Using network meta-analyses to increase the power of a subsequent trial with a new treatment

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Introduction

Randomized controlled trials remain a critical way to assess interventions in feedlot production. For areas where effective interventions are known to exist, increasingly, the question of interest is about non-inferiority of alternatives, i.e., is a new treatment at least equivalent to a currently used product. The question of non-inferiority is often more meaningful and realistic than asking if the new treatment is superior to current therapy. The new product might be equal in efficacy, but cheaper or have other favorable attributes which would still motivate switching products. Given the desire to assess non-inferiority, the next step is to design a trial. Usually, this would involve determining the sample size, however, some feedlots are limited in the sample size that can be enrolled. In these circumstances, the question is, given this sample size, what is the power of a non-inferiority study? Here, we propose a method that prospectively plans to incorporate the new trial results into a network meta-analysis. With this plan, data from the meta-analysis can be considered in power calculations resulting in a more powerful design than traditional stand-alone approaches.

Materials and methods

The scenario developed was about 3 possible treatments of interest (A, B, and C). Two of the treatments of interest were not novel and, studies comparing these 2 treatments are already available from previous work (A and B). This means that the network of prior evidence contains information about the comparative efficacy of the prior 2 treatments (A compared to B). In the simulated scenario, 2 treatments (B and C) were equivalent to each other, and both were superior to the third treatments (B and C were superior to A). Using 10,000 simulations, we evaluated 3 approaches to estimating the power of the question about non-inferiority and superiority. As B and C were equal, only one question of superiority was needed because the power of assessing the superiority of C to A is equal to the power of B to A. After developing these scenarios, we conducted 3 power calculations:

1) the standard power calculations independent of the prior network of evidence;
2) an approach that determined the power of the testing, when we considered the evidence available, would include both the direct evidence from the 3-arm trial and borrowed the indirect evidence from the prior trial network;
3) an approach that determined the power of the testing using an uneven allocation approach. This method incorporated the frequency of estimates of A and B in the network, the direct evidence from the 3-arm trial, and the indirect evidence from the prior trial network. The method then optimized the allocation of animals to the 3-arm trial for the most powerful trial.

Results

The results of the simulations clearly showed that adding the network of evidence was associated with increased power when the sample size is fixed. For one scenario, for a study that had 65% to assess non-inferiority, the power was increased to 70% with the use of the second method (borrowing indirect information from the network) and 80% for the third method. In another example, for a study that had 80% to assess superiority using traditional approaches, the power increased to 90% with the use of the second method and 95% for the third method. This result implies that technically few animals could be enrolled if the goal was to maintain 80% with considerable cost savings. The exact power gained, and the change in allocation needed was dependent upon 1) the definition of non-inferiority, 2) the distribution of studies in the network, and 3) the between-study variation.

Significance

We have developed an approach of increasing the power of trials with a novel treatment and in fixed sample sizes, that borrows information from a network of evidence. Being able to conduct more power studies from fewer animals is an enormous advantage as trials are expensive. Further, leveraging information from prior trials that are exchangeable with the current trial maximizes the value of investments made in prior trials. The approach we have developed has been added as an online web application that would allow end-users to assess how they can incorporate evidence from prior networks (either published or private networks) to increase the power of trials of interest.

