Randomized Controlled Trials

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Controlled trial

• Definition
  • A planned experiment carried out on subjects in their normal environment
  – Real populations
    • Treatment is allocated to groups of animals in a random fashion

  – Purpose
    • Often designed to evaluate a type of intervention (vaccine, new antimicrobial drug, diagnostic procedure, etc.)
    • Often only one intervention per study
Controlled trials
Clinical pharmaceutical research

4 phases

• Phase I
  » Evaluate safety on healthy animals
  » Safe dose range
  » Side effects (formulation trials)

• Phase II
  » First evaluation of drug in small number of animals with the disease of interest (target population)
  » Document activity of the drug
  » Often before/after comparison, no control group
Clinical pharmaceutical research, continued

• Phase III
  » Large-scale experimental studies to determine efficacy
  » Normal clinical population, treatment randomly assigned (often involves a placebo)
  » Monitoring side effects
  » Compare the drug with other available treatments

• Phase IV
  » Post-registration trials carried out to evaluate the most effective way to use the drug
  » Should be randomized
Stating the objectives

• Clearly defined
  • Definition of intervention
  • Primary outcome to be measured
  • One or two primary objectives
  • SMALL number of secondary objectives

• Two-arm studies
  • Comparison of two groups (e.g. standard treatment vs. new treatment, placebo vs. new treatment)
  • This can be a way of getting around the ethical dilemma of a non-treated control group or a “positive control”
Defining study population

• Subject (unit of concern)
  • Often an animal, but can be
    » litter, sea cage, pen, herd, etc.

• Participant
  • Animal owner
  • Volunteer
  • Representative of target population?
  • Eligibility criteria: Animal handling facilities, adequate records, clear case definitions
Allocation of subjects

• (Historical controlled trial) – Compare level of outcome before intervention with level of outcome after intervention; requires predictable outcome, well-known disease documented through a database, constant and specific diagnostic criteria and no change in environmental factors of subjects

• Random:
  – Systematic random - blinding of personnel should be used
  – Simple random - all animals must be numbered
  – Stratified random (e.g. within age groups)
  – Block randomization
  – Cross-over studies - a subject gets both tx, which one is first is random
  – Cluster randomization - allocation at cluster level (e.g. pen level, outcome at animal level)
Blinding (Masking)

*Why? To prevent bias*

- **Single blind**
  - Participants (animal-owners) are blinded to animal status

- **Double blind**
  - Participants and personnel are blinded to animal status

- **Triple blind**
  - Participants, personnel and analyst are blinded to animal status (uncommon)
Follow-up and compliance

• Equal and rigorous for all groups
  – Lengthy, to measure all outcomes

• Sample size should be adjusted to allow for **LOSS TO FOLLOW-UP**
  – Drop-outs: Try and get information about reason for withdrawal

• Incentives to minimize losses
  (e.g. free treatment)
Measuring the outcome

• Outcomes should be clinically relevant
  – 1 or 2 primary outcomes
  – Few secondary outcomes
  – Otherwise ‘multiple comparisons’ problem

• Specify
  • Criteria for outcomes (e.g. scores for clinical signs)
  • Objective measurements (such as body temp.)
  • Diagnostic tools to diagnose cases
Ethical considerations

- Ethics review by board
- Animal welfare committee
- Investigation justifiable
- Sample size appropriate (next lecture!)
- Procedures to minimize risk and maximize benefits for subjects
- Participation on informed consent
- Option to withdraw
- Confidentiality of data
On-farm culture project
Dr. Kim MacDonald & Dr. Greg Keefe

• 46 farms enrolled
  • mainly NCDF farms

• Aim: 1000 clinical cases
  • 50% allocated to treatment group
    (treatment with a specific intramammary antimicrobial)
  • 50% allocated to control group

• Randomization
  • “Treatment” or “control” in an envelope in culture kit
  • Equal number of each envelopes in each kit
  • Producer instructed to treatment or not, but not blinded
On-farm culture project
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Laboratory culture

• Personnel blinded to result of total aerobic count Petrifilm™ and coliform count Petrifilm™ in the on-farm culture kits

• Follow up (drop-outs)
  • Cases that ended up needing more treatment than the specific drug in the protocol
  • Missed follow-up milk samples
  • Missed recording of milk returned to tank
  • Cow was sold, culled or died for unknown reasons
  • Failure to record culture results for cultured cows
Questions?