

# Procedures and methods for modifying the CONSORT statement for livestock interventions studies

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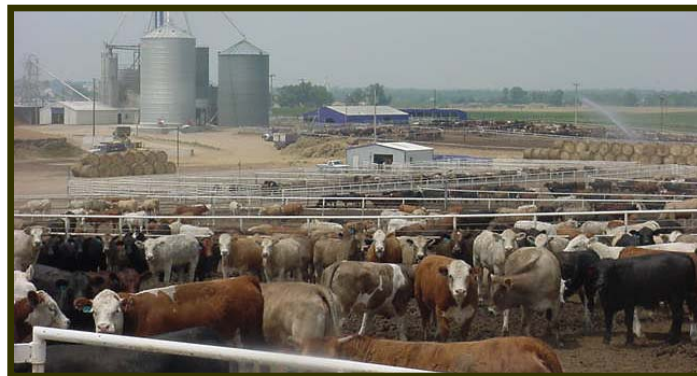
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# Outline

- What are intervention studies?
- Is there evidence of a problem in veterinary science?
- Approaches have been used in other fields?
- Methods and procedures used by our group?

# Randomized controlled trials (RCTs)

- Experimental units (individuals or groups) are assigned to treatment or control and followed over time to compare disease incidence between groups
- The [gold standard](#) for evaluating efficacy of treatments / interventions under “real-world” conditions
- Veterinary science has a unique design- [the challenge study](#)
- Methodological features to reduce bias are known
- Biased results can mislead decision making at all levels; from treatment decisions to policy decision making



Is reporting of important methodological features a problem in veterinary trials ?



# Evidence that reporting of key trial features may be a problem

- The assumption is that researchers report what they do
- Failure to reporting a design feature likely means it was not employed

# Evidence that reporting of key trial features may be a problem

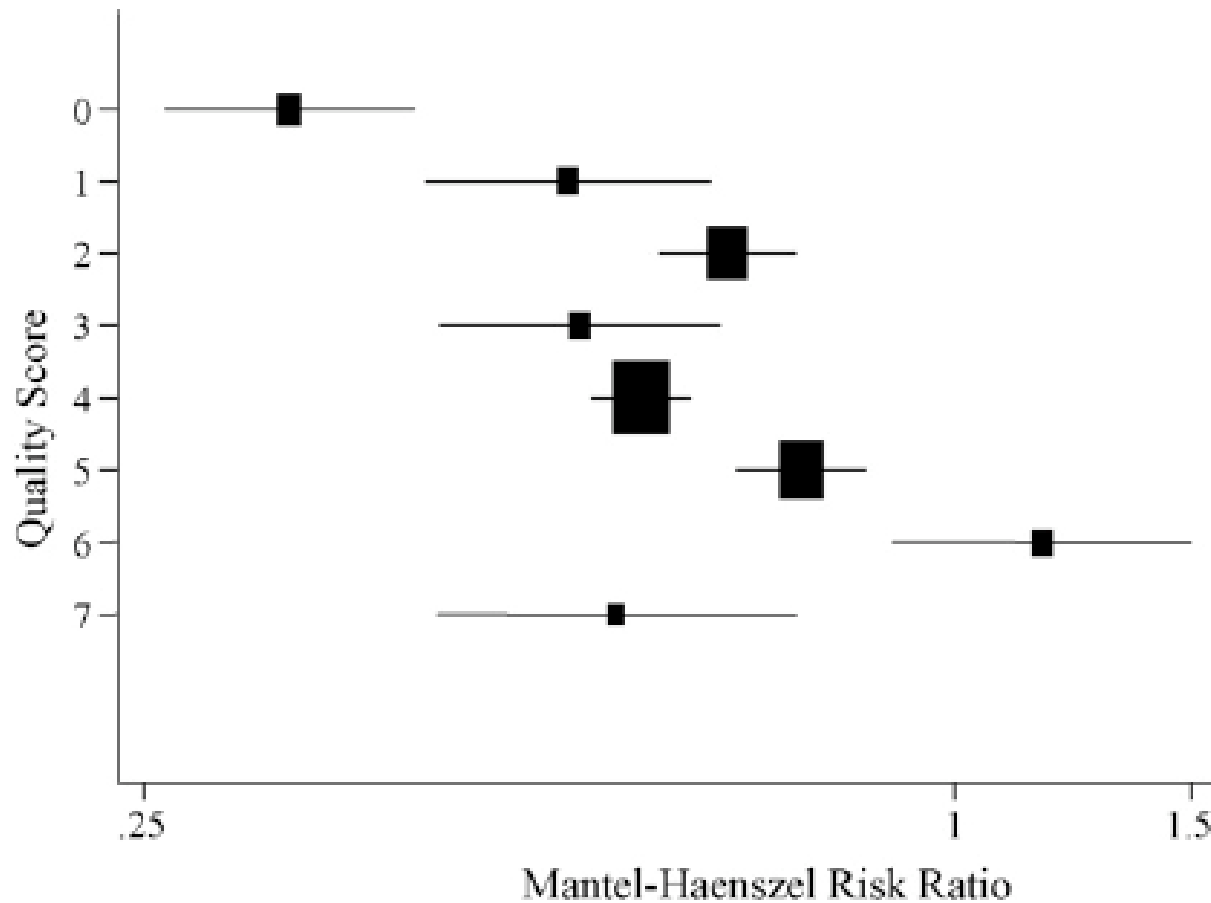
- Recent systematic reviews have highlighted issues with reporting in published trials:
  - What is the quality of reporting?
  - Is there evidence of bias being introduced?
- 3 studies of quality of reporting of intervention studies
  - Burns and O'Connor, 2008
  - O'Connor et al, 2009 (submitted)
  - Sargeant et al, 2009

# Association between design features and outcome

- Review of 127 pinkeye vaccine studies
- Evaluated for 7 design features
  - study population (breed and age);
  - vaccine regimen (vaccine strain, adjuvant, dose, route, and frequency); placebo or adjuvant as the control (versus non-vaccination);
  - explicitly stated case definition;
  - frequency and duration of disease assessment following vaccination;
  - control of confounding through randomization or blocking when assigning animals to treatment groups
  - blinding of investigators to animals' vaccination status.

# Association between design features and outcome

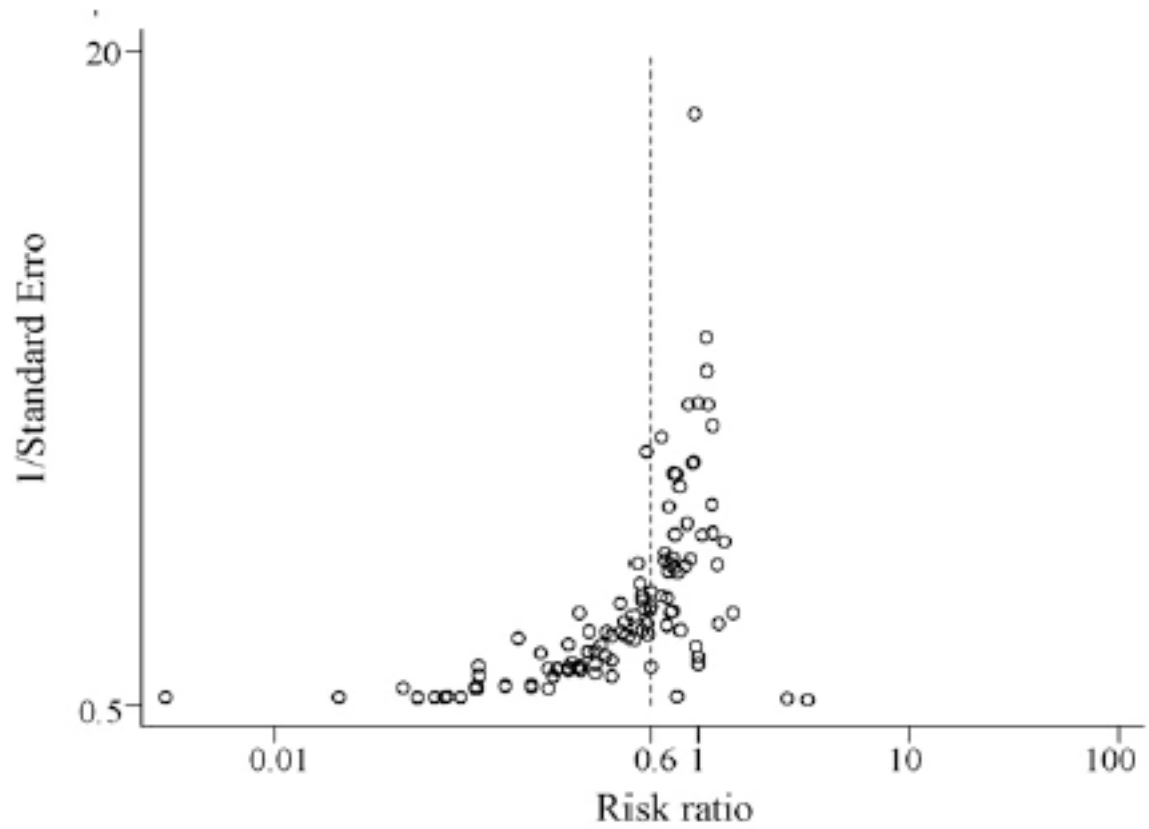
- 0 features - 7 trials
- 1 feature - 3 trials
- 2 features- 15 trials
- 3 features- 7 trials
- 4 features- 48 trial
- 5 features- 25 trials,
- 6 features- 4 trials
- 7 features- 4 trials.



**Fig. 4** The summary Mantel–Haenszel risk ratio for each descriptive score group of trials ( $N=118$ ).

# Empirical evidence of bias

- Of 15 trials that reported randomization and blinding 3 (20%) reported effective vaccines
- Of the 107 trials that didn't report randomization 43% reported effective vaccines



**Fig. 3** Funnel plot describing the distribution of study risk ratio compared to inverse of the standard error of risk ratio.

# 29 manuscripts about Bovine Respiratory Disease Therapy

- 12 of the 29 manuscripts did not disclose a funding source
- 21 of the 29 manuscripts had an author who was clearly identified as an employee of a pharmaceutical company.

# BRD Therapy Studies

- 36 of the 41 studies reported using a random method of treatment allocation.
- In some cases it seemed possible that a non-random process was described as random, i.e. “calves were ranked from highest to lowest weight, and randomly assigned alternatively to either the florfenicol or the tilmisocin group”

# BRD Therapy Studies

- 3 of 41 studies included a study size justification.
- No studies described the null hypothesis
- Unclear if the studies were inferiority or superiority studies i.e. “as effective”, “equivalent to”.
- 37 of the studies had at least 3 outcomes. The largest number of outcomes reported was 14. for the majority of studies.

# Assessing the methodological quality of trials in veterinary medicine

- Objectives:
  - 1) Document current quality of reporting of important methodological features and completeness of reporting for clinical trials of interventions in small animals, food animals, and on-farm food safety
  - 2) Evaluate associations between quality assessment of the trials and the probability of finding a positive treatment effect
- “Trials” included:
  - Clinical trials in client owned animals
  - Clinical trials in research herds / colonies
  - Challenge trials (deliberate exposure of study subjects to infectious disease outcome)

# Sample of Results: Methodological criteria

	SA (N=100)	LA (N=100)	FS (N=100)
Number of animals housed together per group clearly stated	NA	35	52
Level of treatment allocation described	NA	94	90
Treatment groups randomly assigned (explicitly reported)	74	65	45
Outcome assessor blinded to treatment allocation	40 / 91	17 / 95	5 / 100
Lost to follow up reported	80	62	52
Formal statistical analysis performed	95	91	92
Statistical analysis described for each outcome	88	80	83

# Sample of Results: Completeness of reporting

	SA (N=100)	LA (N=100)	FS (N=100)
Objectives stated	95	91	91
Inclusion /exclusion criteria for study subjects described	42	39	16
Study subject signalment described	68	42	37
Intervention protocol described in sufficient detail for replication	93	80	88
Measurement of all outcomes described	98	79	85
Sample size justified	3	5	1
Baseline differences between treatment groups evaluated	33	14	10

## Associations with probability of a reporting a positive treatment effect

- Studies that stated allocation to treatment was **random** did not have a higher proportion of positive results than studies that did state allocation to treatment was random ( $p=0.398$ ) [except for large animal trials]
- Studies reporting that **outcome assessor was blinded to treatment allocation** had a lower proportion of positive treatment effects ( $p<0.001$ )
- Studies reporting **number lost to follow up** had a lower proportion of positive treatment effects ( $p=0.001$ )

# We may have a problem ...

- Reporting of key methodological features and completeness of reporting is not ideal
- This may be associated with trial results
- Standardized checklists for reporting clinical trials would aid authors, reviewers, and editors in ensuring that important aspects of trial design and reporting are considered



# Modified the CONSORT

- The CONSORT statement is a document that contains a checklist of 22 items that should be included in a report of an intervention trial
- It was simultaneously published in Lancet, Annual of Internal Medicine, Biomed and British Medical Journal in 2001
- Endorsed as the standard in over 160 journals

# Consensus Meeting

- 2 days in Chicago in November 2008 and numerous edits since

# Relevance to Livestock

- Few differences
  - Need to expand the housing description for livestock
  - Need to address unit of allocation
  - Need to address challenge studies

# Consensus Meeting Participants

- 1 - poultry production and food safety,
- 1 - familiar with aquaculture
- 5 -beef food safety and production
- 3 -swine food safety and production
- 5 -dairy food safety and production .
- 2- PhD level statisticians
- 5- microbiologists / food safety researchers.
- 3 government employees.

# Consensus Meeting Participants

- 7 were senior/assistant/associate editors.
- 1 from Australia, Germany, 5 in Canada, and the remainder in the United States.

# Methods and Processes

- Methods and Processes of the REFLECT-LFS statement: Reporting guidelines For randomized Control Trials in Livestock and Food Safety: Modifying the CONSORT statement
- A. M. O'Connor, J. M. Sargeant, I A. Gardner, J. S. Dickson, M. E. Torrence and consensus meeting participants: C. Dewey, I.R. Dohoo, R. B. Evans, J T. Gray, M Greiner, G. Keefe, S. L. Lefebvre , P. S. Morley, A. Ramirez, W. Sicho, D Smith ,K. Snedeker, J. Sofos, M. Ward, R. Wills

<b>PAPER SECTION And topic</b>	Item	Description of item.
TITLE & ABSTRACT	1	How study units were allocated to interventions (e.g., "random allocation", "randomized", or "randomly assigned"). Clearly state whether the outcome was the result of natural exposure or was the result of a deliberate agent challenge.
INTRODUCTION Background	2	Scientific background and explanation of rationale.
METHODS Participants	3	Eligibility criteria for owner / managers and study units at each level of the organizational structure, and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group, the level at which the intervention was allocated, and how and when interventions were actually administered.
	4b	Precise details of the agent and the challenge model, if a challenge study design was used.
Objectives	5	Specific objectives and hypotheses. Clearly state primary and secondary objectives (if applicable).
Outcomes	6	Clearly defined primary and secondary outcome measures and the level at which they were measured, and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. Sample size considerations should include sample size determinations at each level of the organizational structure and the assumptions used to account for any non-independence among groups or individuals within a group.
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence at all relevant levels of the organizational structure, including details of any restrictions (e.g., blocking, stratification)
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence at all relevant levels of the organizational structure, (e.g., numbered containers), clarifying whether the sequence was concealed until interventions were assigned.
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled study units, and who assigned study units to their groups at all relevant levels of the organizational structure.
Blinding (masking)	11	Whether or not those administering the interventions, caregivers and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. Provide justification for not using blinding if it was not used.
Statistical methods	12	Statistical methods used to compare groups for all outcome(s); Clearly state the level of statistical analysis and methods used to account for the organizational structure, where applicable. Methods for additional analyses, such as subgroup analyses and adjusted analyses.
RESULTS Participant flow	13	Flow of study units through each stage for each level of the organization structure of the study (a diagram is strongly recommended). Specifically, for each group report the numbers of study units randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.

# Item 7

## Sample size

- How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. Sample size considerations should include sample size determinations at each level of the organizational structure and the assumptions used to account for any non-independence among groups or individuals within a group.

# Explanation and Elaboration

- The REFLECT-LFS statement: Reporting guidelines For randomizEd Control Trials in Livestock and Food Safety: Explanation and Elaboration
- J. M. Sargeant, A. M. O'Connor, I A. Gardner, J. S. Dickson, M. E. Torrence and consensus meeting participants: I.R. Dohoo, S. L. Lefebvre , P. S. Morley, A. Ramirez

# *Examples*

- A sample size of 699 animals in each group was calculated to have an 80% power to detect a difference in means of 1.5 kg, assuming that the common standard deviation was 10 kg using an ANOVA with a consecutive two group *t*-test and a 5% two-sided significance level. For compensation of possible drop outs a total of 1542 healthy piglets from three consecutive farrowing batches, each comprising approximately 500 animals were included into this study (34).

# Elaboration

- Use of an adequate sample size to detect treatment differences that are economically and biologically important is fundamental to sound trial design. The main statistical considerations in sample size calculation are the magnitude of the effect size (e.g. difference in proportions, means, survival times etc), standard deviation of the outcome (if the outcome is continuous), power ( $1 - \beta$  (type II error) = probability of accepting the null hypothesis when it was not true) and the

# Journals for Publication

- Journal of Internal Veterinary Medicine
- Journal of Swine Health and Production
- Journal of Food Protection
- Zoonoses and Public Health
- Preventive Veterinary Medicine
- Foodborne Pathogens and Disease
- Journal of American Veterinary Association

# Funding provided by:

- USDA-funded Food Safety and Response Network
- National Pork Board
- Laboratory for Foodborne Zoonoses in the Public Health Agency of Canada
- Canadian Institutes of Health Research (Applied Public Health Research Chair program)
- The Association for Veterinary Epidemiology and Preventive Medicine
- The American Meat Institute Foundation.

# Questions / comments?



## PROBLEMS

NO MATTER HOW GREAT AND DESTRUCTIVE YOUR PROBLEMS MAY SEEM NOW,  
REMEMBER, YOU'VE PROBABLY ONLY SEEN THE TIP OF THEM.

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