

Statistical View of Clinical Trials: Industry  
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### Introduction

The statistical techniques used in the design and analysis of veterinary clinical trials are similar to nonclinical trials, possibly with one major exception. There is a need to consider the severity of an infection or condition in an animal when planning for the design and analysis. With this one exception the principles considered in this paper are similar for all animal trials. This paper will briefly discuss basic principles of design, implementation and analysis of clinical trials. The model used in this paper will consider the design of trials for a coccidiostat in broilers.

### Design Considerations

Since statistics is a tool to assist the scientist in making decisions in the face of uncertainty, the importance of planning the trials and executing the plan cannot be overstated. Too often the role of a statistician is thought to be only analysis of the trials, when in fact the analysis follows the design.

This implies that if there is no design in the plan to use statistics, then there is no analysis. In a strict sense this is true. How do we design trials so that a natural analysis follows? Let's illustrate some basic principles by using the example of a coccidiostat in broilers, restricting this example to field trials with a new coccidiostat.

The usual method in research for developing a plan is through the use of a research protocol. Since the development of a drug in the field, such as a coccidiostat, requires conduct of trials at multiple sites, a procedure called protocol guideline has been developed in the animal science division at Lilly. A protocol guideline specifies the general requirements for each individual trial. Table 1 lists general areas covered in a protocol guideline. Individual trial protocols are then developed using a protocol guideline as a guide.

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Table 1. General Content of a Protocol Guideline

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1. Objective(s)
    - a. Primary
    - b. Secondary
  2. Animal description - breed, age, sex, weight, source, history, number, identification, etc.
  3. Study design
    - a. Treatments - brief, concise description
    - b. Design - experimental unit, randomization procedures, number of replications, treatment allotment procedures
  4. Trial facilities
    - a. Location
    - b. Size - dimensions, number required, construction, etc.
    - c. Feeding and watering equipment
    - d. Weighing and handling facilities
  5. Feed formulations and feeding procedures
    - a. Feed formulations - kind, number, nutrient levels, mixing procedures, etc.
    - b. Feeding procedures - how, when, where, duration
    - c. Nutrient assays - sampling procedure, schedule, etc.
  6. Drug formulation and administration
    - a. Formulation - type, source, concentration
    - b. Administration - how, when, where, duration
    - c. Drug assays - sampling procedure and schedule, no samples, etc.
  7. Special considerations - techniques, animal removal, necropsy/autopsy, specimens, etc.
  8. Measurements and records - variable name, schedule, collection procedures
  9. Statistical analysis - method of analysis, variables analyzed
  10. Concomitant animal health therapy - procedures, permitted drugs
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Statistical inputs may be required in all areas of the protocol. In the example of a new coccidiostat, initial field trials are commonly dose response studies. The statistician is often asked for advice on the number of doses, spacing of the doses, and the number of replications and randomization procedures. Individual trials are often considered a block in the total design. Although each trial can be analyzed individually, the plan is usually to include the individual trials in an overall analysis, often called a pooled analysis.

From the aspect of the anticipated pooled analysis, the statistician should consider the power of a test, i.e. the ability of a statistical procedure to detect differences between treatments. In order to determine power in a simple experiment with two treatments, the statistician would need an estimate of difference to be detected, variability (variance), and acceptable error rates for significance and detection of a specified difference. Too often power estimates are not obtained prior to experimentation. Power estimates give a scientist the probability of success for detecting a difference of interest.

#### Trial Implementation

Statisticians should also be interested in trial implementation. Too often statisticians may feel that their involvement has been adequate if they have been involved in the design and analysis of the trial. However, the implementation step is also critical for the statistician. Suppose in our example of a coccidiostat trial, the basic design within a trial is a randomized block, i.e. treatments are allocated to a block, such as a section of a facility, and there are a number of blocks. A portion of the birds are sacrificed at 28 days of age for interim intestinal lesion scoring by selecting birds from each pen across all blocks. To implement the design correctly, birds are selected from each pen within a block. The lesions are then scored for birds within a block before scoring birds in another block.

Scoring by blocks allows the scientist to minimize the variability within block and to maximize the variability between blocks. For example, lesions could be scored for Block A in the a.m. and Block B in the p.m. Any difference due to a.m. and p.m. readings would be removed from the analysis; comparison of treatment effects within blocks would be more precise. If the protocol is not followed during scoring of lesions, i.e. blocking is ignored, treatment and blocking effects will be confounded and the residual variation (error) is probably inflated.

Since the scoring of lesions is a subjective measurement, concealing treatment identity during the scoring process is essential to removal of bias. The scientist may be influenced subconsciously by knowledge of treatment assignment during the lesion scoring process. The question is not one of honesty, but of subconscious influence. This concern has not been readily accepted by the scientist, but experience would suggest that factors that may cause biased evaluation should be consciously evaluated and eliminated.

These are just two examples of why implementation of a design is essential for preserving the design and eliminating bias. Every aspect of a design should be carefully evaluated to assure proper implementation.

#### Trial Analysis

The analysis flows naturally from the design and the successful implementation of the design. Since there are many methods for trial analysis, emphasis will be given to some general techniques.

Clinical trials are conducted for two purposes: hypothesis testing and/or estimation. In the example of the dose response trial with a coccidiostat, the primary purpose is to model the dose response relationship. The significance of the response can be tested, but the primary task is one of estimation. The general form of the analysis illustrated in Table 2 can be used for testing the significance of the coccidiostat in the reduction of intestinal lesions (hypothesis testing) or estimating the dose response relationship (estimation).

Table 2 Analysis of Clinical Trials

<u>Source of Variation</u>	<u>Degrees of Freedom</u>
Clinical Trials (b)	b-1
Treatments (t)	t-1
Trial by treatment	(b-1) (t-1)
Residual-Replication within trial by treatment (n)	(n-1) bt

In this model each individual trial is considered a block for purposes of analysis. The interaction of trial and treatment, i.e. the variability of a treatment effect across trials, is the appropriate term to test the significance of treatment. Often the interaction of trial and treatment is pooled with the remainder following a test of the interaction with the residual term. This is a reasonable and practical thing to do. If a drug is to have broad application, the response should be similar in all trials, i.e. no trial by treatment interaction.

However, on occasion there is a significant trial by treatment interaction. The cause should be investigated. A common cause in clinical trials such as for coccidiostats is variation in severity of infection. Trials with no infection in the controls contribute nothing to determining the dose response relationship and should be eliminated from the analysis. If a trial by treatment interaction still exists, another technique is to analyze trials by severity of infection, say light and severe.

Each individual trial should also be examined for outliers. Presence of outliers can result in biased estimates of treatment effects and inflated estimates of error. Statistical techniques can be used to detect outliers; experimental reasons should be examined for eliminating outliers from the study. Coding errors and dilution errors are a common cause of outliers. As a last resort, outliers can be eliminated from a study for statistical reasons.

#### Summary

The statistician should be involved in all phases of a trial -- design, implementation, and analysis. This degree of involvement by the statistician gives greater assurance that statistics will be used successfully as a tool for making decisions in the face of uncertainty.