Designing a Field Trial

The Devil is in the Details

Julie Levy
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Study Design

- Appropriate controls
- Masked (AKA blinded) to avoid bias
- Strong data analysis plan (statistics)
- Powered to get statistically significant results
- Defined enrollment criteria
- Clear end points
- Well defined study schedule

Write it Down!

- Develop a detailed protocol
- Include "Case report forms" – pages where everything you want to record has a place.
- Data – the lifeblood of a study – if you didn't write it down, it didn't happen.

What is in a protocol?

- Everything! (see list)
- Think of everything that could go wrong and plan for it
  - Wrong treatment given
  - Lost to follow up
  - Mix up in animal ID
  - Missing data points

Changing the protocol and deviations

- No matter how well you plan, "s…. happens"!
- Amendments – planned changes
- When a deviation from the protocol (AKA mistake) happens, document it and evaluate its impact on the integrity of the study

Training

- Everyone involved in the study should be trained on the protocol and forms
- Document the training – who did it and when
- Train on amendments

Data

- Make an effort to record who collected the data and when
- Signatures and dates on forms
- Keep it safe! Originals are important.

Final Report

- Study final report is different from a research publication
- Include all details – helps with analysis later
- Journal publications can be 'extracted' from final study report

Getting Involved in Field Testing of Non-surgical Contraceptives: Lessons Learned, and what Organizations and Veterinarians Should Consider when Getting Involved

Ethical & Welfare Considerations in Field Trials for Products Destined for Underprivileged Populations

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Why clinical field trials?

- Performed after initial proof-of-concept and safety studies
- Large sample size of relevant participants
- Realistic treatment environment
- Less oversight or less expensive than laboratory studies?

Ethical standards for field trials

- Sound research protocols
- Institutional review
- Transparency
- Protection of participants
- Implications of working with disadvantaged communities
- Human trials: guided by the Declaration of Helsinki
- Animal trials: no international standard

The need for research in the developing world and among disadvantaged populations

NUFFIELD COUNCIL ON BIOETHICS

- "Each year £35-40 billion is spent on healthcare research worldwide
- Only 10 percent of this is devoted to the health problems of 90 percent of the world's population
- Developing countries urgently need research to help prevent and treat diseases such as TB and malaria
- Many countries have limited funds and a lack of trained staff to conduct their own research"

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

New AIDS Cases in Africa Outpace Treatment Gains

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

Ezekiel J. Emanuel, David Wendler, Jack Killen, and Christine Grady
Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland

(See the editorial commentary by Kuritzkes, on pages 796–8.)

- Poverty, limited health-care services, illiteracy, cultural and linguistic differences, and limited understanding of the nature of scientific research increases risk
- Local regulatory infrastructure may be inadequate to protect participants
- Participants and communities should both benefit from research during and after the trial

Whose standards of care?

Sponsor's standards or local standards?

- Control groups
  - Placebo?
  - Best local standard?
  - Best known standard?
- Treatment of adverse events
- Post-trial definitive treatment
- Post-trial ongoing care and disposition

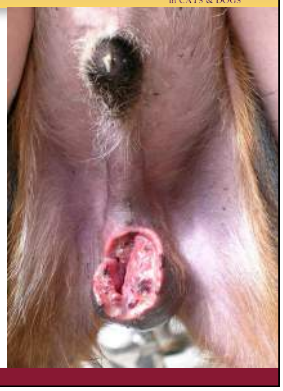
Review and informed consent

- External review
  - IACUC (animals)
  - IRB (people)
  - Home institution and study site if different
- Informed consent
  - Pet owner
  - Who consents for community animals?

American veterinary students performing surgery in Latin America in compliance with the local standard of care

Good enough?

- Field trial team must be prepared to adapt to unexpected events
- Example: Neutersol reactions in the Galapagos 2004
  - Suspended product use
  - Surgical treatment for effected dogs
  - House-to-house visits to examine dogs
  - Findings published
  - Re-think approach, refine procedures, more work in dogs in USA



5th International Symposium on Non-Surgical Contraceptive Methods of Pet Population Control

- Field trials are necessary to demonstrate safety and efficacy in populations targeted for treatment
- Animals, like children, are particularly vulnerable, particularly if they lack effective guardians or live in under-resourced communities
- Investigators are obligated to protect their animal subjects both during and after clinical trials, including management of adverse events
- Results of clinical trials should be shared transparently with regulators, colleagues, and communities