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The REFLECT statement: Methods and processes of creating Reporting Guidelines For Randomized Controlled Trials for livestock and food safety☆

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ABSTRACT

The conduct of randomized controlled trials in livestock with production, health, and food-safety outcomes presents unique challenges that may not be adequately reported in trial reports. The objective of this project was to modify the CONSORT (Consolidated Standards of Reporting Trials) statement to reflect the unique aspects of reporting these livestock trials. A two-day consensus meeting was held on November 18–19, 2008 in Chicago, IL, United States of America, to achieve the objective. Prior to the meeting, a Web-based survey was conducted to identify issues for discussion. The 24 attendees were biostatisticians, epidemiologists, food-safety researchers, livestock-production specialists, journal editors, assistant editors, and associate editors. Prior to the meeting, the attendees

☆ **Note from the editor**: The REFLECT statement is also published in Journal of Food Protection, Journal of Veterinary Internal Medicine, Zoonoses and Public Health, and Journal of Swine Health and Production. The Editorial board of this journal believes that the contents of this report will be an important forward step in standardizing the design and implementation of randomized clinical trials in animal health and food safety research arena. Authors can use any one of these references when citing REFLECT. Furthermore, the REFLECT Statement should be read in conjunction with the REFLECT Explanation and Elaboration Document which are available, at the REFLECT statement website www.reflect-statement.org.

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completed a Web-based survey indicating which CONSORT statement items may need to be modified to address unique issues for livestock trials. The consensus meeting resulted in the production of the REFLECT (Reporting Guidelines For Randomized Control Trials) statement for livestock and food safety (LFS) and 22-item checklist. Fourteen items were modified from the CONSORT checklist, and an additional sub-item was proposed to address challenge trials. The REFLECT statement proposes new terminology, more consistent with common usage in livestock production, to describe study subjects. Evidence was not always available to support modification to or inclusion of an item. The use of the REFLECT statement, which addresses issues unique to livestock trials, should improve the quality of reporting and design for trials reporting production, health, and food-safety outcomes.

Randomized controlled trials (RCT) are considered the gold standard for evaluation of the efficacy of interventions in human and veterinary medicine. In human medicine, inconsistencies with the reporting of intervention studies have been documented over the past 10–15 years (DerSimonian et al., 1982; Pocock et al., 1987; Gotzsche, 1989; Schulz et al., 1994; Sonis and Joines, 1994; Ah-See and Molony, 1998). To address these deficiencies, several initiatives were implemented to improve the transparency of the conduct and reporting of intervention studies. The best-known initiative is the CONSORT statement (Consolidated Standards of Reporting Trials). The CONSORT statement was published in 1996 (Begg et al., 1996), with a revised version published in multiple journals in 2001 (Moher et al., 2001a,b,c,d). The CONSORT statement is based on a two-group parallel design. Extensions of the CONSORT statement deal with the unique features of different designs, such as cluster trials (Campbell et al., 2004, 2005, 2006), harms (Ioannidis et al., 2004), herbal interventions (Gagnier et al., 2005, 2006a,b,c), and nonpharmacological interventions (Boutron et al., 2008a). These CONSORT statements are intended to improve the reporting of RCTs and consequently to assist readers in understanding a trial's design, conduct, analysis, and interpretation and in assessing the internal and external validity of a trial's results. The CONSORT statement emphasizes that this can only be achieved through complete transparency from authors. The revision of the original CONSORT statement and the subsequent extension for cluster trials has been adopted as the standard by at least 100 medical journals. There is evidence that use of the CONSORT statement in human medical journals has improved the quality of reporting of RCTs (Plint et al., 2006; Kane et al., 2007).

The issue of inferior quality of veterinary RCT reports was first raised in editorials and commentaries in veterinary journals in the early to mid-1990s (Chanter and Wood, 1994; Elbers and Schukken, 1995; Higgins, 1997). Recently, several systematic reviews of therapeutic, preventive, and food-safety trials in livestock species have highlighted the need for better reporting (O'Connor et al., 2006, 2008; Sargeant et al., 2007; Wellman and O'Connor, 2007; Burns and O'Connor, 2008). Better design, analysis, and reporting are critical to having a high-quality body of evidence that can be used for better decision making. Although the use of the 22-item checklist from the CONSORT statement could form the basis of an instrument to improve the quality of reporting for trials in livestock species, there are differences between human and livestock trials that necessitate some modifications to the existing CONSORT statement to maximize the benefits of its use for livestock species. The differences include two types of "participants" (the animals' owners/managers who consent to participation in a trial, and the animals who are the actual study subjects), the common use of clustered study designs, the use of a deliberate challenge to animals with infectious agents in some trials (a.k.a. challenge trials), and non-clinical outcomes (e.g., production indices). These differences make the direct use of the CONSORT statement challenging.

The aim of this report is to describe the methods and processes used to develop an extension of the CONSORT statement that could form the basis for standardized reporting guidelines for trials using livestock and that addresses issues unique to livestock research with production, health, and food-safety outcomes.

1. Methods

The process for extending the CONSORT statement to other applications is well documented (Hopewell et al., 2008; Boutron et al., 2008b). We used these reports to design the approach used for the modification reported here.

1.1. Steering committee

A steering committee was responsible for the development of the revised CONSORT statement. This group of six members was formed in March 2008. The committee agreed on the need to modify the original CONSORT statement and to use the approach reported previously as the guideline for the modification (Boutron et al., 2008b). The committee secured funding for the project, identified potential participants, invited the potential participants to attend a consensus meeting, organized the meeting, and was responsible for subsequent steps involved in report preparation and publication.

1.2. Funding

Funding was required to cover the costs of the consensus meeting (e.g., travel, accommodation, meeting

rooms). The decision was made by the steering committee not to seek funding from pharmaceutical or biological companies commonly associated with livestock production. Efforts to obtain funding were limited to government agencies and not-for-profit, non-government organizations. Funding was received from the USDA Food Safety and Response Network (Grant 2005-35212-15287), National Pork Board; Laboratory for Foodborne Zoonoses (Public Health Agency of Canada), Applied Public Health Research Chair program sponsored by the Canadian Institutes of Health Research's Institute of Population and Public Health and the Public Health Agency of Canada, The Association for Veterinary Epidemiology and Preventive Medicine, and The American Meat Institute Foundation. Sufficient funds were obtained to pay for all expenses for the participants at the consensus meeting. Sufficient money was not obtained to fund travel costs for all participants; therefore, some participants funded their own travel and the source of these funds was not identified.

1.3. Identification of participants

The committee's aim was to bring together a group of experts familiar with field trials or challenge studies in livestock species with production, health, and food-safety outcomes. Another aim was to include at least one representative from each major animal-protein production system (beef, dairy, swine, poultry, and aquaculture). Representation from major livestock-trading nations was also solicited because of different regulations governing interventions for protein-based foods around the world. The end users of the data, including but not limited to editors, government officials, and risk assessors, were also represented.

The committee decided to limit the size of the meeting to 26 participants, including the six committee members. The size limitation was arbitrary, but based on funding and the need for a group size that facilitated interaction. Using the previously described criteria for the desired mix of participants, the steering committee identified 20 experts, many with multiple areas of expertise, for invitation. The list of 20 experts was divided among the steering-committee members, who then extended an invitation to the experts. When the initial invitation was declined, the committee discussed an alternate who was then contacted.

1.4. Identification of specific issues

Using the approach described previously (Boutron et al., 2008b), a survey was sent to the invitees and committee members soliciting input on each CONSORT statement checklist item to improve relevance to livestock health, production, and food safety. This survey was administered by staff at Iowa State University and was granted an exception from human subjects approval by the ISU institutional review board. The survey included the 22 items of the original CONSORT statement and asked the participants to indicate if each item should be modified (yes/no) and if yes, to describe the rationale for modification. The survey was administered using Web-based software, or the participants could fill out a Microsoft Word copy of the survey and return it to a member of the steering committee.

After the surveys were returned, the responses for each checklist item were compiled. This included the number of respondents who had indicated yes/no for modification and the associated comments. The names of the participants were removed from their comments.

Boutron et al. (2008b) ranked the CONSORT checklist items based on the number of "votes" for modification; however, ranking was not done prior to this particular meeting. The rationale for modifying the approach was to allow more discussion about the items and to ensure that issues with few comments were also considered at the meeting.

1.5. The consensus meeting

A two-day consensus meeting was held on November 18–19, 2008, in Chicago, IL, USA. At the meeting, participants were provided with the following materials: (1) a copy of the CONSORT statement (Moher et al., 2001c), (2) a copy of the CONSORT explanation and elaboration document (Altman et al., 2001), and (3) a copy of the document describing the process of modifying the CONSORT statement for extensions to an additional application (Boutron et al., 2008b). The participants were also provided with a complete list of the comments from the Web-based survey and a list describing how often each CONSORT item had been reported in a study of 100 livestock trials reporting production or health outcomes, and 100 trials reporting pre-harvest food-safety outcomes (Sargeant et al., 2009a,b).

The meeting began with several presentations about the CONSORT statement, the results from the reviews of livestock-trial reporting, and a discussion of the approach to reaching consensus that would be used. Three voting criteria were suggested and discussed as indicators of consensus: 100% of participants must agree, >80% of participants must agree, or a simple majority (>50%). A secret ballot was taken to determine the level of agreement that would represent consensus. Participants indicated their preference on a blank piece of paper. The ballots were collected, counted, and reported to the group.

For the remainder of the meeting, the following approach was used for CONSORT checklist items 1–22. First, the participants were divided into three groups (determined by the steering committee) to include a mix of expertise from each subgroup (biostatisticians, epidemiologist, food-safety researchers, livestock-production specialists) and asked to discuss a CONSORT checklist item. At the end of the time designated for discussion (approximately 20 min per item), representatives from each group presented the opinions of the group. After all groups had presented their opinions, a discussion followed, and a proposed modification (or not) was drafted. Each group kept notes of the discussion which included many comments about issues that should be included in the explanation and elaboration document.

The discussion sessions were moderated by one of two members of the steering committee (AOC and JMS). At the

Table 1
Voting responses for modification of a CONSORT item in the pre-meeting Web-based survey and during the consensus meeting (yes votes/total votes).

CONSORT item	Pre-meeting survey[a]	Votes to accept the modification proposed during the consensus meeting[b]
1	5/25	21/21[c]
2	6/25	21/22
3	14/23	22/22
4	4/17	20/23
5	4/20	23/23[c]
6	4/18	22/23[c]
7	7/21	20/23[c]
8	3/22	19/23
9	4/23	21/21
10	5/22	19/23
11	8/17	23/23
12	6/23	22/22
13	5/22	23/23
14	6/22	22/23
15	7/23	21/21
16	3/20	21/21
17	5/21	21/21
18	0/22	21/21
19	3/21	21/21
20	3/22	21/21
21	4/22	21/21
22	0/21	21/21

[a] A "yes" vote indicated that the original CONSORT item (Table 3) required modification to address intervention studies in livestock and food safety.
[b] A "yes" vote indicated acceptance for the proposed modification as listed in Table 3.
[c] Item tabled and voted on at the end of the day.

end of discussion, participants were asked to vote yes or no for the proposed item (modification or not) and paper ballots were collected, counted, and reported to the group. If an item received sufficient votes to indicate consensus, it was accepted; if it did not, it was tabled for further discussion at the end of the meeting.

1.6. Preparation of reporting guidelines

After the meeting, the steering committee compiled a draft report of the meeting which included the proposed modifications, an explanation and elaboration document, and a request for feedback from participants. The steering committee collated the comments and suggested revisions and then developed the modified CONSORT statement for trials in livestock species with production, health, and food-safety outcomes.

2. Results

Twenty-four experts were invited and 20 accepted, but one subsequently was unable to attend. Of the six steering-committee members, five attended. The meeting was attended by 24 experts (19 invitees and five steering-committee members), as well as a postdoctoral fellow working for one of the steering-committee members (JMS) and one record keeper. The 24 experts included biostatisticians, epidemiologists, food-safety researchers, and livestock-production specialists. Some participants had multiple areas of expertise. Among the group members, seven were journal editors or assistant/associate editors. One participant was working in Australia, another in Germany; five were working in Canada, and the remainder in the United States. One expert worked almost exclusively in poultry production and food safety, one expert was familiar with aquaculture (although not exclusively), five worked extensively on food safety and/or production issues in beef production, three worked extensively on food safely and/or production in swine, and five worked extensively in dairy food safety and/or production. The group included two PhD-level statisticians with many years experience in livestock-industry research. Five participants frequently conducted challenge trials with production and food-safety outcomes. Three participants were employed by government agencies.

The pre-meeting, Web-based survey was completed by 25 of the invited experts and steering-committee members; however, two invitees provided the responses on the day before the meeting, and these could not be incorporated into the materials for the meeting. All of the steering-committee members completed the Web-based survey. The results of the survey are presented in Table 1. It was unclear why respondents did not answer some questions. This might have been related to the individual respondent's level of familiarity with specific CONSORT statement items prior to the meeting or to an individual's area of expertise, e.g., some participants may not have felt qualified to comment on the presentation of statistical methods.

Table 2
Checklist of items for the REFLECT statement: Reporting Guidelines For Randomized Controlled Trials in livestock and food safety.

Paper section and topic	Item	Descriptor of REFLECT statement item	Reported on page #
Title and 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.	

Table 2 (*Continued*)

Paper section and topic	Item	Descriptor of REFLECT statement item	Reported on page #
	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 levels 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 the relevant level 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 the relevant level of the organizational structure, (e.g., numbered containers ~~or central telephone~~), 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 the relevant level of the organizational structure.	
Blinding (masking)	11	Whether or not ~~participants~~ 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 **Study** 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.	
Baseline data	15	Baseline demographic and clinical characteristics of each group, **explicitly providing information for each relevant level of the organizational structure. Data should be reported in such a way that secondary analysis, such as risk assessment, is possible**.	
Numbers analyzed	16	Number **of study units** (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, **accounting for each relevant level of the organizational structure, and** the estimated effect size and its precision (e.g., 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Discussion Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. **Where relevant, a discussion of herd immunity should be included. If applicable, a discussion of the relevance of the disease challenge should be included**.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Text in bold are modifications from the original CONSORT description (Moher et al., 2001a,b,c,d).

Voting rights were extended to everyone at the meeting except the record keeper. The moderators for the item discussion sessions (AOC and JMS) abstained from voting for the CONSORT item modifications. It was decided that >80% of votes would represent consensus. Hence, with two abstentions from the moderators, 19 of 23 votes were required to achieve the threshold for consensus (80%), although due to the absence from the room, occasionally fewer than 23 people voted. The meeting participants voted to accept the wording presented in (Table 2). For 14 items, this meant voting for wording that modified the original CONSORT item; in the other instances, this meant accepting no change in the wording from the original CONSORT item; and in one instance, the vote was to add one sub-item (Table 3). Four items (1, 5, 6, and 7) were tabled for further discussion before voting. Tabling

Table 3
Definitions used in the checklist for reporting trials in livestock with production, health, and food-safety outcomes.

Checklist description	Definition
Participant	The owner/manager of the study facility who consented to participate in the trial.
Allocation unit	The study unit allocated to receive the intervention. The allocation unit can occur at one level only of the organizational structure.
Outcome unit	The study unit at which outcomes are measured. Common outcomes in livestock production include weight gain, disease occurrence, and presence or absence of an infectious disease agent. The outcome unit can occur at one level only of the organizational structure, and may be at the same level of the organizational structure as the allocation unit, or at a lower level.
Primary outcome	The primary outcome refers to the outcome measure used to determine the study sample size.
Secondary outcome	Another outcome measure of interest, but which was not used to determine the sample size.
Organizational structure	Organizational structure refers to the manner in which the allocation and outcome units are organized within a production system. The structure may not always be hierarchical. Knowledge of the structure is important for understanding the internal validity of the study, particularly the appropriateness of the data analysis. Knowledge of the structure is also important for assessing the external validity/generalizability of the study.

involved returning to the item for further discussion later in the meeting. After this further discussion, the vote was taken for the modified wording for items 1, 5, and 7 (Table 2) and to retain the exact CONSORT item wording for item 6. The majority of changes were made to address the issue of clustering of animal populations (items 3, 7–13, 15). It was deemed critical that this information be conveyed correctly to ensure understanding of the study design and therefore must be part of the CONSORT statement rather than just be further clarified in the supporting documents. There is a need for clear identification of the unit of allocation of the intervention and the unit of assessment and inference. Interventions can be allocated at any level of the organizational structure and the outcome assessed at the same or lower level. A clear understanding of the level of allocation and outcome assessment is essential for assessing both the internal and external validity of a study.

Another issue was associated with the housing used for animals. In livestock trials, non-independence of observations can arise because animals are often housed and managed in groups. Animals housed together have something more in common than animals housed separately, as they share the same microclimate, ration, health-management procedures, etc. Failure to properly account for non-independence of the data in the statistical analysis results in a violation of the association of independence that underlies many statistical procedures. For example, beef calves at several cow-calf farms may be allocated to treatment and then transported to several feedlots, where calves from multiple farms are commingled in pens. Calves from the same farm or housed in the same pen or feedlot have something more in common than calves at a different farm or in a different pen or feedlot. This organizational structure must be conveyed and accounted for in the analysis. In the above example, the organizational structure is not hierarchical, as the farm is not always nested within pens or feedlot, i.e., calves from one farm may go to multiple pens or feedlots. In other studies, the organizational structure may be hierarchical. For example, swine may be studied within pens, within barns, within sites, and within production companies. In poultry studies, hens may be studied in multi-hen cages within houses, within sites, and within production companies. As the organizational structure is not always hierarchical, the recommendation is to use the term "organizational structure" rather than "hierarchy" when requesting this information. Attendees agreed that, in addition to modifying several of the items, further discussion of this issue would be included in an explanation and elaboration document.

The proposed additional item (sub-item 4b) referred to challenge studies. Livestock trials with production, health, and food-safety outcomes are frequently conducted in research settings in which experimental challenge of trial animals (often with pathogenic organisms) is under the control of the researcher. Many of the issues of allocation to treatment and blinding apply equally to field and challenge studies; however, there was agreement that the reporting of the challenge regimen was critical to understanding a study, but was poorly reported in many studies. Therefore, this additional item (4b) and the corresponding explanation and elaboration were added. Other modifications that addressed challenge studies included items 1 and 20.

In addition, the use of "participant" in the original CONSORT statement was limited to refer to animals' owners/managers, who consent to participation in the trial. The term "study unit" was preferred for the units within the study. Study units may further be classified as "allocation units" and "outcome units." For example, a study may allocate udder halves to receive the treatment, therefore the allocation unit is the udder half; however, the outcome may be measured on the individual teat, i.e., the outcome unit.

3. Discussion

Quality reporting is essential because it allows the reader to assess the conduct of design, analysis, and reported outcomes and make appropriate judgment about the internal and external validity of the study. Improving the quality of information available to end users of research, such as veterinarians, producers, industry bodies, and regulatory authorities, was the primary motivation for this initiative. Decision makers at all levels of animal-

protein production from the farm to the fork are constantly pressured to provide science-based rationale for recommendations. Without high-quality reporting, this is extremely difficult.

In recent years, several reviews have reported an erratic quality of reporting (O'Connor et al., 2006; Sargeant et al., 2007; Wellman and O'Connor, 2007; Burns and O'Connor, 2008). These reviews have shown empirical evidence of potential biases associated with the lack of reporting of some basic trial features, such as randomization and blinding (items 8–11) (Burns and O'Connor, 2008). In these instances, there is good indication for the inclusion of the item in the checklist. For other modifications, clear evidence of bias introduced by failure to report the item has not been documented. However, the request for information about the challenge model used (if it was a challenge study) and about the organization of animal housing are all directed at allowing the consumers of the research to determine if the study design applies to their application. These issues affect the internal and external validity of the trial. As an example of the impact of animal housing, a feedlot veterinarian may expect a different outcome from a vaccine allocated to individual animals, compared to group-level application. Similarly, a challenge study that used 100 times the normal dose of *Salmonella* to induce *Salmonella* shedding may have questionable external validity. The CONSORT statement modifications should help the researcher report the study in such a manner that the unit of allocation and the organizational structure of the data are discernible, and provide a more structured framework for discussion of how these issues affected the analysis.

We believe that reporting trials using the modified CONSORT statement, i.e., the REFLECT statement for livestock and food safety as a minimum standard, will substantially improve the reporting of trials on production, health, and food-safety outcomes. Although the REFLECT statement directly applies to reporting of studies, it may also be consulted and useful in the design and conduct stages of a trial. Researchers may find it helpful when designing trials to consider items that will be requested in the report of the trial. Considering the rationale behind the requirement for each checklist item, be it internal validity, external validity, or both, may lead to a better design. The rationale for the inclusion of each item, and examples of how to report livestock trials with production, health, and food-safety outcomes, are contained in a companion Example and Elaboration Document (Sargeant et al., 2010a,b).

Conflict of interest

None disclosed.

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Appendix A. Participating members of the consensus meeting and steering committee

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