Conducting successful on-farm clinical trials

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Abstract

One of the greatest values we can bring to our clients is information and the ability to apply that information to their farm business for the improvement of the lives of their cattle and employees, and their financial well-being. Our knowledge base comes from a variety of sources, each with their own strengths and limitations. Scientific literature, presentations at professional meetings, our own clinical observations, and networking with colleagues provide the source for most of our knowledge base. When we are unable to find answers, on farm clinical trials can serve as an immensely valuable resource. Conducted properly, this tool can provide timely, targeted and specific answers to important questions. However, caution is necessary before embarking on this journey. It is important to remember that trials are very involved, time consuming and a great deal of work. Failure to properly design, execute and interpret data from an on-farm trial can be frustrating, expensive and detrimental to the farm. On farm trials represent a great opportunity for veterinarians to provide valuable information to their clients but should be conducted with great planning and oversight.

Overview of study design

There are many different types of study designs, each with their own advantages and disadvantages. It is important to understand the different types of studies to understand the benefits and limitations of each. A simple initial distinction is to categorize the study as descriptive or analytical[1,2]. Descriptive trials are purely observational. In these studies, a specific case (or number of cases) or factors of interest about a population are reviewed. These studies provide detailed accounts of what happened (case report) or serve to describe the characteristics of a population (survey or census). They are retrospective, non-randomized, and unable to evaluate causal relationships. Descriptive studies are useful for understanding the prevalence of a disease (survey or census) and for describing an emerging or rare disease.

Analytical studies can be subdivided as experimental or observational. Experimental trials involve applying an intervention to a group and then monitoring that intervention's impact[2]. Experimental trials involve a treatment group and a control group, with animals assigned randomly to one group or the other[2]. With proper randomization of the experimental unit (animals, pens, quarters, feet, etc.) to a treatment or control group, the researcher can be reasonably assured that each group will be of a similar size and confounding variables, both known and unknown, will impact both groups in a similar fashion. When performed properly, prospective randomized clinical trials can be a very valuable tool and provide the researcher with a high degree of confidence in the outcome[2]. While an excellent tool, it is also important to consider that these studies are time consuming, costly and typically require large populations.

Observational studies involve monitoring a population. These types of studies do not involve an intervention, rather just an observation of exposures or interventions and outcomes of interest. Observational studies attempt to find an association between some variable and some outcome. Cohort studies, case control studies and cross-sectional studies are all observational[1]. Cohort studies are non-randomized trials that group animals based on an exposure or a factor of interest[1]. (e.g. cows with an elevated blood BHB concentration versus cows with a low BHB concentration). Once the exposure of interest is identified, each group is studied for potential outcomes (often a disease) to determine associations between exposure and outcome. Case control studies are also non-randomized trials that separate animals into groups based on outcomes and attempt to determine association between outcomes and exposures (e.g. studying animals that did or did not have mastitis). Cohort studies separate groups based on exposure to some factor of interest while case control studies separate groups based on some outcome or disease of interest. The validity of cohort studies and case control studies increases in general as the sample size increases and if the animals within the 2 non-randomized treatment groups are similar overall (similar parity, days in milk, breed, etc.). Cross-sectional studies are an additional type of observational study that help describe a population. They look at diseases and exposures at a single point in time and help to describe the population by measuring the prevalence of a disease.

All types of trials can be useful. Prospective randomized clinical trials are the best tool for evaluating cause and effect but are expensive, time consuming, and the conclusions only apply to a very precise set of circumstances. Observational trials are useful for describing a population and identifying potential risk factors that are correlated with outcomes, however, they lack the ability to clearly evaluate causal relationships.

Factors to consider when designing the trial

Every trial begins with a question or hypothesis. A careful review of existing data should be performed to identify if there is a true knowledge gap and if the trial is necessary[3]. If trials have previously been performed to answer the question of interest but there is a need or desire to proceed anyway, a review of the current body of research can be useful to help with experimental design and setting up your trial 2,3. Developing a hypothesis allows the researcher to achieve the following goals: 1) select the appropriate study design, 2) choose the right sample population and sample size to measure the difference that is clinically relevant, 3) establish a "how to" guide for daily study activities such as assigning animals to treatment group and collecting data, and 4) guides the investigator towards appropriate methods to analyze data[2].

Failure to properly define the question(s) you are asking and the methods with which you will answer that question is like building a house without any architectural plans. The study protocol cannot be made up as you go along. A clear outline of the question being asked and how you are going to answer it is critical to conducting a valid study.

Before proceeding with a study, it is important to determine the number of animals or experimental units needed to achieve your stated goal. Sample size calculations are based on the

magnitude of the difference that you would like to measure and the confidence that is desired in the answer. The difference that you would like to measure between treatment groups should be realistic and practical. The smaller the difference you are looking at, the larger the sample size needed. Determining the appropriate sample size before the study will help you identify the farms that would be capable of conducting a study and help everyone understand how long the study will take4. This will prevent later frustration with regard to the expense and effort required to complete the study. Statistical power is the chance of detecting a difference between the treatment and control group, if a difference truly exists4. The greater the statistical power desired, the larger the sample size needed. Sample size calculations are performed using a power analysis. This is a great time to enlist the help of a statistician (if you haven't already). As stated above, it is important to understand the total number of subjects needed to find the relationship and magnitude of relationship that you are looking for before you begin the study.

Control groups provide a critical role and are an essential part of the study design[1]. The control group should be as similar as possible to the treatment group but will not receive the exposure or intervention of interest. The control group serves as a vital comparison against the treatment group to evaluate if the intervention or exposure of interest causes the outcome being studied[1].

Some studies may require the use of a placebo in place of the control group. The placebo minimizes any confounding bias by administering all aspects of the treatment or intervention being studied except for the actual treatment. In the case of a study to evaluate a new antibiotic, the treatment group would receive the new antibiotic and the control group would receive all components of the new drug (preservatives, vehicle, etc.) minus the actual antibiotic. In this way, the study can truly measure the impact of the antibiotic and not the process of the animal getting injected or the other components of the new drug.

Animals should be allocated to treatment group by randomization. This process assigns animals to treatment group using chance (random number table, computer program, flipping a coin) and helps to minimize the risk of selection bias1. Ideally, the control and study populations should be similar in composition with respect to any potential confounders.

Blinding (also known as masking) helps prevent informational or observer bias[1]. In a blinded study, the researchers making observations and collecting data do not know which animals are in the treatment group or the control group. Blinding is difficult and can be quite costly to achieve. It requires additional personnel and assigns personnel to specific roles for the duration of the trial. There may be times when blinding is not possible. An example would be evaluating the impact of displaced abomasum correction (surgery versus toggle pin fixation) on production and mortality. It would be impossible to blind the observer to treatment in this case. When blinding is not part of the study, it is important to make outcomes as objective as possible and discuss the potential for bias amongst all research personnel.

The experimental unit or entity being assigned to treatment group and analyzed statistically does not always have to be an animal. While the experimental unit is often and animal, it may be a pen of animals, an individual teat or quarter of an udder, an individual foot and so on. When individual anatomical parts are assigned to be the experimental unit, care must be taken to remove or control for confounding variables that affect the animal as a whole and therefore may potentially affect all the body parts of an animal in addition to the impact of the treatment or intervention being studied. For example, if a teat is the experimental unit in a teat dip trial, caution must be taken to control for cow level factors that may influence the teats of one cow more than another (stage of lactation, milk production, exposure to weather) above and beyond the impact of the teat dip itself.

While planning your study, take care not to overlook some of the more mundane aspects of the study. Simple topics such as data recording, the method of randomization, who will be involved in the trial and what tasks they will perform, and whether blinding will be practiced or not should not be ignored. More help is usually better than less help. Students, undergraduate and veterinary, are engaged, competent and enthusiastic participants. Conduct meetings with all personnel that will be involved in the trial to clearly explain how animals will be enrolled, where they will be housed, if they are to be handled differently than other cows on the farm and if the trial will impact non-study personnel such as the feeder or AI technician. Lists of animals requiring daily trial activities, automated data capture of outcomes such as milk production and an easy way to retrieve study data are very valuable and can be accomplished on the dairy farm with herd management programs such as Dairy Comp 305 (Valley Ag Software) and Microsoft Excel (Microsoft Corporation). Funding is also important to discuss with the farm before the trial begins. Establish who will be responsible for the study product, on farm labor, sample analysis and your time as a researcher prior to the study. On farm trials can be lengthy and costly and it is important that the farm is committed to the entire process and fully understands how it will impact their daily activities prior to starting.

Minimizing bias and confounders

Bias is a prejudice or imbalance that favors one group or another in a study population[3]. Bias can be intentional or unintentional. In either case, it creates a systematic error and provides a false impression of whether a factor is important or not. Bias can be introduced when assigning animals to study group (selection bias)3. An example of this would be treating animals for coliform mastitis. Cows that are very sick may get treated more aggressively while cows that are mild to moderately sick receive a different therapy. The result of treatment in this case is not only influenced by the treatment, but also by the severity of the disease making it impossible to truly evaluate the impact of treatment alone. Selection bias can be minimized by clearly defining the population of interest and randomly enrolling animals in the trial.

Bias can also be the result of some confounding variable[3,5]. This is any factor, outside of the exposure or intervention of interest, which influences the study population being evaluated. Confounding variables make it difficult to determine if the outcome is a result of the exposure or intervention of interest or the confounding variable. A confounding variable may mask an association that exists or may create the appearance of an association that doesn't exist[5].

Informational bias occurs when there are differences in data collection between treatment groups. This may occur when the observer is not blinded or there is some subjectivity in the measurements being made. Informational bias may also occur when a poor or inconsistent test is being used to measure the outcome. Information bias can be reduced by using accurate and precise measurement tools or specific classification systems that reduce the subjectivity of the measurement.

Selecting the proper study farm

There are several factors to consider when deciding if a farm is a suitable candidate for a clinical trial. Chief among these factors is the farm's ability to record data, retrieve it easily and follow directions. Compliance with on farm treatment protocols and policies is critical. If the farm doesn't routinely follow the treatment protocols and other farm specific procedures, they are unlikely to follow the trial protocol. The results will be frustrating. Communication is also essential. Many issues arise during a trial that require discussion between the researcher and the farm. Addressing issues early and being open about concerns or the ability to adequately follow the trial protocol are vital to success. From a practical perspective, farm size should be considered. Performing a prospective randomized clinical trial to evaluate a specific treatment or intervention is simply not possible on a small farm (unless the trial lasts for many years). The disease will not occur often enough to achieve the desired sample population in a short period of time. Location should not be overlooked. Study sites will be visited continuously throughout the trial making the selection of a study farm close to the researcher's location very convenient.

Summary

On farm studies are a very useful tool for providing valuable information to clients. They provide veterinarians with the opportunity to help the farm answer specific questions to enhance animal health and performance. Conducting on farm studies can be very rewarding but great care should be taken to conceive, design, conduct, and analyze the study to maximize validity and minimize the risk of forming a conclusion that is not accurate.

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