REFLECT statement – Reporting guidelines for randomized controlled trials in livestock and food safety research

A O’Connor and J Sargeant
Outline

- Why does it matter that we do what we say and say what we did?
- Is there evidence of a problem in veterinary science?
- Approaches that have been used in other fields?
- Methods and procedures used by our group?
- Next steps?
Outline

Why does it matter that we do what we say and say what we did?

The basic principle of research is that we provide a reproducible description of the work so others can

- Reproduce to assess chance
- Assess biases for alternative explanations of the outcome
- Incorporate into research synthesis methods
- Animal ethics issue
Outline

- Why does it matter that we do what we say and say what we did?
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Research to evaluate interventions: Study design and evidence for decision-making

Building evidence for efficacy under "real-world" conditions

- Systematic review / meta-analysis of RCTs
- Randomized Controlled Trials (RCTs) (evaluation of interventions)
  - Cohort (hypothesis testing under real-world conditions)
  - Case-control (hypothesis testing under real-world conditions)
- Cross-sectional observational (hypothesis generating)
- Animal models (proof of concept)
- Laboratory models (proof of concept)
- Expert opinion
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
Evidence that reporting of key trial features may be a problem

- The assumption is that researchers report what they do (and this is the only information available to the reader)
- 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?

- Many studies of quality of reporting of intervention studies
  - Burns and O'Connor, 2008
  - Sargeant et al, 2009 (3 pubs)
  - Denagmange et al 2008
  - O’Connor et al, 2010 in press
  - Denagamange et al 2010 in press
Infectious Bovine Keratoconjunctivitis
Association between design features and outcome: Infectious Bovine Keratoconjunctivitis

- 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.

Burns and O’Connor, 2009
Number of designs features described within 127 Pinkeye vaccine studies

Burns and O'Connor, 2009
Evidence that quality reporting matters

Was the vaccine effective?

Authors did not report randomization and blinding (103 trials)

47% reported effective vaccines

Authors did report randomization and blinding (15 trials)

20% reported effective vaccines

Burns and O’Connor, 2008
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 (potential for bias)

“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)

Sargeant et al, 2009
Assessing the methodological quality of trials in veterinary medicine: Methods

- 300 trials were selected using structured search protocol:
  - 100 Small animal (2006 – 2008)
  - 100 Livestock (2006 – 2008)
  - 100 on-farm food safety (1998 – 2008)

- Structured checklists used to evaluate:
  - Quality and completeness of reporting
  - Number of outcomes and association of each outcome with intervention
  - 2 individuals evaluated each trial (separate for 2 checklists) with disagreements resolved by consensus
## Sample of Results: Methodological criteria

<table>
<thead>
<tr>
<th>Methodological Criteria</th>
<th>SA (N=100)</th>
<th>LA (N=100)</th>
<th>FS (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of comparison group</td>
<td><strong>85</strong></td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Number of animals housed together per group clearly stated</td>
<td>NA</td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>Level of treatment allocation described (herd, pen, animal)</td>
<td>NA</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Treatment groups randomly assigned (explicitly reported)</td>
<td>82 %</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>Double blinding</td>
<td>14 / 73</td>
<td>5 / 72</td>
<td>0 / 97</td>
</tr>
<tr>
<td>Lost to follow-up reported</td>
<td>75 %</td>
<td>62</td>
<td>52</td>
</tr>
<tr>
<td>Statistical analysis described for each outcome</td>
<td>89 %</td>
<td>80</td>
<td>83</td>
</tr>
</tbody>
</table>

Sargeant et al., 2009
Sample of Results: Complete reporting

<table>
<thead>
<tr>
<th></th>
<th>SA (N=85)</th>
<th>LA (N=100)</th>
<th>FS (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives stated</td>
<td>95%</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>Inclusion /exclusion criteria for study subjects described</td>
<td>44</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>Study subject signalment described</td>
<td>68</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Intervention protocol described in sufficient detail for replication</td>
<td>93</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>Measurement of all outcomes described</td>
<td>87</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td>Sample size justified</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Baseline differences between treatment groups evaluated</td>
<td>34</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

Sargeant et al, 2009
Assessing the methodological quality of trials in veterinary medicine: Outcomes

- Number of outcomes per trial ranged from 1 - 51
- Analysis of associations between treatment and outcomes (or not!):
  - Descriptive reporting of outcome results (i.e. no formal analysis for that outcome)
    - Small animals: 31% of outcomes
    - Large animals: 40% of outcomes
    - Food safety: 23% of outcomes
  - Outcome described in methods, but not reported in results
    - Small animals: 3.6% of outcomes
    - Large animals: 1% of outcomes
    - Food safety: 6.8% of outcomes
Associations with probability of a reporting a positive treatment effect

- Studies were more likely to reject the null hypothesis if they did not report
  - random allocation to group (p=<0.001) - confounding
  - blinded to group allocation (p<0.001) - misclassification
  - number lost to follow up (p=0.001) - selection bias

- All study features designed to reduce bias
We may have a problem …
Outline

- Why does it matter that we do what we say and say what we did?
- Is there evidence of a problem in veterinary science?
- **Approaches that have been used in other fields.**
- Methods and procedures used by our group.
- Next steps?
CONSORT-STATEMENT

- 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.
- Revised version published in 8 journals in 2010.
- Empirical evidence that CONSORT has led to improvements in reporting of clinical trials.
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- Next steps?
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Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety
Consensus Meeting

- 2 days in Chicago in November 2008 and numerous edits since
Relevance to Livestock

- Few differences
  - 2 levels of participant recruitment and eligibility: Owners and animals
  - 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.
<table>
<thead>
<tr>
<th>PAPER SECTION And topic</th>
<th>Item</th>
<th>Description of item.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE &amp; ABSTRACT</td>
<td>1</td>
<td>How study units were allocated to interventions (e.g., &quot;random allocation&quot;, &quot;randomized&quot;, or &quot;randomly assigned&quot;). Clearly state whether the outcome was the result of natural exposure or was the result of a deliberate agent challenge.</td>
</tr>
<tr>
<td>INTRODUCTION Background</td>
<td>2</td>
<td>Scientific background and explanation of rationale.</td>
</tr>
<tr>
<td>METHODS Participants</td>
<td>3</td>
<td>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.</td>
</tr>
<tr>
<td>Interventions</td>
<td>4</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Precise details of the agent and the challenge model, if a challenge study design was used.</td>
</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>Specific objectives and hypotheses. Clearly state primary and secondary objectives (if applicable).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>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).</td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>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.</td>
</tr>
<tr>
<td>Randomization -- Sequence generation</td>
<td>8</td>
<td>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)</td>
</tr>
<tr>
<td>Randomization -- Allocation concealment</td>
<td>9</td>
<td>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.</td>
</tr>
<tr>
<td>Randomization -- Implementation</td>
<td>10</td>
<td>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.</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>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.</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>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.</td>
</tr>
<tr>
<td>RESULTS Participant flow</td>
<td>13</td>
<td>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.</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>Dates defining the periods of recruitment and follow-up.</td>
</tr>
</tbody>
</table>
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

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 significance level ($\alpha$ = type I error = the probability of rejecting the null hypothesis when it was true).
Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety

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¹Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, Iowa ²Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada. ³USDA/FSIS/OPPPD/RMD 1400 Independence Ave, SW Washington, DC 20250 ⁴Department of Medicine and Epidemiology, 2415A Tupper Hall, One Shields Avenue, University of California, Davis, CA 95616 ⁵Room 4-2194 5601 Sunnyside Ave. GWCC-BLTSVL Beltsville, MD, 20705
Journals that have Published REFLECT

- Journal of Internal Veterinary Medicine
- Journal of Swine Health and Production
- Journal of Food Protection
- Zoonoses and Public Health
- Preventive Veterinary Medicine
Other Outlets for REFLECT

- Equator Network
- National Libraries of Medicine Reporting Guidelines site
- www.reflect-statement.org
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- Why does it matter that we do what we say and say what we did?
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Adoption and Endorsement

- We are explicitly asking for journals to actively adopt and endorse the REFLECT statement
- Why?
  - Reproduce to assess chance
  - Assess biases for alternative explanations of the outcome
  - Incorporate into research synthesis methods
  - Animal ethics issue
Adoption and Endorsement

- We want to partner with journal editors to make reporting more comprehensive and reviewing easier
- Poor reporting has been long known
- CONSORT has been the most successful initiative because of the support of editors
  - Editorial support and enthusiasm for improved reporting is key to success
Adoption and Endorsement

- How effective is the use of reporting guidelines?
  - Empirical evidence that CONSORT improves quality but not the panacea
Evaluation of the impact of CONSORT


- Devereaux PJ, Manns BJ, Ghali WA et al. The reporting of methodological factors in randomized controlled trials and the association with a journal policy to promote adherence to the Consolidated Standards of Reporting Trials (CONSORT) checklist. Control Clin Trials 2002; 23:380–8;
Adoption and Endorsement

- What does endorsement imply?
  - “Authors of interventions studies involving animals are encouraged to consult the REFLECT statement checklist while preparing their submission.”
  - Some impact but not the maximum potential
Adoption and Endorsement

- Effective endorsement:
  - “Authors of interventions studies involving animals such as challenge studies or field studies are required to include a completed REFLECT statement checklist as a supplementary document with their submission.”
  - Add checkboxes to submission process:
    - Is this an intervention study, if yes - have you submitted a REFLECT statement checklist?
    - Halt submission until checklist is received.
    - These steps will increase compliance and make life easier for the reviewer and editors.
Adoption and Endorsement

How we can help?

- Help authors have access to the materials
- Dedicated website for authors to download the checklist and accompanying documents
- Translations: French and Spanish checklists available, German coming
- REFLECT is listed at other locations – Equator and NLM
The REFLECT Statement

REFLECT stands for Reporting guidelines for randomized controlled trials for livestock and food safety. It is an evidence-based minimum set of items for trials reporting production, health, and food-safety outcomes.

The aim of the REFLECT Statement is to help authors improve the reporting of livestock trials with production, health, and food-safety outcomes. We have focused on both types of randomized trials, field trials and challenge studies in livestock, and the interventions may be therapeutic or preventive.

The REFLECT Statement consists of a 22-item checklist (listed below). It is an evolving document that is subject to change periodically as new evidence emerges. This website contains the current definitive version of the REFLECT Statement. The full text of the REFLECT statement is now available:

- Preventive Veterinary Medicine - PDF
- Journal of Food Protection - PDF
- Journal of Veterinary Internal Medicine - PDF
- Journal of Swine Health and Production - PDF
- Zoonoses and Public Health - PDF

The REFLECT Statement should be used in conjunction with the Explanation and Elaboration Document.

The REFLECT Statement: Reporting Guidelines for Randomized Controlled Trials in Livestock and Food Safety: Explanation and Elaboration.

Sargeant JM, O'Connor AM, Gardner IA, Dickson JS, Torrence ME, Dohoo IR, Lefebvre SL, Morley PS, Ramirez A, Snedeker K.
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