

Study Information

1. Title

The reporting characteristics of swine intervention trials published prior to and following publication of the REFLECT statement

2. Authorship

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Expected investigator contributions statements

CAAM – developed the study proposal, extraction of data, data analysis and prepared drafts of the manuscript

ST – assisted with development of the risk of bias forms, assisted with data extraction and reviewed drafts of the manuscript

JS – developed the study proposal, and reviewed drafts of the manuscript

DCLL – developed the study proposal, extraction of data, and reviewed drafts of the manuscript

TOS – developed the study proposal, and reviewed drafts of the manuscript

AOC – developed the study proposal, extraction of data, data analysis and reviewed drafts of the manuscript

If other students are involved in data extraction – I propose they be acknowledged but I am interested to hear what others think. We can perhaps change that if some students become more involved and provide more than data extraction assistance.

3. Research Questions

- Aim 1 will seek to describe the **reporting of the allocation method** used to assign study units to treatment group in controlled trials using vaccines directed against infectious disease pathogens or food safety pathogens, and if changes in the prevalence of reporting have occurred post-2010. The rationale for this aim is that allocation approaches are an important aspect of assessing bias in clinical trials; however, as several REFLECT statement checklist items are conditional on random allocation, this information would not be captured by assessing only the REFLECT items. Our working hypothesis is that reporting of the allocation methods has improved; however, reporting will likely still be incomplete.
- Aim 2 will seek to describe the **reporting of a truly random allocation method** used to assign study units to treatment group, and if changes have occurred post-2010. The rationale for this aim is that reporting of allocation may have improved; however, prior evidence suggests some misunderstanding in the veterinary sciences of the difference between random and pseudo-random allocation approaches. Therefore, it is important to determine whether the type of allocation reported is random and the approach to describing this. We will also evaluate how frequently authors use systematic allocation, and how often authors report randomization but provide no evidence to support this assertion.
- Aim 3 is to describe the **prevalence of reporting of 18 REFLECT items**. The rationale for the 18 items selected is that these items represent factual information. The remaining REFLECT checklist items are judgment-based, and are therefore excluded from this study.

For example, it is factual to answer if authors reported randomizing animals to the treatment groups; however, it is subjective to determine if the introduction provides a suitable rationale for the study.

- Aim 4 will be to **determine if the risk of bias is lower in studies** conducted after publication of the REFLECT statement compared to studies published before. The rationale for this aim is that although the REFLECT statement (and other reporting guidelines) aim to improve reporting, there is also the inference that improved reporting might also result in fewer omissions in reporting and therefore improved ability to recognize studies conducted with a low risk of bias.

4. Hypotheses

- Aim 1: That the **prevalence of reporting an allocation method** has increased in manuscripts published from 2011 onwards in the five journals that published the REFLECT statement when compared to the prevalence of reporting an allocation method in manuscripts published prior to 2011.
- Aims 2,3, and 4: These are secondary outcomes, and we would prefer not to conduct multiple hypothesis tests. For the outcomes arising from these aims, we propose effect size estimation and confidence intervals.

Sampling Plan

5. Existing data

As of the date of submission, the data exist i.e., the studies are published and indexed

6. Explanation of existing data

The data of interest are published studies describing controlled trials in the five journals that published the REFLECT statement, and therefore by definition, they are already available. However, at the time of writing the protocol we have conducted some preliminary assessment of the available studies to determine if we are likely to find sufficient studies to have the power to address Aim 1, which is our testable hypothesis (see sample size rationale).

7. Data collection procedures.

Study population

The current study will be a cross-sectional observational survey. The population of interest will be controlled trials reported in any of the 5 journals that published the REFLECT statement where at least one arm is a vaccine targeted at infectious disease pathogens or food safety pathogens assessed in swine. Vaccines are defined as products designed to stimulate an immune response in the host. The outcome reported by the authors does not impact eligibility. The study designs of interest are controlled trials i.e., a concurrent/parallel comparison arm. Studies that use an artificial challenge or disease model are included in the relevant population. The journals are PREVENTIVE VETERINARY MEDICINE, JOURNAL OF FOOD PROTECTION, JOURNAL OF VETERINARY INTERNAL MEDICINE, JOURNAL OF SWINE HEALTH AND PRODUCTION, and ZOONOSES AND PUBLIC HEALTH.

Study selection

The literature search will be conducted in Web of Science™ (ISU license) using the CABI database, based on the following search provided in Table 1.

Search no	Search string	# Hits
1	TS= (swine OR pig* OR piglet* OR gilt* OR boar* OR sow* OR weaner* OR hog* OR porcine OR pork* OR "Sus scrofa" OR "Sus domesticus")	645,575
2	TS= (Vaccin* OR immuniz*)	149,140
3	SO= (PREVENTIVE VETERINARY MEDICINE OR JOURNAL OF FOOD PROTECTION OR JOURNAL OF VETERINARY INTERNAL MEDICINE OR SWINE HEALTH "AND" PRODUCTION OR JOURNAL OF SWINE HEALTH "AND" PRODUCTION OR ZOONOSES "AND" PUBLIC HEALTH)	17,169
4	#1 AND #2 AND #3	234

All search results will be exported to DistillerSR® (Ottawa, ON, Canada), where they will be de-duplicated, although no duplicates are expected based on the approach to the search. Two reviewers will then independently screen each record for relevance to the study in DistillerSR®.

Eligible manuscripts will have:

- 1) An individual- or group-level study population of swine,
- 2) At least one treatment arm that is a vaccine, which has as a target an infectious-disease pathogen or a food-safety pathogen i.e., a biological preparation that provides active acquired immunity to a particular disease. We are not limiting the outcome of interest reported by the authors i.e., it could be disease, production, injection sites issues, behavior, and
- 3) A concurrent comparison arm (placebo or active control) i.e., controlled trials.

Relevance screening

Two levels of screening will be used to identify eligible manuscripts. The proposed 1st level screening questions is:

- 1) Does the title or abstract appear to report an experimental study design, with at least one arm that is a vaccine for an infectious disease pathogen or food safety pathogen in swine?

The proposed full-text screening questions are:

1. Was the study conducted in swine?
2. Does the study include a concurrent comparison arm (placebo or active control) i.e., is this an experimental study design?

3. Did at least 1 arm of the study include a vaccine that has as a target an infectious disease pathogen or food safety pathogen i.e., a biological preparation that provides active acquired immunity to a particular disease?

Conflicts between reviewers will be resolved by discussion or, when consensus cannot be reached, by consulting with a third reviewer (AOC). If at the end of relevance screening, if more than 120 papers are available, we will randomly select the necessary 120 papers from the relevant studies.

Data collection for Aim1 and 2.

For Aim 1, we will extract information on whether an allocation method was described; a "yes" will refer to a study where the authors described any approach to allocation of the study units to intervention groups, i.e., random, pseudo-random, haphazard, or convenience. If no approach to allocation was reported, this will be considered a "no". For example, the sentence "Pigs were assigned to groups after balancing of sex and weight" describes the allocation and would be a "yes". However, it would not be considered a random method.

Data collection for Aim 2.

Aim 2 will be conditional on studies that reported an allocation method. Only studies that include a description of the random allocation process will be considered as a positive outcome. We will classify the studies based on four different criteria:

- a. Studies that reported randomization and provided details of allocation sequence generation.
- b. Studies that reported randomized but did not provide any details of the allocation sequence generation.
- c. Studies that reported systematic randomization or a similar alternation approach
- d. Studies that reported other allocation approaches (neither random nor systematic random)

Relevant terms that the authors might include (but are not limited to) computer-generated, flipping of a coin, generated by a statistician, will all be considered evidence of a random sequence generation method.

All other variables for Aim 3 and Aim 4 will be measured based on the text, and will be binary variables ("yes" or "no"). A pre-testing phase will be conducted to ensure high agreement between reviewers in the assessment of reporting.

Data collection for Aim 3.

A comprehensive reporting assessment form will be based on the REFLECT Statement guidelines and modified for swine (1)[ST submitted]. Only the reporting of 18 of the 22 items of the REFLECT Statement will be assessed, as items 2, 20, 21, and 22 are too subjective for simple assessment. Some changes will be made to the language of the REFLECT items to ensure that the questions are sensible for assessment. For example, item 10 of REFLECT is worded, in part, as instructions for authors "Who generated the allocation sequence?", and this will be modified to: "Did the authors describe who generated the allocation sequence?".

Item 6 will refer only to the primary outcome, and we will consider this reported if the authors use the terms "primary" or "main", or for the outcome used in the sample size calculation. Some REFLECT items which refer to more than one piece of information will be split to capture information about each concept included in the item. For example:

- Item 3 (eligibility and setting/location) will be split into two questions: one related to the reporting of eligibility criterion and one related to reporting of information on the setting/location
- Item 10 (generation of sequence, enrolment, and assignment of study units) will be split into three questions
- Item 11 (blinding of allocation, caregiver and outcome assessment) will be split into three questions

Regarding items 8, 9, and 10, these would only be answered if the authors describe the process of allocation as random (not pseudo or systematic randomization). Regarding item 18, because multiplicity takes many forms and the need for adjustment is debated, we will limit our evaluation of multiplicity to the primary outcome, if one is reported, or for studies with more than 2 treatment arms. We will only evaluate this if authors conducted pairwise comparisons and if the authors reported using p-value adjustment for multiple comparisons methods (such as Tukey's test, Duncan's new multiple range test, Fisher's least significant difference, and the Bonferroni method). Such studies might naturally be expected to consider multiple pairwise comparisons between treatment groups, and therefore a clearer case can be made for authors needing to discuss multiple testing.

Data collection for Aim 4

The risk of bias (ROB - <https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool>) assessment tools proposed by Cochrane ROB 2 will be used for individual or cluster-randomized trials. Two algorithms will be used to determine overall bias levels. We propose to use the Cochrane ROB 2 tool with one modification to the risk-of-bias algorithm. Cochrane indicates that failure to conceal allocation always results in a high risk of bias; however, we propose that in the study populations we are evaluating, the risk of bias from failure to conceal allocation is low. Our rationale for this conclusion is that the Cochrane ROB tool suggests concealment is required because of the potential for a differential value of study participants at enrolment. However, we do not anticipate such differentiation is possible for pigs in production settings.

Data collection process

The comprehensive reporting assessment and ROB forms will be pre-tested by three reviewers (AOC, CAAM, DCLL) to ensure consistency and relevance to the study population. The modified ROB algorithms will be developed with assistance from AOC, CAAM, DCLL, and JS. Two reviewers will assess the REFLECT item reporting and ROB for each publication. If a publication contains a description of more than one trial, the data from only the first relevant trial will be assessed and extracted. The reviewers will not be blind to publication dates because the date on which the study was conducted is usually reported in the Methods section and is part of the assessment of reporting.

8. Sample size calculation

The primary outcome for the sample size calculation is the number of studies that report an allocation method. Sargeant et al, 2009 reported that 67% of 100 randomly selected trials in livestock reported randomization, and we used this as a basis for our sample size calculation. It might be expected that over 90% of studies in the 5 REFLECT publication journals since 2011

will describe an allocation method. We rounded the 67% to 65% and anticipate a ratio of 2:1 for trials published pre-2011 and 2011 onwards. With 90% power and an alpha of 0.05, we determined that the needed sample size to detect such a difference would be a total of 120. Of course, this is an observational study, and therefore we cannot control the number of available studies. However, an a priori sample size calculation allowed us to address the feasibility of the project, given the anticipated volume of literature available.

This calculation was performed in R, using the epiR package, epi.propsiz function)(2):

```
epi.propsiz(treat = 0.90, control = 0.65, n = NA, power = 0.80, sided.test = 2, conf.level = 0.95
```

9. Sample size rationale

The expected sample size is approximately 120 manuscripts. To evaluate study feasibility, we conducted a preliminary search in CABI (see Table 1) and found the studies likely to be included. We also determined that the studies published from 2011 onwards represented around 1/3 of the papers. This information was used for our sample size calculation. We have not read the papers, although we are familiar with some of them due to our expertise. We have read the title and abstract of many of the titles retrieved by the search to estimate roughly how many would be relevant to the review, again to verify that we might have enough papers. As this study is observational, it is important that we determine that the study population exists that can likely have sufficient power to answer our study question.

10. Stopping rule

This is not applicable to our study.

Variables

11. Measured variables

All variables are binary indicator variables (feature present/feature absent).

Design Plan

12. Blinding

Ideally, reviewers would be blind to the year of study publication, because it is an explanatory variable. However, the year of study is also part of the assessment, i.e., REFLECT item 3 asks if the authors reported the setting and location, and Item 14 asks about reporting of the year of recruitment; therefore blinding is not possible. The authorship of the paper on the title page will be redacted prior to evaluation; however, based on the location, and the small community of researchers in the content area, it is not possible to ensure blinding occurs.

13. Study design

This is a cross-sectional survey of controlled trials with trial as the unit of concern. If a publication contains a description of more than one trial, the data from only the first relevant trial will be assessed and extracted.

14. Randomization

This is not applicable to our study design.

Analysis Plan

15. Statistical models for confirmative analysis

For Aim 1 data, the prevalence ratio will be calculated for allocation reported (yes/ no) as the primary outcome and the binary indicator variable for publication period (**PP** -- 2010 and prior compared to 2011 and post) as the explanatory variable. Studies published in 2010 will be considered pre-2010, as they would have been submitted prior to REFLECT publication. A chi-square test will be used to compare the proportions.

16. Transformations

All variables are dichotomous or polychotomous. We do not anticipate any transformation of the data except for combining unclear and high-risk categories in the ROB assessment for Aim 4.

17. Follow-up analyses

This is not applicable to our research question.

18. Inference criteria

The inferential criteria for the primary outcome in Aim 1 will be a $p < 0.05$. We will also estimate the prevalence ratio and precision estimate.

For all secondary outcomes related to Aim 2, Aim 3, and Aim 4, we will provide effect estimates and precision estimates only.

19. Data exclusion

We see no reason for data exclusion from Aim 1, as all studies will either have this information or not. The same can be said for Aim 2 and Aim 3 and Aim 4.

20. Missing data

We see no reason for data exclusion from Aim 1, as all studies will either have this information or not. The same can be said for Aim 2 and Aim 3 and Aim 4.

21. Exploratory analysis

For Aims 2, 3, and 4, we propose to summarize the data by frequency counts of each item in the controlled trials based on the publishing period (**PP**). Prevalence ratios and 95% confidence intervals will be calculated for:

- the proportion of studies that report a truly random component in the allocation sequence (Aim 2)
- the 18 items of the REFLECT Statement (Aim 3)
- results from each risk domain (low versus high/unclear) (Aim 4).

We will construct a regression model with r/n outcome for each manuscript¹ and publication period (**PP**) as the explanatory variable. (r = number of positive items, n = number of checklist

¹ r = number of positive reflect items and n = number of items assessed

items). We propose to use a log or logit link. We expect a numerically positive coefficient for both explanatory variables i.e., reporting improves with time and in studies that describe randomization. Similarly, we will conduct a logistic or log model with r/n outcome for Aim 4: (r = number of low ROB items, n = number of risk domains)

For Aim 3 and Aim 4, which have multiple estimates, we propose to present the data using a forest plot of the **publication period** prevalence ratios using the meta package (Schwarzer, 2007) in R 3.4.1 (3). A plot comparing the prevalence of checklist items and risk domains for the publishing periods will also be created. This type of graph allows comparison of the point estimates and better illustrates the underlying prevalence of reporting for the time periods.

Script

```
# Example Aim1 data were generated using random allocation to Allocation methods (AM) and Publication Period (PP)
Aim1 <- read.csv("Aim1.csv")
names(Aim1)
summary(Aim1)
Aim1$AM<-as.factor(Aim1$AM)
TabAim1<-table(Aim1)
TabAim1
library("epiR")
epi.2by2(TabAim1, method = "cross.sectional", conf.level = 0.95, units = 100,homogeneity =
"breslow.day", outcome = "as.columns")

# Aim2 would be analyzed the same way as Aim 1.

# Aim 3 and Aim 4 example code
library(plyr)
Aim3 <- read.csv("Aim3.csv")
names(Aim3)
summary(Aim3)
data_aim3 <- ddply(Aim3, c("Paper", "PP"), summarise,
sumR = sum(Repted_rand),
n=length(PP))
mod0 <- glm(sumR/n ~ PP,
data = data_aim3, family = poisson)
summary(mod0)
mod1 <- glm(sumR/n ~ PP,
data = data_aim3, family = binomial)
summary(mod1)
```


Risk of Bias algorithm for the Swine REFLECT study

We propose for this project to use the Cochrane risk of bias 2.0 tool as available on 20th Nov 2017 at the following website. <https://sites.google.com/site/riskofbiastool//welcome/rob-2-0-tool>

ROB domain 1: "biases arising from the randomization process"

The current algorithm for ROB domain 1: "biases arising from the randomization process" is provided in Figure 1. Allocation concealment aims to prevent knowledge of intended allocation from impacting enrollment decisions. In some situations, in livestock production, allocation concealment will be necessary. For example, in a study of dairy cattle in a hospital pen, ideally animals are selected for the study, placed in the chute, and then the allocation is determined. If alternatively, trial staff determined the next treatment and then selected the next animal to be removed from the pen and brought to the chute for treatment, this has the potential to create a bias, as the staff with knowledge of allocation might choose a particular animal to receive the treatment. This approach, however, implies that animals have differential economic or emotional value to the person enrolling the animals. However, in many settings in livestock production such as in poultry and swine production, the economic value of the animal is not known at the time of enrolment, and all animals have equal emotional value. In these scenarios, the potential for selection bias due to the knowledge of the allocation sequence is minimal. We, therefore, propose that in this review that Q 1.2 of ROB 2 "bias due to randomization process" be ignored and bias be assessed based on the responses to Q 1.1 and Q 1.3 only.

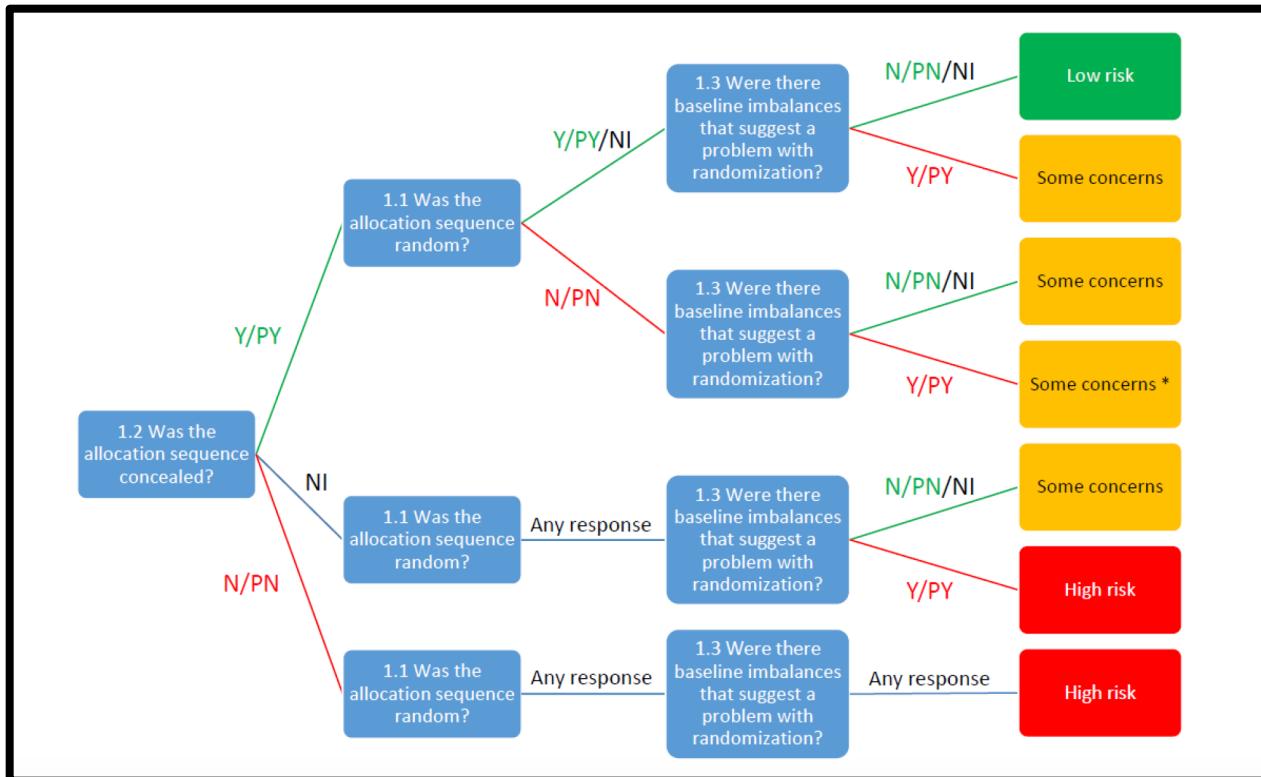


Figure 1: Cochrane ROB 2 algorithm for biases arising from the randomization process.

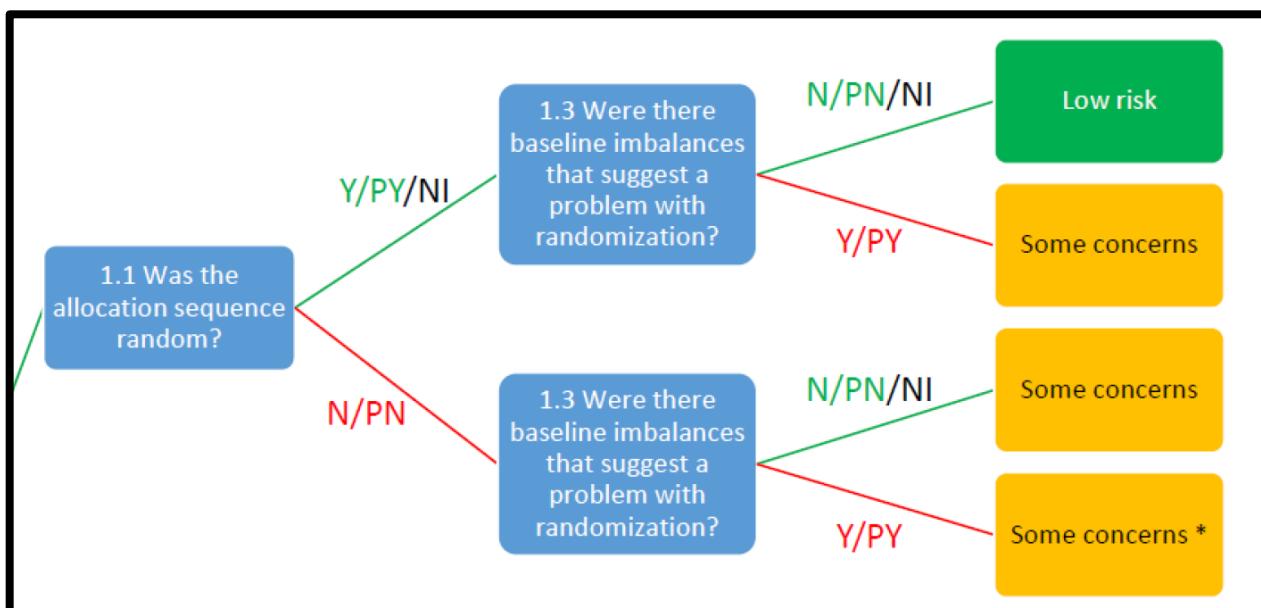


Figure 2: Modified Cochrane ROB tool for Swine REFLECT Impact study

Addition interpretation for Q1.1: Was the allocation sequence random?

"Probably Yes" - If the authors reported that the study was conducted under FDA or Good Clinical Practices management.

"No Information" – If the authors reported random allocation but provided no details as to how randomization was achieved.

"Probably no" – If the authors did not discuss any allocation methods or used systematic allocation.

Addition interpretation for Q1.3: Were there baseline imbalances that suggest a problem with the randomization process?

"Probably No" - If the study was conducted under FDA or Good Clinical Practices management, group size was > 100 for each treatment for each site of randomization (not overall), and there was no baseline data for each group, as it is very unlikely that such imbalances would occur.

"No Information" - If the study was conducted under FDA or Good Clinical Practices management, group size was < 100 each, and there was no baseline data for each group.

"No Information" -If the study was neither FDA or Good Clinical Practices management, and there was no baseline data, regardless of group sizes or Q1.1 response.

ROB biases arising from deviations from intended interventions**Additional interpretation for Q2.1: Were participants aware of their assigned intervention during the trial?**

"No" (Participants are animals and cannot be aware of their assigned interventions.)

Additional interpretation for Q2.2: Were caregivers and trial personnel aware of participants' assigned intervention during the trial?

Most veterinary studies do not report if the caregivers are blinded. Also, most veterinary studies do not report if the caregivers are the outcome assessors. Unless specifically stated, we assume that outcome assessors and caregivers are different people and therefore saying outcome assessors are blinded is not considered equivalent to saying caregivers are blinded. In Europe especially, outcome assessors are often veterinarians, while farm staff are caregivers. If the study was not an FDA or GCP study and blinding isn't mentioned, the study had a negative control group, and animals were penned separately by treatment group, answer "Probably Yes".

For challenge studies where the different groups were housed in different rooms i.e., modified live vaccines with animals in different rooms, it is likely that the caregivers were aware of the status, therefore answer "probably yes" unless there is evidence to the contrary i.e., multiple rooms and the authors reported blinding of **all study personnel**.

Answer "Probably No" if the study reported explicitly that **all study personnel** were blinded (not just outcome/clinical assessment).

Answer "Probably No" if the study is reported to have been conducted for FDA regulatory purposes or Good Clinical Practices management. The reason for this is that FDA or all guidance for many years has suggested blinding of all personnel².

Additional interpretation for Q2.3: Were there deviations from the intended intervention beyond what would be expected in usual practice?

This question is asking if caregivers' knowledge of the treatment allocation could cause a bias in care i.e., where some animals are given special care. In livestock trials, for example, sick animals might be placed in a hospital pen. However, most often this is part of the treatment, and not actually a deviation from the treatment protocol; regardless of allocated group, sick animals will be moved to a hospital pen. In this situation, the additional care is given to ALL sick animals regardless of group, not differentiated by the treatment group. Here we are looking for bias due to group i.e., more bedding, extra rations, etc.

"No information": In almost livestock studies published today, discussion of differential care is missing.

²

[\(https://www.fda.gov/downloads/AnimalVeteri](https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052372.pdf)

nary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052417.pdf)

"Probably No": In livestock studies, if animals from different treatments are co-mingled in the same housing group (pen or barn), then the potential for differential care is minimal i.e., the ration and bedding cannot be modified based on the caregivers' knowledge of the treatment status. Therefore, the potential for bias due to the knowledge of the allocation is minimal in this situation, and we would propose "probably no" as a reasonable answer.

Additional interpretation for Q2.4 (If Y/PY to Q2.3): Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?

Nothing more is needed--just remember that any differential care must impact the outcome meaningfully.

Additional interpretation for Q2.5. (If Y/PY to Q2.3): Were any participants analyzed in a group different from the one to which they were assigned?

"Probably no": Most biological interventions in livestock production (i.e., antibiotics, vaccines) will be administered to the vast majority of animals and the potential for deviation from the assigned intervention is minimal. Even if a few do not get the intervention, it is often too few to impact the group-level outcome metric.

"No information": Long-term interventions such as changes in diet, in-feed medications, in-water medications, may be more susceptible to failure to adhere to interventions, so reviewers may decide for such interventions that "no information" is a reasonable answer.

Additional interpretation for Q2.6 If Y/PY/NI to Q2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analyzing participants in the wrong group?

None provided

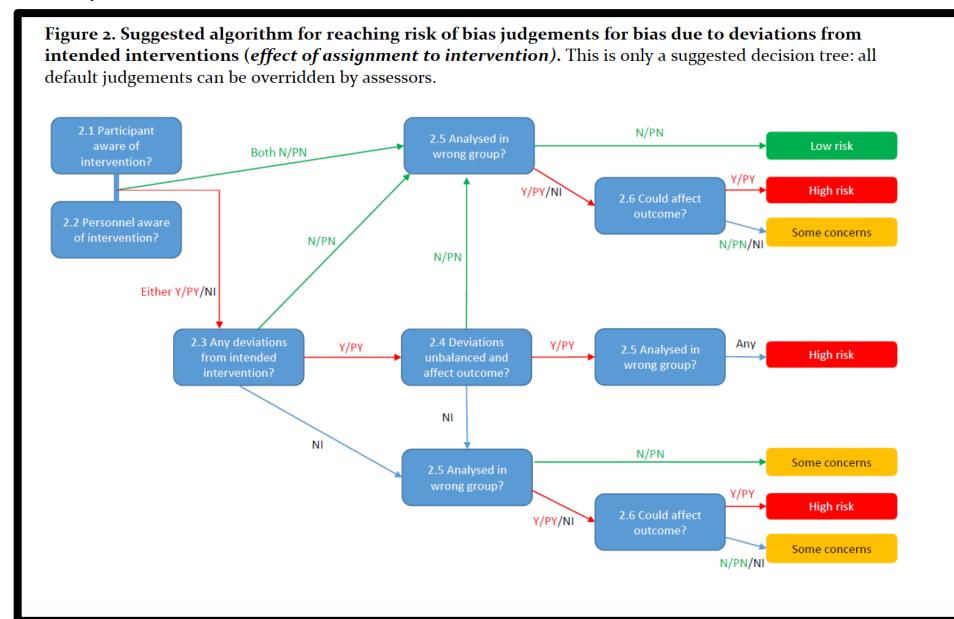


Figure 3: Cochrane ROB algorithm for domain 2: bias arising from deviations from interventions

Domain 3: Risk of bias due to missing outcome data

Additional interpretation for Q3.1: Were outcome data available for all, or nearly all, participants randomized?

"No information": If the authors did not provide information on losses during the study i.e., they only reported the numbers analyzed, then "no information" is an appropriate answer.

"Probably Yes": If the authors did provide information on losses during the study but they did not differentiate by the groups, however, the number lost is a small % of the total say < 5% then "Probably Yes" is likely an appropriate answer.

"No": If the authors did provide information on losses at an entire site, and the entire site is reported from the study, then "No" is still appropriate. This will not automatically result in high ROB because of subsequent responses.

Additional interpretation for Q3.2 If N/PN/NI to Q3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?

"Probably Yes": If the authors did provide information on losses about an entire site/pen/barn and site/pen/barn was a block, then we can assume the loss of data is similar across the treatment groups.

"Probably No": If the authors did provide information on losses about an entire site/pen/barn and site/pen/barn was the unit of concern, then we can assume the loss of data is not similar across the treatment groups.

Additional interpretation for Q3.3 If N/PN/NI to Q3.1: Is there evidence that results were robust to the presence of missing outcome data?

No additional notes

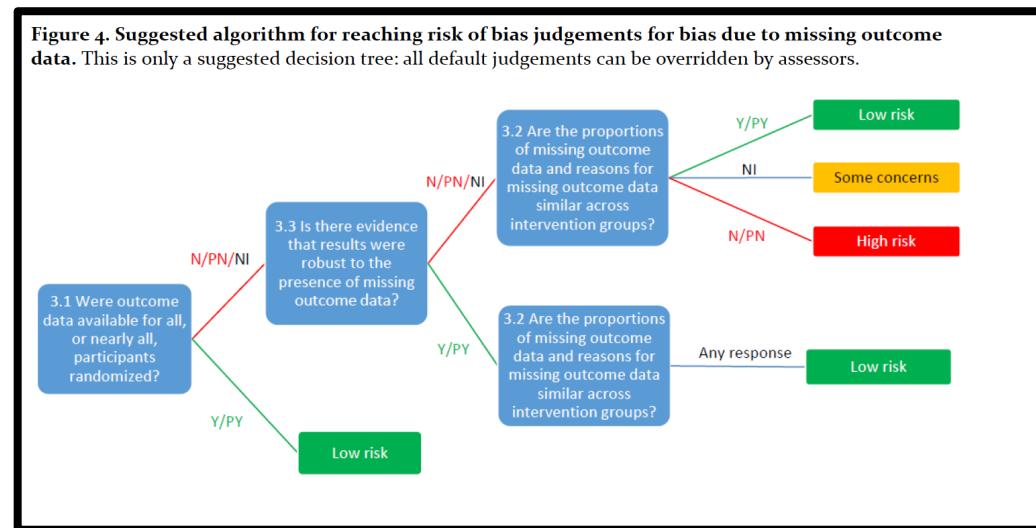


Figure 4: Cochrane ROB algorithm for domain 3: bias arising from missing outcome data

Domain 4: Bias in measurement of the outcome

Additional interpretation for Q4.1: Were outcome assessors aware of the intervention received by study participants?

Note that Cochrane says: "To assess the risk of bias, the reviewer should also take into account the degree of expectation and vested interest of the outcome assessor regarding the beneficial effect of the experimental intervention."

"Probably Yes": If the study was conducted by the company staff or funded by company staff and blinding was not discussed.

"Probably Yes": If this was not an FDA or GCP study and if blinding wasn't mentioned anywhere in the paper, and if there was a negative control group and pigs were penned by treatment group, "Probably Yes" seems reasonable

"Probably Yes": If this is a challenge study and if blinding wasn't mentioned anywhere in the paper, "Probably Yes" seems reasonable.

"Probably No" or "No": If the study was an FDA or GCP study.

Additional interpretation for Q4.2. If Y/PY/NI to Q4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?

"No": If the authors used a quantifiable metric for the outcome, such as temperature, or SP cut-off as all or part of the outcome criteria AND the authors reported the cut-off used to define the outcome.

"No Information": If the authors used a quantifiable metric for the outcome, such as temperature, or SP cut-off as all or part of the outcome criteria but the authors did not report the cut-off used to define the outcome.

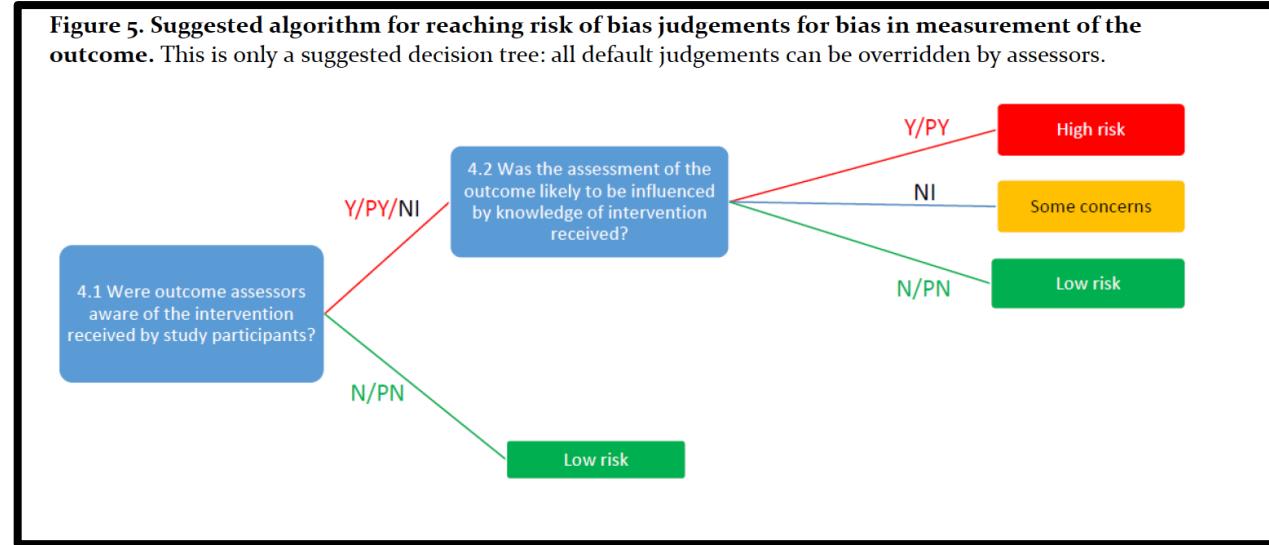


Figure 5: Cochrane ROB domain 4: Bias arising from the measurement of the outcome

Doman 5: Bias in selection of the reported result

Cochrane ROB 2.0 says this item refers to different outcome measurements. *"Examples include: reporting only one or a subset of time points for which the outcome was measured; use of multiple measurement instruments (e.g. pain scales), and only reporting data for the*

instrument with the most favourable result; having multiple assessors measure an outcome domain (e.g. clinician-rated and patient-rated depression scales) and only reporting data for the measure with the most favourable result; and reporting only the most favourable subscale (or a subset of subscales) for an instrument when measurements for other subscales were available."

Our interpretation of this item is that the following would be examples:

- A study clearly reported measurement of efficacy at multiple time points but only reported efficacy at one time point i.e., ADG or viremia levels might be measured over 7, 14, or 21 days, but results were only reported for Day 7.
- A study assessed multiple measures of the same outcome, e.g. ADG, FCE, feed intake
- A study used a composite metric (a cough, dyspnoea, temperature) to create an outcome with no information suggesting the metric was approved prior to data analysis i.e., the definition of swine respiratory disease or bovine respiratory disease.

"No information" is reasonable if the study protocol is missing or there is no discussion of an *a priori* plan.

"No" or "probably no" might be reasonable if the manuscript is the actual FDA or GCP report however that might not be the case if it is a conference proceeding or journal article of a FDA or CGP study- as there is nothing to stop the investigators adding outcomes in additional reports.

Additional information 5.2. Are the reported outcome data likely to have been selected, on the basis of the results, from multiple analyses of the data?

Our interpretation of this question is that it requires the same outcome data i.e., the same "y". For example, in the above item measuring ADG at multiple time points means that the "y" is actually different. However, for this question, we would be talking about measuring ADG at "say" day 7 for all animals, and then only a subset. Similarly, looking at adjusted or unadjusted regression models with the same outcome.

"No information" is reasonable if the study protocol is missing or there is no discussion of an *a priori* plan.

"No" or "probably no" might be reasonable if the manuscript is the actual FDA or GCP report; however, that might not be the case if it is a conference proceeding or journal article of an FDA or CGP study, as there is nothing to stop the investigators adding outcomes in additional reports.

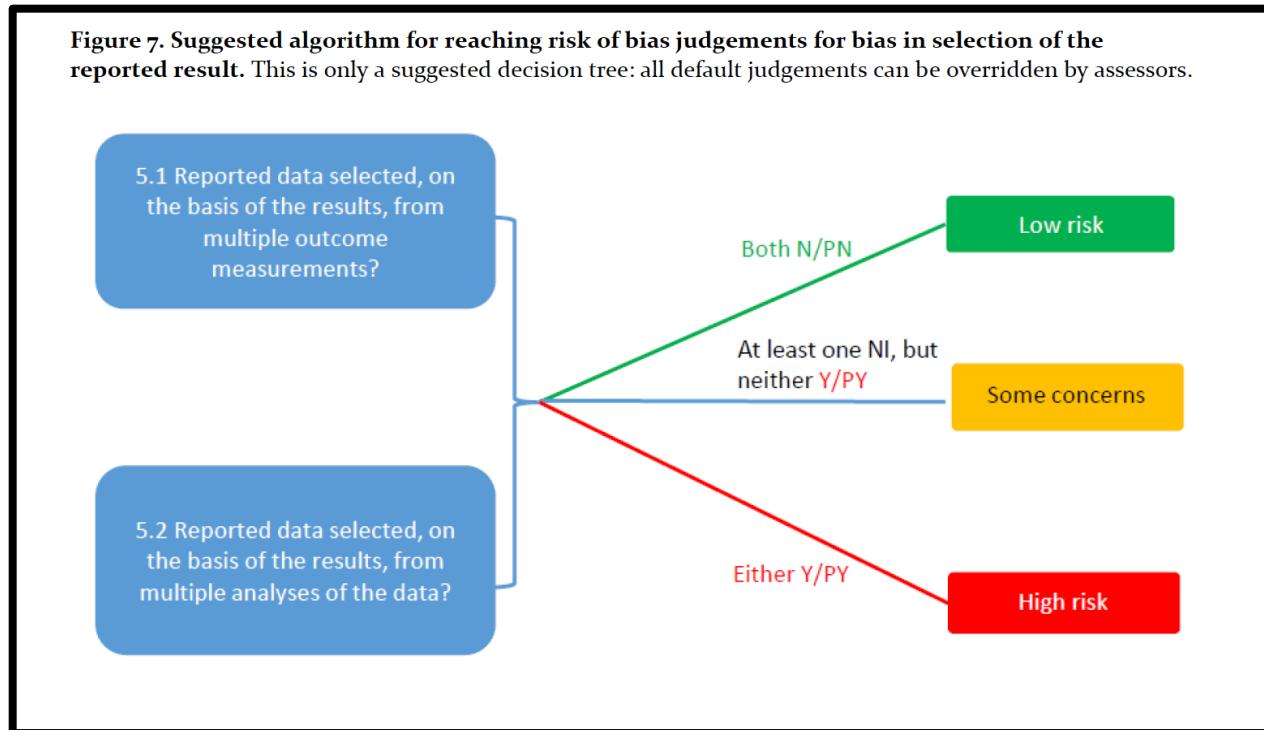


Figure 6:Cochrane ROB for bias arising from selection of outcomes reported

1. O'Connor A, Sargeant J, Gardner I, Dickson J, Torrence M. The REFLECT statement: methods and processes of creating reporting guidelines for randomized controlled trials for livestock and food safety. *Journal of Swine Health and Production*. 2010;18(1):18-26.
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3. Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.

On Wed, Nov 22, 2017 at 4:57 PM, O'Connor, Annette M [VDPAM] <oconnor@iastate.edu> wrote:

Hi Annette,

I have no objection to having my name on this protocol. I've made some changes using Track Changes. There was nowhere for me to sign my name, though. Do I need to do that on a separate form, or is my approval in this email sufficient?

Thanks,

Sarah

**Study Information****Jan Sargeant 22nd Nov 2017**

1. Title

The reporting characteristics of swine intervention trials published prior to and following publication of the REFLECT statement

2. Authorship

Cesar August Amorim Moura, Sarah Totton, Jan M Sargeant, Daniel Correia Lima Linhares, Teri O'Sullivan, Annette M. O'Connor

Expected investigator contributions statements

CAAM – developed the study proposal, extraction of data, data analysis and prepared drafts of the manuscript

ST – assisted with development of the risk of bias forms, assisted with data extraction and reviewed drafts of the manuscript

JS – developed the study proposal, and reviewed drafts of the manuscript

DCLL – developed the study proposal, extraction of data, and reviewed drafts of the manuscript

TOS – developed the study proposal, and reviewed drafts of the manuscript

AOC – developed the study proposal, extraction of data, data analysis and reviewed drafts of the manuscript

Project protocol. Page 1

Study Information

Terri O'Sullivan

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email=tosulliv@uoguelph.ca, c=CA
Date: 2017.11.22 16:57:35 -05'00'

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Project protocol. Page 1

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Terri O'Sullivan

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Daniel Linhares
Nov 22, 2017

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