Study design and EIPH Analysis of BC-2013-EIPH Study

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Background

- DVM, MSc
- Professor Large Animal Internal Medicine
- Epidemiologist
- Research Scientist
  - Critical analysis – scientific literature
  - Study design
  - Data analysis, Data presentation, Statistics

Barlett's Childers b. 1716

HAGYARD

Equine Medical Institute

Breeders' Cup 2013 EIPH Data

Dr. Nathan Slovis – Study Coordinator

Dr. Mike Spirito

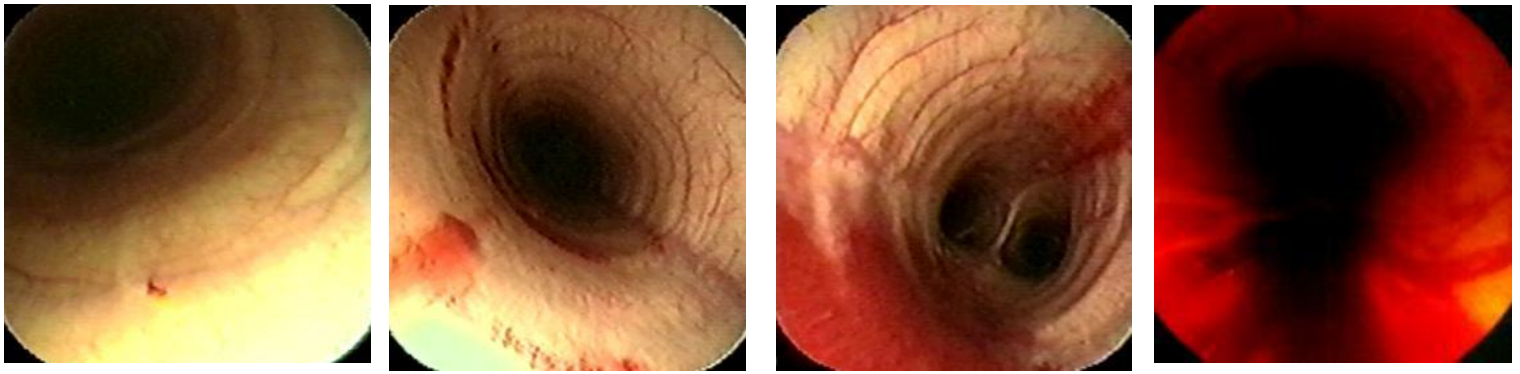
Dr. Barry David

Dr. Noah Cohen: Data Analyst

Breeders Cup EIPH Study

PURPOSE

Study the impact of prohibiting Furosemide on the occurrence and severity of blood in the trachea during/after racing



Study Design

- Study population 78 starters 2013 Breeders Cup
- 7/22 races over 2 days
- Non-BC horses were treated – BC horses were not
- Examined 14/28 non-BC and 41/50 BC horses (55/78)

Race	Fillies/Colts	Breeders Cup	Furosemide	Started	Scoped	Dirt/ Turf	Furlongs
Golden Stakes Juvenile	Colts	No	Yes	9	14	Dirt	8
Golden Stakes Juvenile Fillies	Fillies	No	Yes	10		Dirt	8
Juvenile Turf Sprint	Both	No	No	9	0	Turf	6.5
Juvenile Fillies	Fillies	Yes	No	10	41	Dirt	8.5
Juvenile	Colts	Yes	No	13		Dirt	8.5
Juvenile Turf	Colts	Yes	No	13		Turf	8
Juvenile Fillies Turf	Fillies	Yes	No	14		Turf	8

Non-Breeders Cup			
Treated	Scoped	Not Scoped	Total
Yes	14	5	19
No	0	9	9
Total	14	14	28

Breeders Cup			
Treated	Scoped	Not Scoped	Total
Yes	0	0	0
No	41	9	50
Total	41	9	50

Results and Conclusions

Results

- Treated horses were more likely to bleed and bled more severely than non-treated horses
- Bleeding was not more severe in non-treated Breeders Cup horses as compare to treated non-Breeders Cup Horses

Conclusions

- Results must be interpreted with caution
  - Concerned about design of the study

Limitations Noted in the Report

- Best study design = randomized, blinded, controlled study
- None of the BC horses were treated
- All of the non-BC horses were treated
  - Makes it impossible to determine if differences in bleeding was due to the treatment or the method of selection
  - Impossible to correct the problem through data analysis
- Examiners knew the treatment status of the horses
- Small number of horses in the study

My Assignment

- Provide an assessment of the BC-EIPH study
  - Quality of design
  - Quality of data
  - Validity of conclusions

Starting points for a valid animal trial

- Clearly described and defined objectives
- Controlled
- Unbiased
  - Randomized
  - Masked/blinded
- Appropriate power
- Amenable to valid statistical analysis

ORIGINAL ARTICLE

The REFLECT Statement: Methods and Processes of Creating Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety by 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. E. Dewey, I. R. Dohoo, R. B. Evans, J. T. Gray, M. Greiner, G. Keefe, S. L. Lefebvre, P. S. Morley, A. Ramirez, W. Sischo, D. R. Smith, K. Snedeker, J. Sofos, M. P. Ward and R. Wills

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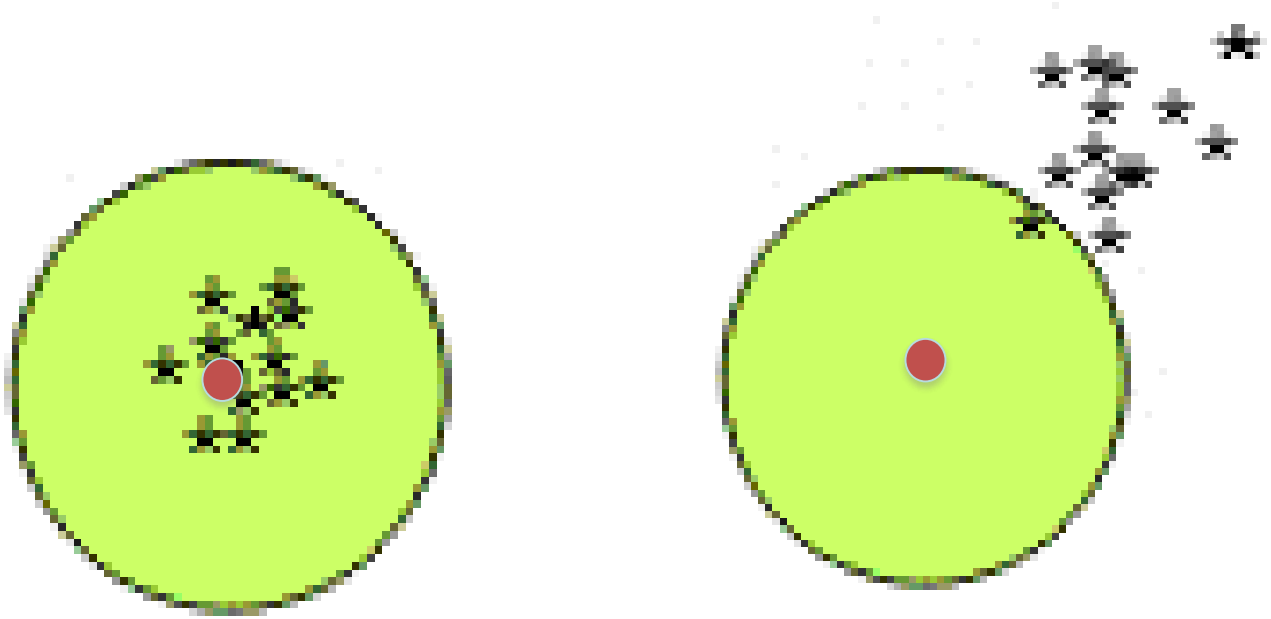
Bias is more common in studies not following guidelines

Bias
Systematic deviation from truth



Generally unintentional

Preventing study bias

- Clear primary objective
- Randomized
  - Groups are same/similar – except for the Rx
- Blinded
  - Investigators not aware of the Rx status of individual animals
- Controlled
  - Appropriate group to compare with the Rx group
- Adequate numbers of experimental units
  - Individuals or groups – depending on the study design
- Adequate/appropriate challenge

Randomization

- Formal procedure
  - Computer program
  - Random numbers table
- No difference between groups except the treatment
- Treatment must be applied equally within
  - Day
  - Groups
  - Among horses within Race

Randomization is not

- A volunteer
- First animal caught
- First half through the chute
- Every other animal
- Those who volunteer

Blinding/Masking

- Almost always possible
- Double blind
  - Evaluator and patient
- Blind/masking should occur at all levels
  - Treatment group through to statistical analysis
  - Everyone associated with the study
- If you do not do it, be prepared to declare and explain

Group Effects

- Occur in all experiments with >1 group
- Group environment, conditions, interaction among animals will vary among groups
- May significantly influence treatment response
- All treated animals in one group all controls in another
  - Single, trivial comparison (N=1)
  - Valid statistical analysis is not possible

This is a valid experiment

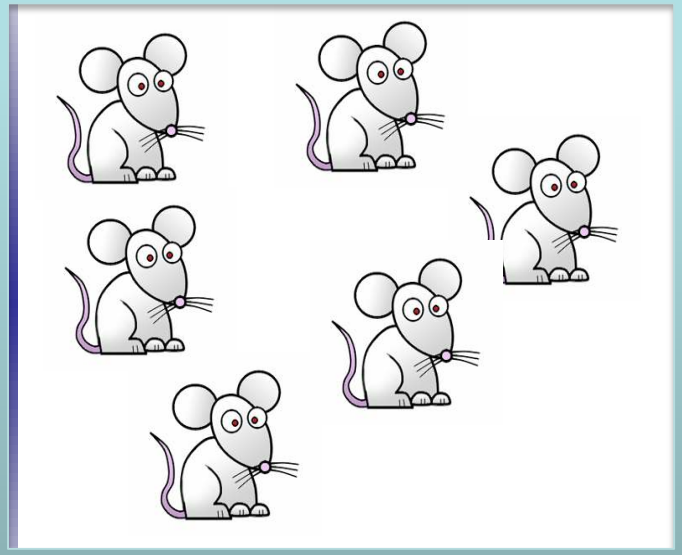
Cage 1

Cage 2

- Treatment effect and cage effect can be separated
- If no significant cage effect then N=6
- Results of statistical analysis valid

This is not a valid experiment

Cage 1



Cage 2

- Treatment effect and cage effect cannot be separated
- N=1
- Results of statistical analysis is not valid

BC - EIPH Study

- Randomized – no
  - Risk of bleeding not uniform across the treatment groups
    - Recruitment – volunteer
    - Missing data
- Blinded – no
  - Evaluations may be biased
- Adequate numbers – no (N=1)
  - FATAL DESIGN FLAW – cannot separate/distinguish between GROUP and TREATMENT effects

How did it happen?

- Rules of the day (2012 & 2013)
  - All Breeders Cup horses raced without Furosemide
  - All comparison stakes horses were treated
- Risk of bleeding +/- similar between groups
- Can't separate treatment and group effect
- Don't know why the stakes horses bleed more than the BC horses
- N=1

Final Remarks

- Study purpose not met
  - Hypothesis could not be tested
  - Study question was not answered
- Study design is fatally flawed
  - Cannot distinguish between potential TREATMENT and any known or unknown GROUP EFFECTS
    - Because N=1
  - Data cannot be analyzed or interpreted
  - No meaningful conclusions to draw

An Analogy