Reporting Guidelines for Randomized, Controlled, Blinded Clinical Trials in Traditional Chinese Veterinary Medicine

Cheryl L Chrisman DVM, MS, EdS, DACVIM; Huisheng Xie DVM, MS, PhD; Aituan Ma PhD; Neal Sivula DVM, PhD; Carolina Medina DVM, DACVSMR; Bruce Ferguson DVM, MS; Mushtaq Memon BVSc, MSc, PhD, DACT

PURPOSE OF THE REPORTING GUIDELINES

- To improve the quality of experimental designs, execution and reporting of clinical trials and other studies described in articles published by the American Journal of Traditional Chinese Veterinary Medicine (AJTCVM)
- To provide a standard format for authors to follow, when composing reports of clinical trial findings
- To achieve complete and transparent reporting so all study findings can be duplicated, critically appraised and accurately interpreted
- To promote evidence-based Traditional Chinese Veterinary Medical (TCVM) principles and treatments

USE OF THE REPORTING GUIDELINES

- The reporting guidelines will be used for authors, editors and reviewers in evaluating manuscripts submitted to AJTCVM.
- Authors will be asked to comment on the items from the list outlined below, if not present in a manuscript, during the editing and reviewing processes.
- The long-term goal of the AJTCVM is to primarily publish reports of randomized, blinded and controlled clinical trials that conform to these guidelines to support the practice of TCVM evidence-based medicine.

CHECKLIST FOR REPORTING GUIDELINES

TITLE AND ABSTRACT

- The abstract should contain a brief summary of the problem, experimental design, pertinent findings, statistical analysis, adverse effects and conclusions in 250 words.
- Indicate if this is a prophylactic or therapeutic clinical trial, the treatments used, outcome(s) of interest, and animal species used in the title.
- If there was randomized assignment of subjects in the study, state “randomized” in the title and abstract.
- If the study was controlled or placebo controlled, state “controlled” in the title and abstract.
- If the study was blinded, state “blinded” in the title and abstract.
- Clearly state whether the problem occurred naturally or was induced (e.g. “A randomized, controlled, blinded clinical trial of the effects of electro-acupuncture for the treatment of naturally occurring back pain in sport horses”).

- No new information should be presented in the abstract, only information found in the paper.

INTRODUCTION

Background Information and Objectives

- Begin with a brief description and importance of the problem to be studied.
- Provide the scientific background of the problem with references to previous pertinent studies and an explanation of study rationale.
- Include an explanation of the benefits and possible adverse reactions of the interventions proposed.
- A specific research question can be included.

Example: Will rest and electro-acupuncture reduce thoracolumbar pain in sport horses better than rest alone and be an effective alternative to phenylbutazone?

- The introduction should end with a clear statement of the research hypothesis and objectives of the study.
- The hypothesis can then be stated. (e.g. "Electro-acupuncture and rest will reduce thoracolumbar pain in sport horses better than rest alone and provide a safe alternative to phenylbutazone").
- Indicate if this is a prophylactic or therapeutic clinical trial, treatments used, outcome(s) of interest, and animal species used in the title.
- Objectives are what the research trial was designed to determine.

Example: "In the current study, sport horses with thoracolumbar pain were treated with a) rest and 3 electro-acupuncture treatments 1 week apart; b) rest and phenylbutazone 4.4 mg/kg of body weight every 12 hours initially, followed by 2.2 mg/kg of body weight every 12 hours for 5 days or c) rest alone to determine: 1) if post treatment pain scores reduced significantly compared to pre-treatment pain scores in each group, 2) if pain scores were significantly reduced in the electro-acupuncture and phenylbutazone group compared to horses receiving rest alone, 3) if pain scores of horses receiving electro-acupuncture were the same or significantly greater or less than those receiving phenylbutazone."

METHODS

- **Animal Care and Use**
- Identify the IACUC protocol or equivalent for animal use approval.
- **Trial design**
- Indicate the type of trial (e.g. double blind, placebo-controlled prospective study).
- **Participants – Study Setting**
- Define the study population (not to be confused with the study sample).
- Clearly explain inclusion and exclusion criteria for case selection.
- Provide species, age, sex, breed and body weight of animals.
- Provide use of animals, such as sport horses, agility dogs, etc.
- Explain where the study took place, how the animals were housed, type of caregivers.
    - If housed in a facility, indicate the standard of care, according to the established standards of a specific group. Example: "The trial was

performed at the University of Florida Veterinary Medical Center (UFVMC), on client-owned dogs, housed with the respective client. The study was approved by the UFVMC Clinical Care and Use committee and consent to study forms were signed by the client for each dog included in the study."

4. Interventions

- Describe each intervention thoroughly including control interventions.
- A researcher reading the report should know exactly how to repeat the study, using the same methods as reported.
- A clinician reading a trial report should know exactly how to perform the intervention, if they choose to use it on a patient.

Acupuncture:

- List all acupoints treated and their indications and actions and depth of needle insertion.
    - These can be shown in a Table form
    - Provide needle gauge, length and type.
    - Indicate manufacturer as a footnote.
- Indicate the technique used. Examples: Dry needles non-manipulated, dry needles manipulated, electro-acupuncture, aqua acupuncture, moxibustion, laser, etc.
- If dry needles were manipulated, provide a detailed description of the manipulation technique, so others can accurately repeat.
- If electro-acupuncture was performed, provide equipment information and the frequencies used including duration of treatment at each frequency.
    - Indicate manufacturer as a footnote.
- If aqua-acupuncture was performed, provide details of the hypodermic needle size, depth inserted, primary substance, substance concentration, dilution substance and amount injected at each site.
    - If different amounts were used for different acupoints, then list in Table form
    - Indicate manufacturers of substances as a footnote
- If moxibustion was performed, provide a complete description of the herb, technique and duration at each acupoint.
    - If different durations were used for different acupoints, then list in Table form ○ Indicate manufacturer as a footnote
- If laser acupuncture was performed, provide equipment information (pulsating/continuous wave, energy output in watts), light wavelength(s), the frequencies used, joules/cm^2stimulation at an acupoint, the duration of acupoint stimulation with laser of each frequency and total duration of each treatment.
    - If different durations were used for different acupoints, then list in Table form ○ Indicate manufacturer as a footnote
- If some other treatment of acupuncture points was performed, provide a detailed description of the technique.
- Clearly indicate duration of each treatment, frequency of treatment, total numbers of treatments and total time period over which treatments were administered.

- May be listed in a Table for clarity.

Herbal medicine:

- Provide details of all herbal medicines and individual herbs used in the study.
- Indicate *Pin-yin* and English names.
- Provide manufacturer as a superscript letter and a footnote.
- State the dose in g/kg body weight.
- Indicate if given before, after or with meals.
- Indicate the form of herbal medicine: teapill, granule, capsule, powder etc.
- Indicate the frequency of dosing per day.
- Indicate total duration of treatment.
- Indicate the ingredients in each Chinese herbal medicine in a Table form and include Pin-*yin* and English names, grams or percent of each herb in the formula and actions of each ingredient.

Tui-na:

- Provide details of all *Tui-na* techniques used in the study.
- Indicate *Pin-yin* and English names and indications for all techniques used.
- May use a Table for clarification.
- Indicate the duration of treatment using each technique.
- Clearly indicate total duration of each treatment session, frequency of treatment, total number of treatments and total time period over which treatments were given.
- May list in a Table for clarity.

Food therapy:

- Provide details of all types and amounts of food used in the study.
- Indicate the rationale and actions for each food.
- Indicate the duration of Food Therapy treatment.
- May list the foods, actions and duration of supplementation in a Table for clarity.

Exercise or Lifestyle:

- Identify and completely define all primary (pre-specified) outcomes or end points by which groups will be compared.
- Provide details of the type, duration and frequency of exercises or training prescribed in the study.
- Provide details of the type, duration and frequency of any other lifestyle alterations prescribed in the study.
- Indicate the total time period (days, weeks, months, etc.) of exercise or lifestyle alteration programs at time of outcome evaluations.
- If indicated, provide the time period between discontinuation of the exercise program and the outcome evaluations.
- May list exercise, duration, frequency and time at evaluation in Table form for clarity.

5. Outcomes

- Identify and completely define all primary (pre-specified) outcomes or end points by which groups will be compared.
- When available, use previously developed and validated scales or consensus guidelines.
    - Example: a previously published and accepted pain scale or body score scale

- Author-generated unpublished scales can contain bias and should be avoided if possible.

- For clinical outcomes where a score is used, clearly define each score and state if sensitivity and specificity of observation/observer(s) is known.
  - Example: Use scoring resistant to bias (blinded observer); Clearly defined basis of how a score is assigned for each severity level of a clinical condition
- A description of secondary outcomes is optional, except when an adverse event occurred.
  - Data of secondary outcomes are used to evaluate additional effects of the intervention, anticipated or not, but are usually not considered in the statistical analysis of the primary outcome.
  - In some trials, circumstances may require a protocol deviation.
  - Example: a change in the way an outcome is assessed or a switch to a different outcome
  - All changes must be described and a detailed explanation of the rationale for all changes provided

6. Sample size, interim analyses and rules for early discontinuation

- A study should be large enough to have a high probability (power) of detecting, as statistically significant, a clinically important difference of a given size, if such a difference exists.
- Consultation with a biostatistician is often needed during the planning stages to determine the sample size necessary to ensure significance at least $p<0.5$ and a 95% confidence level.
- Indicate how the sample size was determined.
  - Explain and justify assumptions used
- A clear explanation should be provided if the actual sample size differed from the originally intended sample size.
- Describe the rationale for other data collection points besides the end point.
- Outline the rules for early discontinuation of the study.
  - Example: severe, unanticipated and/or untoward effects
- Clearly explain the rationale for early discontinuation of a study or parts of a study, in the event this occurs.

7. Randomization

- Randomization has three major advantages:
  1. Eliminates selection bias by balancing both known and unknown prognostic factors, in the assignment of treatments. Without randomization, treatment comparisons may be prejudiced, whether consciously or not, by selection of participants of a particular kind to receive a particular treatment.
  2. Permits the use of probability theory to express the likelihood that any difference in outcome between intervention groups merely reflects chance.
  3. May facilitate blinding the use of treatments to the investigators, animal caretakers and outcome evaluators, possibly by use of a placebo, which reduces bias after assignment of treatments.

- Successful randomization in practice depends upon adequate generation of an unpredictable allocation sequence and concealment of that sequence until assignment occurs.
- Randomized assignment of subjects into groups has three steps:
    - Sequence generation (see 8. below)
    - Allocation concealment (see 9. below)
    - Implementation (see 10. below)

8. Randomization – sequence generation and type

- Describe the technique used for random assignment to test and control groups.
    - Example: random number table, computerized generated randomized name or number list

9. Randomization – mechanism of allocation concealment

- Provide a statement of how the allocation method was concealed from the investigator, project coordinator and client.
- Concealment of the allocated intervention at the time of enrollment reduces bias.
- Blindedness is different as it is concealing group assignment; it is not a method of assignment.

10. Randomization - implementation

- Provide a statement of who generated the allocation sequence, enrolled participants and assigned participants to interventions.
- It is best to have an uninvolved party generate the group assignment, which remains unknown to the investigators or project coordinators until time of admission into the group.
    - Examples: animal numbered and randomly assigned by a technician not involved in the study using a computer-generated program; assignment is concealed in a sealed envelope with the animal number on the front and opened only by the investigator when the intervention is to be performed.

11. Blinding (masking)

- Blinding is an important safeguard against bias, particularly when assessing subjective outcomes.
- Blinding is the withholding of information about the assigned interventions from people involved in the trial, such as investigators and clients who may potentially be influenced by this knowledge.
- Provide a statement of whether or not those administering the interventions, investigators and caretakers evaluating the outcomes were knowledgeable about which intervention an animal received.
- Obviously those administering acupuncture and sham acupuncture treatments cannot be blinded, so the *outcome of the intervention* needs to be accessed by a blinded evaluator and caretaker.
- Report how the success of blinding was evaluated.
    - Example: ask the clients or evaluators whether they think a patient received the experimental or placebo or sham treatment and compare with actual treatment
- Report any known compromises in blinding.

- State the similarity of characteristics of the interventions.
    - Example: appearance, taste, smell and method of administration similar for control and test groups. It is, of course, easier to make herbal medicine, placebo and conventional medication have a similar appearance than acupuncture and sham treatment
- Herbal medicine must be compared with an inert substance of similar appearance in the same capsule at the same dosing frequency or with a conventional standard of care medication.
    - Example: placebo substance can be compounded in a form to appear similar to the herbal medicine; then can be "double blinded" from investigators, evaluators and clients
- In studies utilizing client feedback, investigators may have to separate the client from the animal during acupuncture or sham treatments, so they will not know which was performed.
- If a study was not blinded, provide good justification for not blinding. Studies without blinding usually have bias which seriously impairs the usefulness of the study for addition to the scientific literature.

12. Statistical methods and additional analyses

- Specify which statistical procedure was used for each analysis.
    - Further clarification may be necessary in the results section of the report.
- Study findings are often assessed in terms of their statistical significance, using a *p*-value.
- The *p*-value represents the probability that the observed data (or a more extreme result) could have arisen by chance, when the interventions did not truly differ.
- The mean plus or minus standard deviation (M±SD) with specific *p*-values should be supplied on all data where indicated and are best clearly displayed in Table form.
- Data analyses should be based on counting each participant once for any given outcome.
- Authors should provide a confidence interval for the estimated effect, which may be interpreted as the range of values for the treatment effect that is compatible with the observed data.
- A 95% confidence interval is customary, which gives the range expected to include the true value in 95 of 100 similar studies.
- Subgroup analyses are usually discouraged, as they may confound the overall conclusion.
- If additional analyses are performed between subgroups, authors should clarify the choice of variables that were adjusted for, how continuous variables were handled and whether the analysis was planned or suggested by the data.

RESULTS

1. Participants—flow, losses and exclusions

- Indicate the number of animals that were assessed for eligibility and not included in the study; did not receive the intervention as allocated; did not complete treatment; or were not included in the final analysis.
- This information permits the reader to assess to what extent the estimated efficacy of

therapy might be underestimated in comparison with ideal circumstances.

- State the reasons for lack of complete treatment, follow-up or inclusion in the analysis.

2. Recruitment and reason for discontinuation of a study

- Provide dates defining recruitment and follow-up periods.
- If follow-up times were determined by a specific outcome, then indicate the minimum, maximum and mean duration of follow-up periods.
- If the study was discontinued before originally planned, the reasons should be fully disclosed, including intrinsic and extrinsic factors and who made the decision to stop the trial.
- Indicate the role, if any, the funding agency played in the deliberations and decision to stop the study.

3. Baseline data

- Include baseline data such as clinicopathological test results of study animals before the test or control interventions
    - See **Trial Design** (Methods #2)
- Baseline data can include other differences in study animals not previously described
    - See **Trial Design**
- Baseline data is often put in Table form in a column before interventions, during, and after test or control interventions.
- Comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred.

4. Numbers analyzed

- The number of participants per group should be given for all analyses.
- Give exact numbers of animals with a specific outcome out of the total number of animals evaluated with the percent in parentheses. 87/100 (87%)

5. Outcomes and estimations

- Trial results are often more clearly displayed in a table and should also be described in the text.
- Study results can be reported as a summary of the outcome in each group.
- The number of animals with or without the outcome out of the total or the mean and standard deviation of measurements, together with the difference between the groups is known as the effect size.
- The estimated effect size and its precision, such as 95% confidence interval, should be stated.
- Results should be reported for all planned primary and secondary endpoints, not just for analyses that were statistically significant or “interesting”.
- Selective reporting within a study is a widespread and serious problem.
- Interpretation should focus on the final results at the close of the trial, not the interim results.

6. Ancillary analyses

- Multiple analyses of the same data create a risk for false positive findings and should be avoided.
- Report all analyses performed and clarify which were originally planned and which

were not planned.

- Analyses that were pre-specified in the trial protocol are less biased than those later suggested by the data.
- Adjustment for variables because they differ significantly at baseline is likely to bias the estimated treatment effect.
- If an adjustment was made for baseline variables, both unadjusted and adjusted analyses should be reported.

7. Adverse events

- Report all adverse events or side effects observed in all groups.
- Randomized trials offer the best approach for providing safety data as well as efficacy data.

DISCUSSION

The discussion should include:

- A brief synopsis of the key findings
- A discussion of key findings presented in the results section
- Do not offer new results in this section
- Consideration of possible mechanisms and explanations
- Comparison with relevant findings from other published studies (whenever possible including a systematic review combining the results of the current study with the results of all previous relevant studies)
- Limitations of the present study (and methods used to minimize and compensate for those limitations)
- A brief section that summarizes the clinical and research implications
- A concluding paragraph to summarize findings and recommendations based on the results

1. Limitations

- Discuss trial limitations and include sources of potential bias, imprecision and multiplicity of analysis, if relevant.
- Internal validity is the extent to which the design and conduct of the study eliminate the possibility of bias.

2. Generalization of study results

- External validity is the extent to which the results of a study can be generalized to other patients and circumstances.
- If the internal validity of the study is poor there can be no external validity.
- Applicability of the study findings to similar and other problems should be clearly stated.
- Although some variation in treatment response between an individual patient and the patients in a trial or systematic review is to be expected, the differences tend to be in magnitude rather than direction.

3. Interpretation – overall evidence

- Interpretation of findings should be consistent with results, balancing benefit and risks and considering other relevant evidence.
- Interpret the results in the context of current evidence.

• Bayesian methods can be used to statistically combine the trial data with previous evidence.

OTHER INFORMATION

Registration

• If a trial is registered, provide the number.

Protocol

• If the complete study protocol is available, provide the citation for interested readers.

Funding Source

• State the source of funding. Example: "This study was supported by a grant from the American Association of Traditional Chinese Veterinary Medicine Research Foundation").

* Note: Adapted for reporting of clinical trials in traditional Chinese veterinary medicine from STRICTA, CONSORT, TCM CONSORT and REFLECT Statements[1-6]

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