experience with RCTs in the human medical field and greater cooperation between biostatisticians in veterinary and human medicine and those performing the trials could achieve useful results. Simultaneously, efforts should be made to increase the training of veterinary students, generalists, and specialists in these areas. The issues covered here are just a small sample of the important considerations facing this new era of veterinary RCTs. Increased awareness and attention to these issues will move us faster and farther toward improved care of our patients.

Footnotes

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Challenges in Clinical Trials

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